UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA United States Environmental Protection Agency **Office of Pesticide Programs**

Antimicrobials Division (AD)

Wednesday, October 03, 2012

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 9402-RU
DP Barcode: D403005
Product Name: **HITMAN SPRAY**

From: Ian Blackwell, Biologist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

To: Marshall Swindell, PM 33/ *Demson Fuller*
Regulatory Management Branch
Antimicrobials Division (7510P)

Applicant: Kimberly-Clark Global Sales, LLC

FORMULATION FROM LABEL:

PC Code	Active Ingredient(s):	% by wt.
000595	Hydrogen peroxide	3.30
069208	Didecyldimethyl ammonium carbonate and Didecyldimethyl ammonium bicarbonate	1.38
	Other Ingredient(s):	95.32
	Total:	100.00

I BACKGROUND: Kimberly-Clark has submitted their own review of a set of seven acute toxicity studies they submitted to the EPA earlier this year. The Chemistry and Toxicology Team (CTT) actually reviewed these same studies earlier this year, in a 4/27/2012 review. The goal of this CTT review is not to assess acute toxicity categories and/or to assign precautionary labeling. This submission was sent to CTT for a peer review.

This year, some registrants have submitted acute toxicity reviews that they have written themselves. It is the understanding of CTT that some registrants are now reviewing the acute toxicity studies that they submit in support of their products. It might be their hope that if they can submit their own reviews and have them accepted, it will expedite the registration of their products.

In assessing their review, it is obvious that the writer patterned his or her work after CTT acute toxicity reviews. They appeared to use the same DER templates used by CTT. Much of the wording is very similar to that of CTT reviews.

The submitted review has a section discussing the expected toxicity of the product based upon the components of the formulation. One such statement says: "In addition, the inert ingredients in the Hitman Spray formulation are generally low in toxicity and low in concentration and so were not expected to cause significant toxicity from an acute inhalation exposure."

II RECOMMENDATIONS:

1. The toxicity categories listed in the registrants' acute toxicity profile are the same as those of CTT's acute toxicity profile. Thus, the registrants' reviewer came to the same overall conclusions as CTT.

2. CTT does not agree with the statements concerning the *overall toxicity* of Hitman Spray relative to its inert/ non-active ingredients. While the non-active ingredients might not be highly toxic when considered singly, there are other concerns. CTT (and AD) does not accept acute toxicity citations where the rationale is to obtain the toxicity profile of a product based upon the toxicity of the various chemical ingredients in that pesticide mixture. This is particularly true of blends like File Symbol 9402-RU. When dealing with complicated pesticide blends such as 9402-RU, CTT is concerned with additive or synergistic effects, as well as potentiation.

Attached is the Kimberly-Clark acute toxicity review:

Date:

SUBJECT: Acute Toxicity Review for EPA Reg. No. 9402 - xx
Product Name: Hitman Spray

FROM:

TO: Marshall Swindell, PM-33

APPLICANT: Kimberly-Clark Global Sales, LLC.

FORMULATION FROM THE LABEL:

Active Ingredient(s):	% by wt
Hydrogen Peroxide	3.30
Didecyl dimethyl ammonium carbonate (and) Didecyl dimethyl ammonium bicarbonate	1.68
Other Ingredient(s):	95.02
Total:	100.00

BACKGROUND:

Kimberly-Clark Global Sales, LLC (Kimberly-Clark) is seeking to register Hitman Spray, EPA Reg. No. 9402-xx. Hitman Spray is a one-step disinfectant spray, non-food contact sanitizer, residual self-sanitizer, mildewstat for hard, non-porous surfaces for household environments and sanitizes lightly to moderately soiled soft surfaces.
Kimberly-Clark has submitted a set of seven acute toxicity studies to support the acute toxicity data requirements of their pending registration, "Hitman Spray". This set includes two acute inhalation studies. In addition to the seven studies the following is included:

1. MRID Number xxxxxx-xx: "Acute Toxicity Discussion", Scientific & Regulatory Consultants, Inc. This document has no study date or report number.
2. MRID Number xxxxxx-xx: "Scientific Rationales to Support Acute Inhalation Toxicity", Technology Sciences Group. This document has no study date or report number.

The test substance is identified in the reports as "Hitman disinfectant". The acute toxicity discussion, and letter from the applicant to EPA (dated February 16, 2012), states that Hitman disinfectant is identical to Hitman Spray which is the product for which registration is sought.

FINDINGS/RECOMMENDATIONS:

1. The acute oral toxicity study is acceptable.
2. The acute dermal toxicity study is acceptable.
3. The acute inhalation toxicity study conducted by IITRI, MRID xxxxxx-xx,is acceptable.
4. The acute inhalation toxicity study conducted by MB Laboratories, MRID xxxxxx-xx, is not acceptable

5. The acute eye irritation study is acceptable.
6. The acute dermal irritation study is acceptable.
7. The dermal sensitization study is acceptable.

Kimberly-Clark has presented two limit studies for acute inhalation. The first limit study was a whole-body acute inhalation study conducted by MB Research Laboratories, MRID xxxxxx-xx, and the second a nose-only exposure acute inhalation study, MRID xxxxxx-xx, conducted by IIT Research Institute. Using the limit test paradigm per OPPTS 870.1300, the initial study conducted using a whole body exposure indicated an LC_{50} of less than 2.2 mg/L; however, several observations were unexpected due to the low toxicity of the test article by other routes of exposure, the low toxicity of other similar products, and the low toxicity of the individual components of the formulation at the concentrations tested. These observations led us to look more closely at the results and ultimately conduct a second inhalation toxicity study using a nose-only exposure. In summary the observations noted in the first, whole body inhalation study, included, but were not limited to:

- In-life observation of "fur coated with test article" for all exposed animals for one or more days after exposure, suggesting significant oral exposure from grooming was likely,
- Multiple fatalities associated with weight loss and apparent decreased food consumption,
- Abnormal post-mortem observations including:
    - Lack of toxicity in the respiratory tracts, tissues, or organs
    - Toxic effects centered on the gastrointestinal (GI) tract, particularly stomach and intestines

Therefore, a second inhalation study using nose-only exposure was executed to determine if the effects in the whole body inhalation study may have been due at least partially to the ingestion of test article. Since the initial test lab (MB Research Laboratories) did not have the capability of performing a nose-only study, a second lab (IIT Research Institute) was sourced for this study. The nose-only inhalation study resulted in an LC_{50} of greater than 2.03 mg/L, and none of the abnormal observations noted above in the first study were observed.

Kimberly-Clark provided a summary of the acute inhalation profile of each component of Hitman Spray. Based on information available in the literature, the inhalation toxicity of dilute solutions of the active ingredients, hydrogen peroxide and didecyl dimethyl ammonium carbonate (and) didecyl dimethyl ammonium bicarbonate, was expected to be minimal at the concentration just above the limit dose at 2.2 mg/L, and any effects identified were likely to occur in the respiratory system and not the GI tract. In addition, the inert ingredients in the Hitman Spray formulation are generally low in toxicity and low in concentration and so were not expected to cause significant toxicity from an acute inhalation exposure. These two assessments did not match the results of the whole body exposure study. It was considered that the unexpected effects on the GI tract may have been the result of excessive oral exposure due to test article ingestion from grooming.

A second acute inhalation study using nose-only exposure was conducted on the Hitman Spray formulation based on the following considerations: 1) the higher toxicity than expected in the whole body inhalation exposure study, 2) the occurrence of toxic effects in the GI tract rather than the respiratory tract in the whole body inhalation exposure study, 3) the formulation is designed to stick to surfaces (that may include fur), 4) the study technician observed and recorded that all the test animals had fur coated with test article for at least a full day after exposure, and 5) the knowledge that rats ingest test article from fur when grooming.

The nose-only inhalation study resulted in an LC_{50} of greater than 2.03 mg/L, and was free of the abnormal effects noted in the rats exposed in the whole body chambers. This nose-only inhalation study is a well-conducted, well-documented study that is not confounded by the potential for an uncertain amount of oral exposure from grooming test article off of fur. The nose-only inhalation study supports a determination that Hitman Spray is Toxicity Category IV for the inhalation route of exposure.

The acute toxicity profile for File symbol 9402-xx is currently

Study	MRID Number	Toxicity Category	Status
Acute Oral Toxicity		IV	Acceptable
Acute Dermal Toxicity		IV	Acceptable
Acute Inhalation Toxicity		IV	Acceptable
Acute Inhalation Toxicity		?	Not Acceptable
Primary Eye Irritation		II	Acceptable
Primary Skin Irritation		IV	Acceptable
Dermal Sensitization		Non sensitizer	Acceptable

LABELING:

1. DATE: 02/16/2012
2. EPA Reg. No. 9402-xx
3. The signal word is "Warning". This is based on the product being placed in Category II for the acute eye irritation study.

REQUIRED PRECAUTIONARY LABELING:

KEEP OUT OF REACH OF CHILDREN
WARNING
WARNING: Causes substantial but temporary eye injury. Do not get in eyes or on clothing. Wear (specify appropriate protective eyewear such as goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.

REQUIRED FIRST AID STATEMENTS:

FIRST AID:

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call a poison control center or doctor for treatment advice.

Call a poison control center or doctor for further treatment advice. Have the product container or label with you when calling a poison control center or doctor or going for treatment.

Include information where to call for emergency information

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (OPPTS 870.1100)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: MB 11-20288.01

Testing Laboratory: MB Research Laboratories
Author: Blair Yasso, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception: Prior to study initiation, the Sponsor did not provide test article characterization information. However, following study termination, purity and stability were provided. See Appendix A. The effect of the lack of full test article characterization information cannot be fully assessed. The test article characterization (noted in Appendix A) was not conducted according to the Good Laboratory Practices. This is not expected to have an impact on the outcome of the study.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Dosage: Limit Test: 5,000 mg/kg (administered as received)

Species: 3 Rats; Sprague-Dawley
Sex: Females. Females were nulliparous and non-pregnant.
Age: Young adult (7-10 weeks old)
Weight: 198-214 grams at experimental start
Source: SAGE Labs, Boyertown, PA
Housing: Temperature Range: 13.11 – 25.22° C
Humidity Range: 7.4 – 75.7%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: at least 5 days

Conclusion:
1. **Acute Oral LD_{50} (mg/kg)**: Female Rats: >5,000 mg/kg
2. **Toxicity Category**: IV **Classification**: Acceptable

Procedure (Deviations from 870.1100):

- The guidelines state the animals are to be 8 weeks old at the commencement of dosing. The animals born on July 19, 2011 were 1 day shy of 8 weeks when first

introduced to the test substance. The excursion is minor and has no impact on the study.

- The laboratory reported the following Standard Operating Procedures deviation "The temperature of the animal room was 13.11 to 25.22° C and the relative humidity was 7.4 to 75.7%. Although the temperature and humidity were outside of the Standard Operating Procedures range, this minor deviation was not considered to have had any adverse effect on the results of this study."
- The guidelines state that body weight changes should be calculated and recorded. Individual body weights of test animals were recorded; however, body weight changes were not reported.
- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

Results:

Limit Test

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	1	5,000	S	S
2	2	5,000	S	S
3	3	5,000	S	S

S – Survival

Reported Mortality

Dose Level (mg/kg)	Number Dead / Number Tested		
	Males	Females	Total
5,000	Not tested	0 / 3	N/A

Observations:

All animals survived test substance administration, gained body weight, and appeared active and healthy during the study. Soiling of the anogenital area was briefly observed in one animal on Day 1 and no other abnormal physical signs were observed.

Gross Necropsy Findings:

No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

EPA REG No. 9402 – xx
DP Barcode:

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (OPPTS 870.1200)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: MB 11-20288.02

Testing Laboratory: MB Research Laboratories
Author: Laura J. DiDonato, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception: Prior to study initiation, the Sponsor did not provide test article characterization information. However, following study termination, purity and stability were provided. See Appendix A. The effect of the lack of full test article characterization information cannot be fully assessed. The test article characterization (noted in Appendix A) was not conducted according to the Good Laboratory Practices. This is not expected to have an impact on the outcome of the study.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Dosage: Limit Test: 5,000 mg/kg (administered as received)

Species: 10 Rabbits; New Zealand White
Sex: 5 male, 5 females. Females were nulliparous and non-pregnant.
Age: Young adult (24 -25 weeks old)
Weight: Males: 2.7 -3.1 kg, Females: 2.8 – 3.0 kg; at experimental start
Source: Covance Research Products, Inc., Denver, PA
Housing: Temperature Range: 17.61 – 21.50° C
Humidity Range: 64.2 – 99%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: at least 5 days

Conclusion:
1. **Acute Dermal LD_{50} (mg/kg)**: Female Rats: >5,000 mg/kg
2. **Toxicity Category**: IV **Classification**: Acceptable

Procedure (Deviations from 870.1200):

- No temperature or humidity is provided for the study.

- The guidelines state that body weight changes should be calculated and recorded. Individual body weights of test animals were recorded; however, body weight changes were not reported.
- The laboratory reported the following Standard Operating Procedures deviation "The temperature of the animal room was 17.61 to 21.50° C and the relative humidity was 64.2 to 99%. Although the humidity was outside of the Standard Operating Procedures range, this minor deviation was not considered to have had any adverse effect on the results of this study."
- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

RESULTS and DISCUSSION:

Dose (mg/kg)	Mortality/Number Tested		
	Males	Females	Combined
5,000	0/5	0/5	0/10

Observations:
Other than loss of body weight between Day 7 and 14 noted for two males (1 kg each) and one female (1 kg), all animals survived exposure to the test substance and gained body weight during the study. At 24 hours, erythema was well defined and edema was absent. On Day 14, erythema was absent to very slight with flaking skin and some shiny areas observed. All animals appeared normal during the observation period, with the exception of one incidence of few feces in one female.

Gross Necropsy Findings:
The gross necropsy on animals revealed no observable abnormalities.

EPA REG No. 9402 – xx
DP Barcode:

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (OPPTS 870.1300) (Whole Body Exposure)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: MB 11-20288.05

Testing Laboratory: MB Research Laboratories
Author: Blair Yasso, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception: Prior to study initiation, the Sponsor did not provide test article characterization information. However, following study termination, purity and stability were provided. See Appendix A. The effect of the lack of full test article characterization information cannot be fully assessed. The test article characterization (noted in Appendix A) was not conducted according to the Good Laboratory Practices. This is not expected to have an impact on the outcome of the study.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Dosage: Limit Test: 2.20 mg/L
Species: 10 Rats; Sprague Dawley
Sex: 5 male, 5 females. Females were nulliparous and non-pregnant.
Age: Young adult (9-10 weeks old)
Weight: Males: 292 – 370 grams, Females: 215 – 251 grams; at experimental start
Source: SAGE Labs, Boyertown, PA
Housing: Temperature Range: 19.44 – 21.67° C
Humidity Range: 14.6 – 56.4%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: at least 5 days

Concentration:

Group	Gravimetric Exposure Concentration (mg/L)	Nominal Concentration (mg/L)
I	2.20	40.48

Conclusion:
1. **Acute LC_{50} (mg/L)**: <2.20 mg/kg in male and female rats

2. **The estimate 4-hr acute inhalation LC_{50} of Hitman disinfectant is less than 2.20 mg/L in male and female rats.**
3. **Average MMAD**: 1.92 µm
4. **Toxicity Category**: unknown **Classification**: Not Acceptable

Procedure (Deviations from 870.1200):

- The laboratory reports states "The temperature of the animal room, based on the available data logger readings and daily room records (03 Nov to 10 Nov 2011) was 19.44 – 21.76° C and the relative humidity was 14.6 – 56.4%. Although the humidity was outside of the Standard Operating Procedures range, this minor deviation was not considered to have had any adverse effect on the results of this study."
- The laboratory reported the following Protocol Deviation "The data logger that records the temperature and humidity malfunctioned part of the day on the 03 Nov and 08 Nov 2011. On 04 Nov to 07 Nov 2011 the data logger did not record at all. Based on the individual room records noted on a daily basis, there is no expected impact."
- The guidelines state for the MMAD, fifty percent of the particles by weight will be smaller than the median diameter and 50 percent of the particles will be larger. Table 7 showing the three particle size runs, indicate the 50th percentile is between 2.1 – 3.3 µm. This is not consistent with the reported MMAD of 1.92 µm.
- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

Results:

Reported Mortality

Exposure Concentration (mg/L)	Number Dead / Number Tested		
	Males	Females	Combined
2.20	4*/ 5	3* / 5	7* / 10

*The remaining females and male were sacrificed on Day 7 due to moribund conditions

Chamber Atmosphere

Exp. Conc. (mg/L)	Sample	MMAD (µm)	GSD (µm)	Cumulative % of Particles < Effective Cutoff Diameter (µm)[1]								
				0.0	0.4	0.7	1.1	2.1	3.3	4.7	5.8	9.0

2.20	1	1.70	4.47	12.18	22.76	28.85	33.98	40.71	51.29	67.0	100.01	100.01
	2	2.14	2.84	9.71	16.03	22.80	30.02	38.37	51.69	69.07	100.00	100.00
	3	2.0	3.32	9.09	16.20	21.54	28.85	37.55	50.79	68.97	100.00	100.00

[1]Percent of particles smaller than corresponding effective cutoff diameter

Chamber Environment during Exposure

Exposure Level (mg/L)	**2.20**
Chamber Volume (L)	100L
Average Total Airflow Volume (Lpm)[1]	20
Air Changes Per Hour	At least 10
Mean Oxygen Content (%)	not reported
Temperature Range (°C)	19-21
Relative Humidity Range (%)	0.3

[1]Total air = filtered compressed air + compressed mixing air

Clinical Observations:
Seven out of ten rats died following the 2.20 mg/L four-hour inhalation exposure. Three animals were sacrificed on Day 7, due to moribund condition.

Abnormal physical signs, including wetness of the anogenital area, wetness of the nose/mouth area, test article coated fur, labored breathing, and closed eyes were observed during the inhalation exposure.

The deaths occurred between Day 3 and Day 7. Pre-death and pre-sacrifice abnormal physical signs included dyspnea, test article coated fur, wetness and red staining of the nose/mouth area, soiling of the anogenital area, few feces, chromorhinorrhea, sagging eyelids, chromodacryorrhea, piloerection, bloating of the abdomen, emaciation, unkempt fur, urine darker than normal, and diarrhea.

Body weight loss was observed, at termination or death, for all animals.

Gross necropsy of animals revealed chromodacryorrhea, wetness of the anogenital area, emaciation, spleen smaller than normal, pale and darkened appearance of the liver, chromorhinorrhea, red staining of the nose/mouth area, adrenal glands larger than normal, and abnormalities of the gastrointestinal tract.

EPA REG No. 9402 – x[illegible]
DP Barcode:

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (OPPTS 870.1300) (Nose-Only Exposure)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: 2346, Study No. 1

Testing Laboratory: IIT Research Institute (IITRI)
Author: Dennis Sullivan, M.S., D.A.B.T.

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160. The study data have been reviewed, and the information contained in this report is an accurate representation of the data within the context of the study design and evaluation criteria.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Dosage: Limit Test: 2.03 mg/L

Species: 10 Rats; Sprague Dawley
Sex: 5 male, 5 females. Females were nulliparous and non-pregnant.
Age: Young adult (8 weeks old)
Weight: Males: 245 – 267 grams, Females: 187 – 206 grams; at experimental start
Source: Charles River Laboratories, Portage, MI
Housing: Temperature Range: 21-22° C
Humidity Range: 33-43%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: 6 days

Concentration:

Group	Gravimetric Exposure Concentration (mg/L)	Nominal Concentration (mg/L)
I	2.03	7.22

Conclusion:
1. **Acute LC_{50} (mg/L)**: >2.03 mg/kg in male and female rats
2. **The estimate 4-hr acute inhalation LC_{50} of Hitman disinfectant is greater than 2.03 mg/L in male and female rats.**
3. **Average MMAD**: 1.86 µm
4. **Toxicity Category**: IV **Classification**: Acceptable

Procedure (Deviations from 870.1200):

- The chamber humidity is recorded as 99.9% throughout the four hour exposure. The protocol states "Since the test substance is a liquid, it is expected that the chamber atmosphere relative humidity will be greater than 70% RH." There is no discussion of the impact this may have on the study.
- The laboratory reported the following protocol amendments:
- Replace the first sentence with: Descriptive statistics (mean and standard deviation) will be calculated for body weight and body weight changes using ToxData® version 2.1E.5 (PDS Pathology Data Systems, Bassel, Switzerland). Reason for Amendment: The original protocol sentence was incorrect as only one group of animals was to be exposed to the test substance.
- GLP Compliance ADD: and The study will be conducted in compliance with the following Good Laboratory Practice standards or regulations: U.S. EPA (TSCA) 40CFR792. Reason for Amendment: The sponsor requested the additional GLP Standards.
- The laboratory reported the following protocol deviation:
- The protocol states: "The animals will be observed during the exposure (to the extent possible), immediately after the exposure and at least once daily during a 14-day post-exposure observation period for signs of toxicity." The animals were observed on Study Day 6 for mortality but the clinical observations were not documented in the study records. Effect on Study: No adverse effect would be expected on the overall integrity of the study as the animals were observed for mortality on Study Day 6 and all of the animals were observed to be normal on Study Day 7 through Study Day 15.
- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

Results:

Reported Mortality

Exposure Concentration (mg/L)	Number Dead / Number Tested		
	Males	Females	Combined
2.03	0/ 5	0 / 5	0 / 10

Chamber Atmosphere

Exp. Conc. (mg/L)	Sample	MMAD (µm)	GSD (µm)	Cumulative % of Particles < Effective Cutoff Diameter (µm)[1]				
				0.0	0.4	0.7	1.1	2.1
7.22	1	1.88	2.42	Not provided				
	2	1.83	2.47	Not provided				

[1]Percent of particles smaller than corresponding effective cutoff diameter

Chamber Environment during Exposure

Exposure Level (mg/L)	2.20
Chamber Volume (L)	not reported
Average Total Airflow Volume (Lpm)[1]	28.12
Air Changes Per Hour	not reported
Mean Oxygen Content (%)	20.8
Temperature Range (°C)	22.8 (mean)
Relative Humidity Range (%)	99.9 (mean)

[1]Total air = filtered compressed air + compressed mixing air

Clinical Observations:

C2010-1673 Hitman disinfectant was tested for acute inhalation toxicity (limit) test in rats by observing effects on five male and five female rats following four hours of exposure to an atmosphere generated from aerosolization of the test substance. Following exposure in a nose-only inhalation exposure chamber, the rats were observed daily for adverse clinical signs and were weighed weekly. All rats were euthanized and subjected to a gross necropsy following a 14-day observation period. The total duration of the study was 15 days.

The test atmosphere was generated by aerosolization of the C2010-1673 Hitman disinfectant using a nebulizer. The test atmosphere was diluted to the target concentration with humidified air prior to introduction to the nose-only chamber. The overall mean concentration of the test substance during the exposure was 2.03mg/L (target concentration 2mg/L).

No rats died prior to scheduled sacrifice. Clinical signs of toxicity observed during the first week post-exposure consisted of hypoactivity, salivation, labored breathing, rough coat, rales and redness around the nose fur. No clinical signs of toxicity were observed during the second week of the observation period. One week after exposure to the test substance, mean body weight gains ranged from 1 g for males to 3 g for females. However, during the second week of the observation periods, mean body weight gains increased, ranging from 68 g for males to 33 g for females. No gross lesions were observed in any animal at terminal necropsy.

DATA REVIEW FOR ACUTE EYE TOXICITY TESTING (OPPTS 870.2400)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: MB 11-20288.04

Testing Laboratory: MB Research Laboratories
Author: Debra Hall, LATG

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception: Prior to study initiation, the Sponsor did not provide test article characterization information. However, following study termination, purity and stability were provided. See Appendix A. The effect of the lack of full test article characterization information cannot be fully assessed. The test article characterization (noted in Appendix A) was not conducted according to the Good Laboratory Practices. This is not expected to have an impact on the outcome of the study.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Dosage: 0.1 mL (instilled as received)

Species: 3 Rabbits; New Zealand White
Sex: 2 male, 1 female
Age: Young adult (24 -25 weeks old)
Weight: 2.9 -3.0 kg at experimental start
Source: Covance Research Products, Inc., Denver, PA
Housing: Temperature Range: 21.6 – 21.72° C
Humidity Range: 71.1 – 79.5%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: at least 5 days

Conclusion:
1. **Acute Eye Irritation**: Moderate to severe eye irritant
2. **Toxicity Category**: II **Classification**: Acceptable

Procedure (Deviations from 870.1200):

- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

Results:

Corneal opacity, noted in one out of three eyes, cleared by Day 21. Iritis, noted in one out of three eyes, cleared by Day 7. Conjunctival irritation, noted in three out of three eyes, cleared by Day 21. The control eyes appeared normal at all observation periods. There were no abnormal physical signs noted during the observation period.

Under the conditions of this study, Hitman Spray is classified as a moderate to severe irritant to the eye.

Incidence of Irritation

Time Post Instillation	No. of Animals Testing "Positive" / No. of Animals Tested		
	Corneal Opacity	Iritis	Conjunctivae
1 hour	0 / 3	0 / 3	3 / 3
24 hours	0 / 3	1 / 3	3 / 3
48 hours	1 / 3	1 / 3	3 / 3
72 hours	1 / 3	1 / 3	3 / 3
Day 7	1 / 3	0 / 3	3 / 3
Day 14	0 / 3	0 / 3	3 / 3
Day 21	0 / 3	0 / 3	0 / 3

Individual Scores for Ocular Irritation

Observations	Rabbit No. H4710 (Male)

	Hours After Treatment						
	1	24	48	72	Day 7	Day 14	Day 21
I. Corneal Opacity	0	0h	2	2	2 c	0 c,h	0
II. Iritis	0	1	1	1	0	0	0
III. Conjunctivae							
A. Redness	1	2	2	2	2	0	0
B. Chemosis	3	3	3	3	2	1	0
C. Discharge	2	3	3	2	1	0	0

c = pannus, h= lack of normal luster

Observations	Rabbit No. H4706 (Male)						
	Hours After Treatment						
	1	24	48	72	Day 7	Day 14	Day 21
I. Corneal Opacity	0	0	0	0	0	0	0
II. Iritis	0	0	0	0	0	0	0

III. Conjunctivae							
A. Redness	1	2	2	2	2	1	0
B. Chemosis	2	2	1	1	0	0	0
C. Discharge	2	2	1	1	0	0	0

Observations	Rabbit No. H4726 (Female)						
	Hours After Treatment						
	1	24	48	72	Day 7	Day 14	Day 21
I. Corneal Opacity	0	0 h	0 h	0 h	0 h	0	0
II. Iritis	0	0	0	0	0	0	0
III. Conjunctivae							
A. Redness	2	2	2	2	1	1	0
B. Chemosis	3	3	3	2	1	1	0
C. Discharge	2	2	2	2	1	0	0

c = pannus, h= lack of normal luster

EPA REG No. 9402 – xx
DP Barcode:

DATA REVIEW FOR ACUTE DERMAL IRRITATION TOXICITY TESTING (OPPTS 870.2500)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: MB 11-20288.03

Testing Laboratory: MB Research Laboratories
Author: Laura J. DiDonato, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception: Prior to study initiation, the Sponsor did not provide test article characterization information. However, following study termination, purity and stability were provided. See Appendix A. The effect of the lack of full test article characterization information cannot be fully assessed. The test article characterization (noted in Appendix A) was not conducted according to the Good Laboratory Practices. This is not expected to have an impact on the outcome of the study.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Dosage: 0.5 mL (instilled as received)

Species: 3 Rabbits; New Zealand White
Sex: 2 male, 1 female
Age: Young adult (24 -25 weeks old)
Weight: 2.8 -3.0 kg at experimental start
Source: Covance Research Products, Inc., Denver, PA
Housing: Temperature Range: 21.61 – 23.33° C
Humidity Range: 85.2 – 94.7%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: at least 5 days

Conclusion:
1. **Acute Dermal Irritation**: Non-irritant
2. **Toxicity Category**: unknown **Classification**: Acceptable

Procedure (Deviations from 870.1200):

- The laboratory reported the following Standard Operating Procedures deviation "The temperature of the animal room was 21.61 to 21.72° C and the relative humidity was 71.1 – 79.5%. Although the temperature and humidity were outside of the Standard Operating Procedures range, this minor deviation was not considered to have had any adverse effect on the results of this study."
- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

Results:

There was no erythema and very slight edema observed at 1 hour following the 4 hour exposure. There was no other erythema or edema observed for any animal at any observation period. There were no abnormal physical signs noted during the observation period. One animal gained weight and the other two animals remained the same weight.

The Modified Primary Irritation Index for Hitman disinfectant is 0. Under the conditions of this study, Hitman disinfectant is classified as non-irritating to the skin.

Incidence of Irritation

Time after Patch Removal	Erythema	Edema
1 hour	0 / 3	3 / 3
24 hours	0 / 3	0 / 3
48 hours	0 / 3	0 / 3
72 hours	0 / 3	0 / 3

Individual Skin Irritation Scores

Animal No.	Sex	Erythema / Edema			
		Time After Patch Removal			
		1 hour	24 hours	48 hours	72 hours
4713	M	0 / 1	0 / 0	0 / 0	0 / 0

4714	**M**	0 / 1	0 / 0	0 / 0	0 / 0
4728	**M**	0 / 1	0 / 0	0 / 0	0 / 0
Total	0 / 3	0 / 0	0 / 0	0 / 0	
Mean	0 / 1	0 / 0	0 / 0	0 / 0	

Summary of Skin Irritation Scores[1]

	Time After Patch Removal			
	1 hour	**24 hours**	**48 hours**	**72 hours**
Erythema	0	0	0	0
Edema	1	0	0	0
TOTAL (PDI)[2]	1	0	0	0

[1]Average values for three rabbits
[2]PDI = Average Erythema + Average Edema

EPA REG No. 9402 – xx
DP Barcode:

DATA REVIEW FOR DERMAL SENSITIZATION TOXICITY TESTING (OPPTS 870.2600)

Product Manager: 33 **Reviewers:**
MRID No.: **Completion Date:**
Study No.: MB 11-20288.06

Testing Laboratory: MB Research Laboratories
Author: Debra A. Hall, LATG

Quality Assurance (40 CFR §160.12): A Quality Assurance (QA) statement was included. A statement of Good Laboratory Practice (GLP) compliance was included stating that this study was conducted in compliance with U.S. EPA FIFRA 40 CFR 160 and 792, FDA 21 CFR 58, and as specified in Principles on Good Laboratory Practices, published by the Organization for Economic Cooperation & Development (OECD), 1997, with the following exception: Prior to study initiation, the Sponsor did not provide test article characterization information. However, following study termination, purity and stability were provided. See Appendix A. The effect of the lack of full test article characterization information cannot be fully assessed. The test article characterization (noted in Appendix A) was not conducted according to the Good Laboratory Practices. This is not expected to have an impact on the outcome of the study.

Test Material: C2010-1673 Hitman disinfectant, Lot# SA1255BLB, Lot 4
Positive Control: alpha-Hexylcinnamaldehyde Technical (HCA)
Historical validation study: May 2011

Species: 34 Guinea pigs; Hartley, albino
Sex: Preliminary Irritation: 2 male, 2 female
Test: 10 male, 10 female
Naïve Control: 5 male, 5 female
Age: Young adult (24 -25 weeks old)
Weight: 292-508g for males, 281-489 g for females, at experimental start
Source: Covance Research Products, Inc., Denver, PA
Housing: Temperature Range: 14.44 – 24.05° C
Humidity Range: 29.4 – 96.1%
Photoperiod: 12-hour light/12-hour dark cycle
Acclimation: at least 5 days
Method: Buehler

Conclusion:

1. **Acute Dermal Irritation**: Non-irritant
2. **Toxicity Category**: IV **Classification**: Acceptable

Procedure (Deviations from 870.1200):

- The laboratory reported the following Standard Operating Procedures deviation "The temperature range of the animal room was 14.44 to 24.05° C and the relative humidity was 29.4 to 96.1%. Although the temperature and humidity were outside of the Standard Operating Procedures range, this minor deviation was not considered to have had any adverse effect on the results of this study."
- The laboratory report describes a study conducted for the product Hitman disinfectant. A letter from the applicant to EPA (dated February 16, 2012) states that Hitman disinfectant is identical to Hitman Spray, the product for which registration is sought.

Procedure:

Preliminary Irritation Testing:

Four guinea pigs were used to screen for the highest non-irritation concentration which produced scores no more severe than two scores of 0.5 and two scores of 0. Based on the results of the screen, 25% was chosen as the highest non-irritation concentration for the challenge and was administered to both groups two weeks after the third induction.

Preparation and Selection of Animals: The day prior to the first induction application, Site 1 of all animals was clipped free of hair with an electric clipper. The clipped area was approximately 5 x 10 cm. Any animal with skin irregularities or irritation was eliminated from the study. The treated sites were re-clipped the day prior to each induction application. Thirteen days after the induction application, a naïve site on each animal was clipped free of hair. Sites 2 and 4 (right shoulder and hip areas, respectively) were reserved for alternate sites in the event that severe irritation was noted during the induction phase and/or a re-challenge was required. The day prior to screen dosing, the dorsal area of each animal was clipped free of hair. The clipped area was approximately 10 x 10 cm.

Induction Phase: Group 1, 100%. Ten males and ten females in Group 1 were dosed with four-tenths of a milliliter of the test article. The dose was applied to the left shoulder area (Site1) using a Hill Top Chamber designed to keep the test article on a 25 mm area of the site. Each chamber contained a cotton pad used to facilitate contact of the liquid test article with the site. Each chamber was covered with a strip of rubber dental dam sufficient to cover the treated site. The torso was wrapped with non-

irritating tape to provide occlusion. After 6 hours, the dams and test articles were removed. Any residual test article was cleansed from the sites with distilled water and the sites were dried with soft towelling. This procedure was performed once per week on the same day each week for a three week period, a total of three 6-hour exposures.

Group 2: Five males and five females were untreated for the three week induction period and served as the naïve control.

Screen: Each animal received four concentrations of the test article, one/site. Each concentration (10, 25, 50 or 75%) was placed in a Hilltop Chamber designed to keep the test article on a 25 mm area of the site. Each chamber contained a cotton pad which aided in the retention of the liquid sample on the site. The test sites were covered with a strip of rubber dental dam sufficient to cover the treated sites and wrapped with non-irritating tape to provide occlusion. After six hours, the dams and test articles were removed; the sites were cleansed with distilled water and dried with soft towelling.

Challenge Phase: Fourteen days after the last induction exposure, animals in Groups 1 and 2 were challenged using the same dosing procedure as in the induction phase. Based on the results of the screen, 25% was chosen as the highest non-irritating concentration for the challenge. The doses were applied to a naïve site on the lower left dorsal area (Site 3).

Historical Positive Control: The sensitivity of guinea pigs to a positive control, 85% Hexylcinnamaldehyde (HCA) is confirmed every six months. The historical positive control data for MB 11-19771.06 conducted on May 10, 2011 was included with the report.

Results:
Challenge
Induction Phase: *Test Animals (100% test substance)*:
Induction 1 – Erythema was absent to moderate
Induction 2 and 3 – Erythema was absent to strong with eschar

Challenge Phase: *Test Animals (25% test substance)*:
Erythema was absent to faint.

Naïve Control Animals (25% test substance):
Erythema was absent to very faint in the naïve control group.

Historical Positive Control

Induction Phase:

Historical Positive Control Animals (100% HCA): 1 – 3, Erythema was absent to faint.

Challenge Phase:

Historical Positive Control Animals (50% HCA in acetone): Erythema was absent to faint (0.5 -1) in the induced group.

Historical Naïve Control Animals (50% HCA in acetone): Erythema was absent to very faint (0.5) in the naïve control group.

Sensitization Response Indices

	Incidence Index[1]	Severity Index[2]		
Challenge	24 hours	48 hours	24 hours	48 hours
C2010-1673 Hitman disinfectant, Lot# SA 1255BLB, Lot 4	0.05	0.1	0.08	0.125
Naïve Control	0	0	0.05	0.05
Historical Positive Control				
HCA	0.20	0.30	0.20	0.33
Naïve Control	0	0	0	0.05

[1]Number of animals with a score 1 or greater divided at each time period by the number animals examined following challenge.

[2]Total of all erythema scores following challenge (per time period) divided by the number of scores added.

Test Animal Group Skin Reaction Scores

Treatment Phase	**Induction**	**Challenge**						
	1	**2**	**3**					
Concentration	**100%**	**100%**	**100%**					
Hours		**24**	**48**	**24**	**48**	**24**	**48**	**24**	**48**

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Animal No. /Sex								
D4846/M	0.5	0.5	1	0.5	0	0	0	0
D4847/M	1	0.5	2	2	1	0	0	0
D4848/M	1	0	2	2	3,e	3,e	0	0
D4849/M	0	0	1	1	2	2	0	0
D4850/M	0.5	0.5	1	1	3,e	3,e	1	1
D4851/M	0	0	0.5	0.5	2	3,e	0	0
D4852/M	0	0	0.5	1	2	2	0	0
D4853/M	1	0.5	3,e	3,e	2	2	0	0.5
D4854/M	1	0.5	0.5	0	2	2	0.5	0
D4855/M	1	0	1	1,e	3,e	3,e	0	0
D4856/F	0.5	0	1	1	3,e	3,e	0	0
D4857/F	2	2	1	1	2	2	0	
D4858/F	0	0	0.5	1	3,e	3,e	0	1
D4859/F	0.5	0.5	1	1	2	2	0	0
D4860/F	0	0	1	1	3,e	3,e	0	0
D4861/F	0.5	0	1	0	2	2	0	0
D4862/F	0.5	0	2	3,e	3,e	3,e	0	0
D4863/F	0.5	0	2	0	3,e	3,e	0	0
D4864/F	0.5	0	1	1	2	2	0	0
D4865/F	0.5	0	1	0	2	3	0	0
Naïve Control Group								
D4866/M	--	--	--	--	--	--	0.5	0
D4867/M	--	--	--	--	--	--	0	0.5
D4868/M	--	--	--	--	--	--	0	0
D4869/M	--	--	--	--	--	--	0	0
D4870/M	--	--	--	--	--	--	0	0
D4871/F	--	--	--	--	--	--	0	0
D4872/F	--	--	--	--	--	--	0	0
D4873/F	--	--	--	--	--	--	0	0
D4874/F	--	--	--	--	--	--	0	0
D4875/F	--	--	--	--	--	-	0	0

e = eschar