Renewal Assessment Report

Bacillus thuringiensis subsp. *aizawai strain GC-91*

- Agree 50 WG -

Volume 3 – B.6 Effects on human health

July 2018

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Introduction

Bacillus thuringiensis subsp. *aizawai* GC-91 (in the following abbreviated as Bta GC-91) is a transconjugant strain originating from a Bta and a Bt subsp. *kurstaki* strain. Bta in general occurs ubiquitous in soils on plants as well as in infested insects. Bta acts highly specific against insect species of the order Lepidoptera and is not expected to have any harmful effects on beneficials and other non-target species of other insect orders. The insecticidal activity of Bta is mainly attributed to spore bound insecticidal pro-toxins (Cry toxins) which are ingested by the target pests and activated under alkaline conditions in the midgut of the larvae.

As the manufacturing process of Bta GC-91 has not been changed since original approval, all data submitted for the original approval of the strain are considered fully applicable for the current evaluation.

Besides new information, the submitted dossier includes all data, which have been presented in the DAR (Jan 2008) and DAR addendum (Nov 2012). This information is marked grey with a clear indication where the information is originating from.

B.6 Effects on human health

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4

The results of acute studies show that *Bacillus thuringiensis* subspecies *aizawai* does not pose a toxic, infective or pathogenic hazard to humans. This subspecies does not produce metabolites of concern under representative use conditions. Since most of the studies have been performed with the technical product (namely CGA-237218 technical FL or Agree 50 WP) the results obtained could be adopted also for the formulation itself. Therefore the preparation based on *Bacillus thuringiensis* subspecies *aizawai*, used according the condition of use proposed, should not pose risk to human health.

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.3 / OECD Dossier Doc IIIM, Section 7, Point IIIM 7.2

No cases on hypersensitivity have been reported in production or application of Agree 50 WP.

New data 2016

A new medical surveillance is submitted in Document M-MA, Section 5, Point MA 5.1.2. No cases on hypersensitivity have been reported in production or application of Agree 50 WP.

B.6.1 Basic acute toxicity studies

B.6.1.1 Acute oral toxicity

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.1.1 / OECD Dossier Doc M-IIIM, section 7, Point IIIM 7.1.1

Single doses of CGA-237218 WP FL-910959 as a 30% (w/v) suspension in deionized water at levels of 4000, 5050 or 5500 mg per kg b.w. were administered orally by gavage to each of five female rats, and five male rats received a dose of 5050 mg per kg body weight. Two female rats who had received 5050 mg per kg b.w. died on day 1 after treatment. No further mortalities occurred. No signs of toxicity were noted for the animals that received 4000 or 5500 mg/kg b.w. One male which had received 5050 mg /kg b.w. showed a slight activity decrease, slight nasal discharge and moderate salivation on day 1, while another male showed piloerection and gasping on day 2 and 3. Females which had received 5050 mg/kg b.w. showed piloerection on the day of treatment. Clinical signs of toxicity for the animals found dead included gasping, nasal discharge, piloerection respiration gurgle and salivation. No abnormalities upon macroscopic examination were recorded except for the two animals found dead which had the gastrointestinal tract distended with gas and dark brown paste.

The acute oral LD_{50} of CGA-237218 WP FL-910959 was found to be greater than 5050 mg/kg bw corresponding to 3.2×10^{10} CFU *Bacillus thuringiensis aizawai* per kg bw.

Single doses of Agree FL-920303 (CGA-237218 WP) as a 40% (w/v) suspension in deionized water at level 5050 mg per kg bw were administered orally by gavage to each of five female and five male rats.

One female rat died on day 1 after treatment. No further mortalities occurred. Clinical signs of toxicity for the female animal found dead included gasping, nasal discharge, piloerection and salivation. No abnormalities upon macroscopic examination were recorded except for the female found dead with signs of nasal discharge and salivation, brown liquid in the stomach and brown mucoid material in the large and small intestine.

The acute oral LD_{50} Agree FL-920303 was found to be greater than 5050 mg/kg bw corresponding to 1.2×10^{11} CFU *Bacillus thuringiensis aizawai* per kg bw.

The preparation does not warrant classification on the basis of its acute oral toxicity.

Reference IIIM 7.1.1/01

Report [redacted] (1991a)
CGA-237218 WP FL-910959 Acute oral toxicity study in rats with a microbial pest control agent (MPCA),
Unpublished Report No. 8188-91

Guideline EPA FIFRA 81-1

GLP Yes

Materials and Methods:

The study was conducted during the period 12.06. – 28.06.1991 by [redacted]

Single doses of CGA-237218 WP FL-910959 as a 30% (w/v) suspension in deionized water at levels of 4000, 5050 or 5500 mg per kg b.w. were administered orally by gavage to each of five female rats, and five male rats received a dose of 5050 mg per kg body weight. Body weights were recorded before, 7 and 14 days after treatment and animals observed frequently on day 1 and daily thereafter. Surviving animals were killed on day 15, the end of the observation period and all animals were subjected to a gross necropsy.

Findings:

Two female rats who had received 5050 mg per kg b.w. died on day 1 after treatment. No further mortalities occurred.

No signs of toxicity were noted for the animals that received 4000 or 5500 mg/kg b.w. One male which had received 5050 mg /kg b.w. showed a slight activity decrease, slight nasal discharge and moderate salivation on day 1, while another male showed piloerection and gasping on day 2 and 3. Females which had received 5050 mg/kg b.w. showed piloerection on the day of treatment.

Clinical signs of toxicity for the animals found dead included gasping, nasal discharge, piloerection respiration gurgle and salivation.

No abnormalities upon macroscopic examination were recorded except for the two animals found dead which had the gastrointestinal tract distended with gas and dark brown paste.

Conclusions:

The acute oral LD_{50} of CGA-237218 WP FL-910959 was found to be greater than 5050 mg/kg bw corresponding to 3.2×10^{10} CFU *Bacillus thuringiensis aizawai* per kg bw.

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Reference IIIM 7.1.1/02

Report [redacted] (1992)
Agree FL-920303 (CGA-237218 WP) Acute oral toxicity study in rats with a microbial pest control agent (MPCA),
Unpublished Report No. 8938-92

Guideline EPA FIFRA 81-1

GLP Yes

Materials and Methods:

The study was conducted during the period 29.04. – 13.05.1992 by [redacted]

Single doses of Agree FL-920303 (CGA-237218 WP) as a 40% (w/v) suspension in deionized water at level 5050 mg per kg bw were administered orally by gavage to each of five female and five male rats. Body weights were recorded before, 7 and 14 days after treatment and animals observed frequently on day 1 and daily thereafter. Surviving animals were killed on day 15, the end of the observation period and all animals were subjected to a gross necropsy.

Findings:

One female rat died on day 1 after treatment. No further mortalities occurred.

Clinical signs of toxicity for the female animal found dead included gasping, nasal discharge, piloerection and

salivation.

One animals was without clinical signs. Very slight diarrhoea was noted on the day of treatment for two males and one female and slight or very slight piloerection was noted for all males and four females which disappeared by day 6. One female showed a slight activity decrease, slight nasal discharge, lacrimation and moderate salivation on day 1 and gasping on days 1 to 3. For this animal a reduced body weight gain was observed for the first week, while body weights of the other animals were unaffected.

No abnormalities upon macroscopic examination were recorded except for the female found dead with signs of nasal discharge and salivation, brown liquid in the stomach and brown mucoid material in the large and small intestine.

Conclusions:

The acute oral LD_{50} Agree FL-920303 was found to be greater than 5050 mg/kg bw corresponding to 1.2×10^{11} CFU *Bacillus thuringiensis aizawai* per kg bw.

New data 2016

Data provided for first approval are considered acceptable to cover the current requirements. Available studies on acute oral toxicity were carried out with CGD 97220 I (Agree 50 WP), which was the representative formulation during the first evaluation of Bta GC-91. The current representative formulation is a WG formulation which is very similar to the old WP formulation. The content of Bta GC-91 is the same in both products and they differ by one inert only. The co-formulant present in Agree 50 WG has a more favourable toxicological profile so that the formulation is considered even more harmless than Agree 50 WP. It can thus be concluded that the data submitted previously for Agree 50 WP are fully applicable to support the evaluation of Agree 50 WG. For details of the formulation Agree 50 WP and WG, please refer to Volume 4.

Thus, Agree 50 WG does not warrant classification as being toxic or harmful on the basis of its acute oral toxicity according to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. No hazard statement or signal word is required.

B.6.1.2 Acute inhalation toxicity

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.1.2 / OECD Dossier Doc IIIM, Section 7, Point IIIM 7.1.3

Five rats per sex were exposed to CGA-237218 WP FL-910986 as an aerosol for four hours. Exposure level was 5.78 mg/L corresponding to 1.8×10^8 CFU *Bacillus thuringiensis* /L. Initial clinical signs of toxicity included activity decrease, lacrimation, nasal discharge, piloerection, polyuria and salivation. No clinical signs were noted from day 2 onwards. Body weights or body weight gains were reduced during the first week but recovery was observed during the second week. No abnormalities upon macroscopic examination were recorded. The acute inhalation LC_{50} for CGA-237218 WP FL-910986 in rats was found to be greater than 5.78 mg/L corresponding to 4.2×10^7 *Bacillus thuringiensis aizawai* per L.

Five rats per sex were exposed to Agree FL-921616 as an aerosol for four hours. Exposure level was 0.651 mg/L corresponding to 3.4×10^8 CFU *Bacillus thuringiensis* /L. Animals then were observed for 14 days for clinical signs of systemic toxicity. No mortalities occurred. Initial clinical signs of toxicity were slight or very slight and included activity decrease, lacrimation, nasal discharge, piloerection, polyuria and salivation. No abnormalities upon macroscopic examination were recorded. The acute inhalation LC_{50} for Agree FL-921616 in rats was found to be greater than 0.651 mg/L corresponding to 3.4×10^8 CFU *Bacillus thuringiensis* subsp. *aizawai* per L. clinical signs were noted from day 2 onwards.

The preparation does not warrant classification as being toxic or harmful on the basis of its acute inhalative toxicity.

Reference IIIM 7.1.3/01

Report [redacted] (1991)

CGA-237218 WP FL-910986 Acute inhalation toxicity study in rats with a microbial pest control agent (MPCA),

Unpublished Report No. 8200-91

Guideline EPA 81-3

GLP Yes

Materials and Methods:

The study was conducted during the period 24.05. – 07.06.1991 by [redacted]

In an acute inhalation toxicity study, five rats per sex were exposed to CGA-237218 WP FL-910986 as an aerosol for four hours. Exposure level was 5.78 mg/L corresponding to 1.8×10^8 CFU *Bacillus thuringiensis* /L. Animals then were observed for 14 days for clinical signs of systemic toxicity.

Findings:

Exposure concentration was determined as 5.78 mg/L with an average of 14.8% of particles < 1 µm. A greater proportion of respirable particles was not attainable. Mass median aerodynamic diameter was determined as 11.3 µm with a geometric standard deviation of 8.00. No mortalities occurred. Initial clinical signs of toxicity included activity decrease, lacrimation, nasal discharge, piloerection, polyuria and salivation. No clinical signs were noted from day 2 onwards. Body weights or body weight gains were reduced during the first week but recovery was observed during the second week. No abnormalities upon macroscopic examination were recorded.

Conclusions:

The acute inhalation LC_{50} for CGA-237218 WP FL-910986 in rats was found to be greater than 5.78 mg/L corresponding to 4.2×10^7 CFU *Bacillus thuringiensis aizawai* per L.

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Reference IIIM 7.1.3/02

Report [redacted] (1993)

Agree FL-921616 Acute inhalation toxicity study in rats with a microbial pest control agent (MPCA)

Unpublished Report No. 9398-92

Guideline EPA 81-3

GLP Yes

Materials and Methods:

The study was conducted during the period 30.09. – 14.10.1992 by [redacted]

In an acute inhalation toxicity study, five rats per sex were exposed to Agree FL-921616 as an aerosol for four hours. Exposure level was 0.651 mg/L corresponding to 3.4×10^8 CFU *Bacillus thuringiensis*/L. Animals then were observed for 14 days for clinical signs of systemic toxicity.

Findings:

Exposure concentration was determined as 0.651 mg/L (nominal concentration 1.6 mg/L) with an average of 10.8% of particles < 1 µm. A greater proportion of respirable particles was not attainable. Mass median aerodynamic diameter was determined as 3.2 µm with a geometric standard deviation of 2.6. No mortalities occurred. Initial clinical signs of toxicity were slight or very slight and included activity decrease, lacrimation, nasal discharge, piloerection, polyuria and salivation. No clinical signs were noted from day 2 onwards. Body weights or body weight gains were reduced for females during the first week but recovery was observed during the second week. Weight loss was observed for one male during the second week. No abnormalities upon macroscopic examination were recorded.

Conclusions:

The acute inhalation LC_{50} for Agree FL-921616 in rats was found to be greater than 0.651 mg/L corresponding to 3.4×10^8 CFU *Bacillus thuringiensis aizawai* per L.

New data 2016

Data provided for first approval are considered acceptable to cover the current requirements. Available studies on acute respiratory toxicity were carried out with CGD 97220 I (Agree 50 WP), which was the representative formulation during the first evaluation of Bta GC-91. The current representative formulation is a WG formulation which is very similar to the old WP formulation. The content of Bta GC-91 is the same in both products and they differ by one inert only. The co-formulant present in Agree 50 WG has a more favourable toxicological profile so that the formulation is considered even more harmless than Agree 50 WP. It can thus be concluded that the data submitted previously for Agree 50 WP are fully applicable to support the evaluation of Agree 50 WG. For details of the formulation Agree 50 WP and WG, please refer to Volume 4.

Thus, Agree 50 WG does not warrant classification as being toxic or harmful on the basis of its acute pulmonary toxicity according to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. No hazard statement or signal word is required.

B.6.1.3 Acute percutaneous toxicity

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.1.3 / OECD Dossier Doc IIIM, Section 7, Point IIIM 7.1.2

Five New Zealand white rabbits per sex were exposed to Agree (CGA-237218 WP) FL-911716 by the dermal route. Approximately 10% of the body surface was clipped and treated with 2.85×10^9 CFU per kg b.w. (2020 mg/kg b.w.) for 24. No mortalities were observed and no clinical signs of toxicity were noted. Very slight oedema was observed for one male through day 2 and for one male through day 4. Well defined erythema was observed for two males up to 5 days after removal of the patch. Transient slight erythema (grade 1) were observed 1h after removal of the patch and had resolved after 11 days. No effects were noted for three animals. The acute lethal dermal dose of Agree (CGA-237218 WP) FL-911716 was found to be greater than 2020 mg/kg b.w. corresponding to 2.85×10^9 CFU *Bacillus thuringiensis aizawai* per kg b.w.

The preparation does not warrant classification on the basis of its acute dermal toxicity.

Reference IIIA 1 IIIM 7.1.2/01

Report IIIA 2 [redacted](1991b)
IIIA 3 Agree (CGA-237218 WP) FL-911716 Acute dermal toxicity/irritation study in rabbits with a microbial pest control agent (MPCA),
IIIA 4 Unpublished Report No. 8373-91

Guideline IIIA 5 EPA 152A-11

GLP IIIA 6 Yes

Materials and Methods:

The study was conducted during the period 19.09. – 03.10.1991 by [redacted]

In an acute dermal toxicity study, five New Zealand white rabbits per sex were exposed to Agree (CGA-237218 WP) FL-911716 by the dermal route. Approximately 10% of the body surface was clipped and treated with 2.85×10^9 CFU per kg b.w. (2020 mg/kg b.w.) for 24 h. Animals then were observed for 14 days for clinical signs of systemic toxicity. Examination of the treated skin was made 30 min after removal of the patch and then daily to day 15.

Findings:

No mortalities were observed. No clinical signs of toxicity were noted. Very slight oedema was observed for one male through day 2 and for one male through day 4. Well defined erythema was observed for two males up to 5 days after removal of the patch. Transient slight erythema (grade 1) were observed 1h after removal of the patch and had resolved after 11 days. No effects were noted for three animals.

Table 7.1.2-1 Individual scoring of dermal irritation

	Animal	Days after removal of the patch

	No	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Male	1796	1	2	2	2	1	1	1	0	0	0	0	0	0	0
	1798	0	0	2	2	2	1	1	0	0	0	0	0	0	0
	1800	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1802	1	1	1	1	1	1	1	1	1	1	1	0	0	0
	1804	1	1	0	0	0	0	0	0	0	0	0	0	0	0
female	1799	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	1801	0	1	1	1	0	0	0	0	0	0	0	0	0	0
	1803	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1805	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1807	1	1	1	0	0	0	0	0	0	0	0	0	0	0

IIIA 7 Conclusions:

The acute lethal dermal dose of Agree (CGA-237218 WP) FL-911716 was found to be greater than 2020 mg/kg b.w. corresponding to 2.85×10^9 CFU *Bacillus thuringiensis aizawai* per kg b.w.

New data 2016

Data provided for first approval are considered acceptable to cover the current requirements. The available study on acute dermal toxicity were carried out with CGD 97220 I (Agree 50 WP), which was the representative formulation during the first evaluation of Bta GC-91. The current representative formulation is a WG formulation which is very similar to the old WP formulation. The content of Bta GC-91 is the same in both products and they differ by one inert only. The co-formulant present in Agree 50 WG has a more favourable toxicological profile so that the formulation is considered even more harmless than Agree 50 WP. It can thus be concluded that the data submitted previously for Agree 50 WP are fully applicable to support the evaluation of Agree 50 WG. For details of the formulation Agree 50 WP and WG, please refer to Volume 4.

Thus, Agree 50 WG does not warrant classification as being toxic or harmful on the basis of its acute dermal toxicity according to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. No hazard statement or signal word is required.

B.6.2 Additional acute toxicity studies

B.6.2.1 Skin irritation

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.2.1 / OECD Dossier Doc IIIM, Section 7, Point IIIM 7.1.4

The dermal irritating potential of Agree 50 WP was investigated in a study on dermal toxicity presented in point IIIM 7.1.2/01 [redacted] (1991b), Agree (CGA-237218 WP) FL-911716 Acute dermal toxicity/irritation study in rabbits with a microbial pest control agent (MPCA), Unpublished Report No. 8938-92. Very slight oedema was observed for two of ten animals and had resolved within 4 days. Well defined erythema was observed for two males up to 5 days and transient slight erythema (grade 1) were observed 1 h after removal of the patch and had resolved after 11 days. The preparation does not warrant classification as being irritating to the skin on the basis of this study.

New data 2016

Data provided for first approval are considered acceptable to cover the current requirements. Available studies on dermal toxicity/ irritation were carried out with CGD 97220 I (Agree 50 WP), which was the representative formulation during the first evaluation of Bta GC-91. The current representative formulation is a WG formulation which is very similar to the old WP formulation. The content of Bta GC-91 is the same in both products and they differ by one inert only. The co-formulant present in Agree 50 WG has a more favourable toxicological profile so that the formulation is considered even more harmless than Agree 50 WP. It can thus be concluded that the data submitted previously for Agree 50 WP are fully applicable to support the evaluation of Agree 50 WG. For details of the formulation Agree 50 WP and WG, please refer to Document J, Part B.

Thus, Agree 50 WG is not a skin irritant and does not warrant classification according to the Regulation (EC) No 1272/2008 on classification, labelling, and packaging of substances and mixtures. No hazard statement or signal word is required.

B.6.2.2 Eye irritation

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.2.2 / OECD Dossier Doc IIIM, Section 7, Point IIIM 7.1.5

In an acute eye irritation study 38.8 mg CGA-237218 WP FL-910959 (corresponding to 2.4×10^8 CFU *Bacillus thuringiensis aizawai*) were instilled into one eye of each of nine adult New Zealand white rabbits. The treated eyes of three animals were washed for 1 min with room temperature deionized water 30 sec after instillation. Local effects on the eye were scored and animals were observed for 10 days. The preparation CGA-237218 WP FL-910959 was found to be irritating to the rabbit eye.

On the basis of this study the preparation is classified as eye irritant.

Reference IIIM 7.1.5/01

Report [redacted] (1991c)
CGA-237218 WP FL-910959 Acute oral toxicity study in rabbits with a microbial pest control agent (MPCA),
Unpublished Report No. 8189-91

Guideline EPA FIFRA 152A-14

GLP Yes

Materials and Methods:

The study was conducted during the period 03.06. – 13.06.1991 by [redacted]

In an acute eye irritation study 38.8 mg CGA-237218 WP FL-910959 (corresponding to 2.4×10^8 CFU *Bacillus thuringiensis aizawai*) were instilled into one eye of each of nine adult New Zealand white rabbits. The treated eyes of three animals were washed for 1 min with room temperature deionized water 30 sec after instillation. Local effects on the eye were scored and animals were observed for 10 days.

Findings:

Table 7.1.5-1 Irritant response data for each animal at each observation time (non-washed)

Ocular effect	Animal No	Hours after dosing				Days after dosing		
		1	24	48	72	4	7	10
Redness	1	1	2	1	1	1	1	0
	2	1	2	2	1	1	1	0
	4	1	2	2	1	1	0	0
	5	1	2	2	2	2	1	0
	6	1	2	1	1	0	0	0
Chemosis	1	1	1	1	0	1	0	0
	2	1	2	1	1	1	0	0
	3	1	1	1	1	1	0	0
	4	1	2	1	1	1	0	0
	5	1	2	2	2	2	1	0
	6	1	1	1	0	0	0	0
Discharge	1	2	2	1	1	2	1	0
	2	2	2	2	2	1	0	0
	3	2	2	2	2	0	0	0
	4	2	2	1	1	1	0	0
	5	2	2	2	2	2	1	0
	6	1	2	1	1	0	0	0

Conclusions:

CGA-237218 WP FL-910959 was found to be irritating to the rabbit eye. Washing of the eyes reduced ocular reactions.

On the basis of this study the preparation is classified as eye irritant.

New data 2016

Data provided for first approval are considered acceptable to cover the current requirements. No new study is submitted.

Following the previously submitted eye irritation study in rabbits performed on CGA-237218 WP FL-910959, the test item was classified as eye irritant. This classification is unjustified, as

- no effects on iris or cornea were noted
- conjunctival redness at a mean score (24 - 72 h) of 2 was noted only in two of six animals
- conjunctival chemosis at a mean score (24 - 72 h) of 2 was noted only in one of six animals.

Based on this study a classification as eye irritant is not warranted. In order to allow evaluation of this eye irritation study a detailed summary of the findings is hereinafter provided.

Reference	KMP 7.1.5/01
Report	[redacted] (1991c) CGA-237218 WP FL-910959 Primary eye irritation study in rabbits with a microbial pest control agent (MPCA), Unpublished Report No. 8189-91
Guideline	EPA FIFRA 152A-14
GLP	Yes
Acceptability	Yes

Executive summary

In a primary eye irritation study according to EPA FIFRA 152A-14, 38.8 mg CGA-237218 WP FL-910959 (corresponding to 2.4×10^8 CFU *Bacillus thuringiensis* subsp. *aizawai*) were instilled into one eye of each of nine adult New Zealand white rabbits. The untreated left eye served as comparative control. Thirty seconds after exposure, the treated eyes of three animals were thoroughly washed out with room temperature deionized water for 1 min. Local effects on the eye of the three washed as well as the six non-washed rabbits were scored and observed for 10 days. After completion of the 24 h observations, all treated eyes were washed.

No corneal opacity or iritis were observed. No signs of irritation were noted for the conjunctivae. No corneal opacity or iritis were observed. Conjunctival redness at a mean score (24 - 72 h) of 2 was noted in two of six animals. Conjunctival chemosis at a mean score (24 - 72 h) of 2 was noted in one of six animals. Irritation was clear by day 10 or sooner in washed eyes.

In this study, Bta GC-91 is not an eye irritant and does not require classification.

Material and Methods

Test Item

Designation	CGA-237218 WP FL-910959 ARS-14699
Characteristics	Tan powder
Batch no.	GP-910411
Expiration date	22.04.1992
Purity	2.4×10^8 CFU *Bacillus thuringiensis* subsp. *aizawai*

Test System

Species	New Zealand white rabbits
Age	Young adults (aged 3 to 6 months)
Source	[redacted]
Number	9 animals: 3 males and 6 females

Acclimatisation period	At least one week

Test Conditions

Housing	Caged individually
Food	Purina rabbit chow; presented in measured amounts
Water	Filtered tap water , *ad libitum*

Study Design and Methods

In-life dates	03.06.1991 to 13.06.1991
Exposure	Instillation of the test item into one eye
Vehicle	Distilled water
Post exposure observation:	10 days
Experimental treatment	Both eyes of each animal were examined at least 24 hours prior the treatment with a 1.0% v/v fluorescein sodium ophthalmic solution and again just prior the treatment, but without fluorescein sodium ophthalmic solution. Only animals without eye defects or irritation were selected for testing. 38.8 mg CGA-237218 WP FL-910959 (corresponding to 2.4×10^8 CFU *Bacillus thuringiensis* subsp. *aizawai*) were instilled into one eye of each of nine adult New Zealand white rabbits. The untreated left eye served as comparative control. Thirty seconds after exposure, the treated eyes of three animals were thoroughly washed out with room temperature deionized water for 1 min. After 24 h, all treated eyes were washed.
Observations	Eyes were examined 1, 24, 48, and 72 hours and 4, 7, and 10 days post treatment. Corneas were examined immediately after 24-h observation with a 1.0% v/v fluorescein sodium ophthalmic solution

Findings

No adverse effects on iris or cornea were noted as no positive fluorescein staining did occur in any of the treated eyes. Conjunctival redness (grade 1 - 2) was noted in all animals and lasted from 1 h until 72 h (2 animals), 4 days (1 animal) or 7 days (6 animals). Conjunctival chemosis (grade 1 - 2) was observed for all animals at 1 hour post instillation and lasted until 24 h, 48 h or 72 h (one animal each), 4 days (5 animals) or 7 days (one animal). Conjunctival discharge (grade 1 - 2), was noted for all animals from 1 h and lasted until 48 h (one animal), 72 h (3 animals), 4 days (2 animals) or 7 days (3 animals). Conjunctival effects had reversed on day 10 or sooner after instillation in washed or non-washed eyes.

Generally, lower scores were noted for washed eyes. Individual scores of conjunctivae reactions are summarised in **Tables 7.2.2-1** and **7.2.2-2.**

Table 7.2.2-1 Scoring of ocular reactions (conjunctivae) in non-washed eyes

Ocular effect	Animal No (M: male F: female)	Hours after dosing				Mean score	Reversibility*)	Average time (day) for reversion
		1	24	48	72	24 h -72 h		
Redness	1398-M	1	2	1	1	1.3	c	10
	1442-M	1	2	2	1	1.7	c	10
	1444-M	2	2	2	2	2	c	10
	1163-F	1	2	2	1	1.7	c	7
	1165-F	1	2	2	2	2	c	10
	1443-F	1	2	1	1	1.3	c	7
Chemosis	1398-M	1	1	1	0	0.7	c	7
	1442-M	1	2	1	1	1.3	c	7
	1444-M	1	1	1	1	1	c	7
	1163-F	1	2	1	1	1.3	c	7
	1165-F	1	2	2	2	2	c	10
	1443-F	1	1	1	0	0.7	c	4
Discharge	1398-M	2	2	1	1	1.3	c	10
	1442-M	2	2	2	2	2	c	7
	1444-M	2	2	2	2	2	c	4
	1163-F	2	2	1	1	1.3	c	7
	1165-F	2	2	2	2	2	c	10
	1443-F	1	2	1	1	1.3	c	4

*) Reversibility: c. = completely reversible; n.c. = not completely reversible; n. = not reversible

Table 7.2.2-2 Scoring of ocular reactions (conjunctivae) in washed eyes

Ocular effect	Animal No (M: male F: female)	Hours after dosing				Mean score	Reversibility*)	Average time (day) for reversion
		1*	24	48	72	24 h -72 h		
Redness	1441-F	1	1	1	1	1		4
	1445-F	1	2	1	1	1.3	c	10
	1447-F	1	2	1	1	1.3	c	10
Chemosis	1441-F	1	1	0	0	0.3	c	4
	1445-F	1	1	1	1	1	c	7
	1447-F	1	1	1	1	1	c	4
Discharge	1441-F	1	1	1	0	0.7	c	4
	1445-F	1	2	2	1	1.7	c	4
	1447-F	2	2	2	1	1.7	c	10

*) Reversibility: c. = completely reversible; n.c. = not completely reversible; n. = not reversible
*traces of test substance were noted in the eye at 1 h after instillation and wash

Conclusions

CGA-237218 WP FL-910959 was found to be mildly and reversibly irritating to the rabbit eye. Washing of the eyes reduced ocular reactions. The preparation does not warrant classification as being irritating to the eyes on the basis of this study. It is concluded that also Agree 50 WG is not an eye irritant.

The available study on eye irritation were carried out with CGD 97220 I (Agree 50 WP), which was the representative formulation during the first evaluation of Bta GC-91. The current representative formulation is a WG formulation which is very similar to the old WP formulation. The content of Bta GC-91 is the same in both products and they differ by one inert only. The co-formulant present in Agree 50 WG has a more favourable toxicological profile so that the formulation is considered even more harmless than Agree 50 WP. It can thus be concluded that the data submitted previously for Agree 50 WP are fully applicable to support the evaluation of Agree 50 WG. For details of the formulation Agree 50 WP and WG, please refer to Document J, Part B.

Thus, the preparation Agree 50 WG is not an eye irritant and does not warrant classification according to the Regulation (EC) No 1272/2008 on classification, labelling, and packaging of substances and mixtures. No hazard statement or signal word is required.

B.6.2.3 Skin sensitisation

Information from DAR and DAR addendum (May 2007, February 2013) Volume 3 Point B.6.4.2.3 / OECD Dossier Doc M-IIIM, Section 7, Point IIIM 7.1.6

In a sensitisation study using a protocol according to Magnusson and Kligman with modifications, 10 guinea pigs (Hartley) received double injections of 0.1 mL Agree 50 WP, 0.1 mL of Agree 50 WP and FCA (1:1) and 0.1 mL of FCA in distilled water (1:1). Six days after this induction, 0.5 mL sodium lauryl sulphate (10%) was applied topically followed by topical application of 0.5 mL of Agree 50 WP for 48 h. Challenge was two weeks later with 0.5 mL of Agree 50 WP by topical application for 24 h using an occlusive patch. Skin reaction were scored 1 – 3 d after removal of the patch. In all treated animals a serious erythema with eschar was observed. In control animals slight erythema was observed.

On the basis of the result of this study Agree 50 WP, has been considered sensitizing.

Reference	IIIA 8 IIIM 7.1.6/01
Report	[redacted](1999) Skin sensitization test, Unpublished Report No. 99/1054-1A
Guideline	According to OECD 406 IIIA 9
GLP	IIIA 10 No

Materials and Methods:

The study was conducted during the period March 29.03- 23.04.1999 by [redacted]

In a sensitisation study using a protocol according to Magnusson and Kligman with modifications, 10 guinea pigs (Hartley) received double injections of 0.1 mL Agree 50 WP, 0.1 mL of Agree 50 WP and FCA (1:1) and 0.1 mL of FCA in distilled water (1:1). Six days after this induction, 0.5 mL sodium lauryl sulphate (10%) was applied topically followed by topical application of 0.5 mL of Agree 50 WP for 48 h.

Challenge was two weeks later with 0.5 mL of Agree 50 WP by topical application for 24 h using an occlusive patch. Skin reaction were scored 1 – 3 d after removal of the patch.

Findings:

In all treated animals a serious erythema with eschar was observed. In control animals slight erythema was observed.

IIIA 11 Conclusions:

On the basis of the result of this study Agree 50 WP, can be considered sensitizing.

New data 2016

A study on skin sensitisation was submitted for first approval leading to classification of Agree WP, however, this study showed deficiencies in study design and dose selection. Briefly, the study conducted according to Magnuson & Kligman method showed no pre-study for dose selection [redacted] 1999, IIIM 7.1.6/01). The undiluted product was used for both, induction and challenge phase, although it is required to use the highest concentration of the test substance to cause mild irritation for induction exposure, and the highest non-irritating dose for challenge exposure. During evaluation, serious erythema with escare and slight erythema were observed in all treated and control animals, respectively. Moreover, all treated and control animals showed serious symptomatology of nervous signs. Thus, it is concluded, that the observed dermal reactions elicited by challenge application are rather a result of skin irritation following repeated exposure to Agree 50 WP than a result of skin sensitization.

Based on this study a classification of Agree 50 WP as dermal sensitizer is not warranted. In order to allow evaluation of this skin sensitisation studies, a detailed summary is provided and the study report is submitted as KMP 7.2.3/01.

According to Regulation (EC) 283/2013 (footnote 1 to point 5.2.1 in Part B), the available methods for testing dermal sensitisation are not suitable for testing microorganisms as microorganisms do not penetrate the skin. Therefore, no new studies are submitted.

Thus, Agree 50 WG **does not warrant classification with regard to skin sensitisation** according to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. The notifier recommend to **not using the warning phrase "Contains *B. thuringiensis* subsp. *aizawai*. Micro-organisms may have the potential to provoke sensitising reactions"** for the following reasons:

- For microorganisms currently approved in the EU, positive reports on sensitisation are absent for bacterial species
- As there are no appropriate test methods, it is impossible to demonstrate absence of sensitisation potential and evaluators therefore strongly rely on published literature, where very little reports on sensitisation caused by species used for plant protection are found. Reports on sensitisation caused by microbials are mostly restricted to moulds, often in combination with moisture in buildings. On the other hand, non-pathogenic bacteria are considered to be able to protect human from sensitisation. This is also confirmed by the EFSA External report "Literature search and data collection on RA for human health for MO used as PPP" (Hackl et al. 2015)[1].
- If exposure to microorganisms is during use of plant protection products is compared to "natural" exposure in home or outdoor environments, plant protection products will hardly and only in rare cases exceed natural exposure.
- In other regulatory areas, microorganisms are not considered as potentially sensitising by default although exposure may considerably exceed the one in plant protection. Again sensitisation is restricted to fungi, whereas bacteria and yeasts are considered to be beneficial with respect to human health (Martel et al., 2010).[2]

In the literature search covering the last 10 years and focussing on toxicity, pathogenicity, or sensitisation of Btk on mammals, one article was identified showing increased IgE levels to Btk, which were, however, only qualitatively measured and therefore not correlated to exposure. Moreover, the prevalence rate ratios among exposed increased only marginally over a relatively long observation period of 3-years (Baelum et al, 2012). For more information, please refer to B.6.1.1.2 MA.

Reply RMS

In the EU the default assumption of potential sensitisation for all micro-organisms is currently under discussion. There are indications that certain groups of micro-organisms (eg bacteria) are not sensitising, however, as the discussion in ongoing and no consensus is reached yet, the RMS proposes to use the warning phrase **"Contains *B. thuringiensis* subsp. *aizawai*. Micro-organisms may have the potential to provoke sensitising reactions".**

However, based on the available information, the default assignment of PPE such as gloves and respiratory equipment should be carefully considered. As the product is a nearly dust-free granule (see Volume 3 B.2; Dust content before storage "nearly dust-free (2.99 mg) and after storage: nearly dust-free (3.71 mg) , the respiratory exposure is negligible during mixing and loading, and respiratory equipment is therefore not considered necessary. For skin sensitisation, penetration through the skin is a prerequisite, as systemic exposure is needed to trigger the immune system. Micro-organisms are considered too large to penetrate the skin. Therefore, the assignment of gloves also seems to be redundant. Moreover, it should be kept in mind that there is no proof that Bta GC-91 is a sensitiser, it is only a default assumption that micro-organisms could be potential sensitisers. The RMS is therefore of the opinion that for Bta GC-91 no PPE should be assigned on the basis of the hazard characteristics. However, in the end the final conclusion on the need for PPE is up to Member States at the time of product authorization/renewal.

[1] Evelyn Hackl, Margit Pacher-Zavisin, Laura Sedman, Stefan Arthaber, Ulla Bernkopf, Günter Brader, Markus Gorfer, Birgit Mitter, Aspasia Mitropoulou, Monika Schmoll, Willem van Hoesel, Elisabeth Wischnitzky, and Angela Sessitsch, 2015. Literature search and data collection on RA for human health for microorganisms used as plant protection products Reference. EFSA supporting publication 2015:EN-801. 173 pp.

[2] Martel, Cyril; Nielsen, Gunnar D.; Mari, Adriano; Licht, Tine Rask; Poulsen, Lars Kærgaard. 2010. Bibliographic review on the potential of microorganisms, microbial products and enzymes to induce respiratory sensitization. EFSA supporting publication 2010 Volume 7, Issue 9, 95pp

Report:	KMP 7.2.3/01
Title:	[redacted] (1999) Skin sensitization test Unpublished Report No. 99/1054-1A
Guidelines:	According to OECD 406 (Magnuson & Kligman method)
GLP	Yes
Acceptability:	The study is considered not acceptable.
Deviations:	No pre-study was performed to assess highest concentration of the test substance to cause mild irritation for induction exposure, and the highest non-irritating dose for challenge exposure. No observations were reported after induction exposure. Animals showed signs of systemic toxicity after challenge exposure.
Duplication: (if vertebrate study)	No

Executive summary

In a dermal sensitisation study with Agree 50 WP (undiluted), albino guinea pigs were tested using the method of Magnuson and Kligman. Serious erythema with escare and slight erythema were observed in all treated and control animals, respectively. Moreover, all treated and control animals showed serious symptomatology of nervous signs. Thus, the observed symptoms are rather a result of skin irritation following repeated applications than a result of skin sensitization. The presented study is therefore not considered acceptable to assess sensitising properties of Agree 50 WP.

Material and Methods

Test Item

Designation	Agree 50 WP
Characteristics	Reduced in paste
Batch no.	0222298G
Purity	667 mg/mL

Test System

Species	Albino guinea pigs (Hartley), females
Body weight	350 - 450 g
Source	[redacted]
Number	15 animals: 10 treatment and 5 control group
Acclimatisation period	At least 5 days

Test Conditions

Housing	Caged in groups of ten
Food	Standard complete diet (RIEPER), filtered tap water , both *ad libitum*
Temperature	22 ± 2°C
Photoperiod	12 hours light, 12 hours dark cycle
Humidity	55 ± 15%

Study Design and Methods

In-life dates	29.03. 1999 to 23.04.1999
Exposure	Intradermal injection, topical treatment
Vehicle	Distilled water
Post exposure observation:	25 days
Experimental treatment	24 hours before testing, fur was removed by shaving a 50 cm² area on the back of the animals. *Induction phase - Day 0* Three pairs of 0.1 mL intradermal injections in subscapular region of each animal of: 1.) Test material (undiluted) or vehicle, 2.) Test material or vehicle and FCA (ration 1:1), 3.) FCA in distilled water (ratio 1:1). *Day 6* Topical application of 0.5 mL Sodium Lauril Solfatum (10%) *Induction exposure by topical application - Day 7* An occlusive patch exposure was performed with 0.5 mL of test material or vehicle for a 48-hour period. *Challenge - Day 21* An occlusive patch with 0.5 mL of test material was applied to the left flank of all 15 animals, distilled water on the right side.
Observations	On day 23rd, 24th, and 25th (24 h, 48 h, and 72 h post patch removal) animals were evaluated for skin reaction.

Findings

Serious erythema with escare were observed in all treated animals, whilst in control animals, a slight erythema was observed (**Table 7.2.3-1**). Beside this, all treated and control animals, showed serious symptomatology of nervous type 24 hours post exposure, which regressed 72 hours after appearance of the first symptoms.

Table 7.2.3-1 Skin examinations 24 and 48 hours after 1st and 2nd challenge treatment

Group	n	48 h	72 h
Control	10	1/1/1/1/1	1/1/1/1/1
Test substance	5	3/3/3/3/3/3/3/3/3/3	3/3/3/3/3/3/3/3/3/3

1) Slight erythema
2) Erythema and moderate oedema
3) Erythema and severe oedema

Conclusion

As the undiluted product was applied and no pre-study was conducted to assess a suitable concentration for induction and challenge exposure, the observed symptoms of serious erythema in the treatment groups and the slight erythema in the control animals elicited by challenge application are rather a result of skin irritation than skin sensitization. This is further supported by the nervous symptomatology reported in control and treated animals.

Thus, Agree 50 WP does not warrant classification with regard to skin sensitisation.

B.6.3 Data on exposure

In the absence of any toxicity, pathogenicity or infectivity in the toxicity studies with *Bacillus thuringiensis subsp. aizawa*i GC-91, insecticidal proteins or other metabolites involved in the mode of action no reference values are required and therefore no exposure calculations is needed. Beta-exotoxins, are considered to have

toxic properties but were shown not to be produced by commercial Btk strains. Furthermore, Bta GC-91 is not able to produce cereulide, the highly cytotoxic type of CytK (type 1) and cause foodborne disease by B. cereus-enterotoxins. Therefore, also for these metabolites no reference values are derived and no exposure calculations are necessary.

In conclusion, exposure of operators, workers, bystanders and residents to Agree 50 WG, if even occurring, can be considered safe even with the overly conservative approach.

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

Agree 50 WG does not contain ingredients in concentrations of toxicologically critical concern. The properties of the non-active ingredients and their toxicological data are given in Safety Data Sheets - please refer to the confidential data in Document J. Possible acute toxic and irritating properties are covered by the studies with the products.

B.6.5 Supplementary studies for combinations of plant protection products

Agree 50 WG is not intended for combinations with other adjuvants or pest control products. Furthermore, due to the nature of this biological insecticide, no influence on the toxicological profile of *Bacillus thuringiensis* is to be anticipated from interactions with chemical or other biological plant protection products.

B.6.6 Summary and evaluation of health effects

Information from DAR (2012) Volume 3 Point B.6.5 / OECD Dossier Doc IIIM, Section 7, Point IIIM 7.6

Table 7.6-1: Summary of acute toxicity studies on Agree 50 WP/ CGA-237218 WP

Study type	Test item	Dose level	Findings	Report
Acute oral toxicity rat	CGA-237218 WP FL-910959	4000, 5050 or 5500 mg /kg bw 2.6 – 3.5 × 10^{10} CFU Bta	Mortalities (2/10) at 5050 mg /kg bw Transient clinical signs No adverse effect at 4000 or 5500 mg/kg bw LD_{50} > 5050 mg/kg bw	IIIM 7.1.1/01 [redacted] (1991a)
Acute oral toxicity rat	Agree FL-920303 (CGA-237218 WP)	5050 mg /kg bw 1.2 × 10^{11} CFU Bta	Mortality (1/10) Transient clinical signs LD_{50} > 5050 mg/kg bw	IIIM 7.1.1/02 [redacted] (1992)
Acute dermal toxicity rabbit	Agree (CGA-237218 WP) FL-911716	2020 mg/kg b.w 2.85 × 10^{9} CFU Bta	No adverse effect LD_{50} > 2020 mg/kg bw	IIIM 7.1.2/01 [redacted] (1991b)
Acute inhalation rat	CGA-237218 WP FL-910986	5.78 mg/L corresponding to 4.2 × 10^{7} CFU Bta	Transient clinical signs LC_{50} > 5.78 mg/L 4.2 × 10^{7} CFU	IIIM 7.1.3/01 [redacted] (1991)
Acute inhalation rat	Agree FL-921616	0.651 mg/L corresponding to 3.4 × 10^{8} CFU Bta	Transient clinical signs LC_{50} > 0.651 mg/L 3.4 × 10^{8} CFU	IIIM 7.1.3/02 [redacted] (1993)
Dermal irritation rabbit	Agree (CGA-237218 WP) FL-911716	2020 mg/kg b.w 2.85 × 10^{9} CFU Bta	Non-irritating	IIIM 7.1.2/01 [redacted] (1991b)
Eye irritation/ infectivity rabbit	CGA-237218 WP FL-910959	38.8 mg 2.4 × 10^{8} CFU Bta	Non-irritating	IIIM 7.1.5/01 [redacted] (1991c)
Skin sensitisation Magnusson/ Kligman guinea pig	IIIA 12 Agree 50 WP	0.1 mL / animal	Sensitizing	IIIM 7.1.6/01 [redacted] (1999)

New data 2016

All submitted toxicological studies and supplemental information on *Bacillus thuringiensis* subsp. *aizawai* including Agree 50 WG and Agree 50 WP prove that these are low-toxic and non-infectious to mammals. No reference values are derived for Bta GC-91 and metabolites. As a consequence no exposure calculations are necessary. As a consequence there is no health risk for operators, bystanders or workers.

B.6.7 References relied on

Data point CADDY (ongoing numbering)	Author(s)	Year	Title Owner, Report No. Source (where different from owner) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previously submitted Y/N* If Y => old data point
KMP 7.1.1/01	[redacted]	1991a	CGA-237218 WP FL-910959 ACUTE ORAL TOXICITY STUDY IN RATS WITH A MICROBIAL PEST CONTROL AGENT (MPCA) Certis USA LLC, 8188-91 [redacted] GLP: yes Published: no	no	yes	protected	CEU	Y KIIIM 7.1.1
KMP 7.1.1/02	[redacted]	1992	AGREE FL-920303 (CGA-237218 WP): ACUTE ORAL TOXICITY STUDY IN RATS WITH A MICROBIAL PEST CONTROL AGENT (MPCA), Certis USA LLC, 8938-92 [redacted] GLP: yes Published: no	yes	yes	protected	CEU	Y KIIIM 7.1.1
KMP 7.1.2/01	[redacted]	1991	CGA-237218 WP FL-910986: ACUTE INHALATION TOXICITY STUDY IN RATS WITH A MICROBIAL PEST CONTROL AGENT (MPCA) Certis USA LLC, 8200-91 [redacted] GLP: yes Published: no	yes	yes	protected	CEU	Y KIIIM 7.1.3

Data point CADDY (ongoing numbering)	Author(s)	Year	Title Owner, Report No. Source (where different from owner) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previously submitted Y/N* If Y => old data point
KMP 7.1.2/02	[redacted]	1993	AGREE FL-921616 ACUTE INHALATION TOXICITY STUDY IN RATS WITH A MICROBIAL PEST CONTROL AGENT Certis USA LLC, 9398-92 [redacted] GLP: yes Published: no	yes	yes	protected	CEU	Y KIIIM 7.1.3
KMP 7.1.3/01	[redacted]	1991b	AGREE (CGA-237218 WP) FL-911716: ACUTE DERMAL TOXICITY/IRRITATION STUDY IN RABBITS WITH A MICROBIAL PEST AGENT (MPCA) Certis USA LLC, 8373-91 [redacted] GLP: yes Published: no	yes	yes	protected	CEU	Y KIIIM 7.1.2
KMP 7.2.1/01	[redacted]	1991b	AGREE (CGA-237218 WP) FL-911716: ACUTE DERMAL TOXICITY/IRRITATION STUDY IN RABBITS WITH A MICROBIAL PEST AGENT (MPCA) Certis USA LLC, 8373-91 [redacted] GLP: yes Published: no **Submitted in: KMP 7.1.3/01**	yes	yes	protected	CEU	Y KIIIM 7.1.4
KMP 7.2.2/01	[redacted]	1991c	CGA-237218 WP FL-910959: PRIMARY EYE IRRITATION STUDY IN RABBITS WITH A MICROBIAL PEST CONTROL AGENT (MPCA) Certis USA LLC, 8189-91 [redacted] GLP: yes Published: no	yes	yes	protected	CEU	Y KIIIM 7.1.5

Data point CAD-DY (ongoing numbering)	**Author(s)**	**Year**	**Title** **Owner, Report No.** **Source (where different from owner)** **GLP or GEP status** **Published or not**	**Vertebrate study Y/N**	**Data protection claimed Y/N**	**Justification if data protection is claimed**	**Owner**	**Previously submitted Y/N*** **If Y => old data point**
KMP 7.2.3/01	[redacted]	1999	SKIN SENSITIZATION TEST Certis USA LLC, 99/1054-1A [redacted] GLP/GEP: no Published: no	yes	yes	protected	CEU	Y KIIIM 7.1.6