UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 17, 2002

MEMORANDUM

Subject: D278991
VigorOx™ Citrus XA, EPA Registration No. 65402-6

From: Wallace Powell, Biologist
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Through: Karen P. Hicks, Team Leader
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To: Marshall Swindell, Product Manager, Team 33
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Regulatory Management Branch I
Antimicrobials Division (7510C)

BACKGROUND

The applicant, FMC Corporation, has submitted a registration amendment package for the subject product, VigorOx™ Citrus XA. The package includes two acute toxicity studies: acute oral toxicity (MRID 455238-01) and acute inhalation toxicity (MRID 455238-02). Product Science Branch (PSB) reviews of these studies are attached to this memorandum. The applicant intends for the studies to also support their other products of similar formulation, EPA Registration No[s]. 65402-1 and 65402-2. The applicant apparently wants to change the method of support from Cite-all to Selective for the acute oral and acute inhalation toxicity data requirements.

The registration amendment package also includes a waiver request for the acute dermal toxicity, eye irritation, skin irritation, and skin sensitization data requirements. The applicant has referred to a letter from Special Review and Reregistration Division (SRRD) indicating that waivers of these four requirements had been granted in an 08/07/1997 agency letter.

No label revision was proposed in the applicant's submission.

VigorOx™ Citrus XA is labeled as an institutional/industrial sanitizer, primarily for use on hard surfaces but also for use in fogging applications and in sanitization of ultra filtration and reverse osmosis membranes and their associated distribution systems. The active ingredients in VigorOx™ Citrus XA are peroxyacetic acid (EPA code 063201) at 5.1% of product contents by weight and hydrogen peroxide (EPA code 000595) at 21.7%. Both these chemicals are in Reregistration Case 4072, for which a Peroxy Compounds Reregistration Eligibility Decision (RED) document was issued.

DISCUSSION AND RECOMMENDATION

The three products – EPA Reg. No^s. 65402-1, -2, and -6 – are substantially similar to each other in composition. The recommendations below affect all three products.

Acute oral and acute inhalation toxicity

The two submitted studies are acceptable and place VigorOx™ Citrus XA in acute oral toxicity Category III (or IV, Category III being assigned as worst case) and acute inhalation toxicity Category IV. PSB reviews of these studies are attached to this memorandum.

Eye and skin irritation

Because eye irritation and skin irritation waivers apparently were granted previously, and because these waivers appear reasonable, the requirements can continue to be considered waived.

Eye irritation and skin irritation data can also be considered waived based on the very low pH of the product. The appropriate acute Toxicity Category assignment is Category I for both eye and skin irritation.

Acute dermal toxicity

Because an acute dermal toxicity waiver apparently was granted previously, and because this waiver is reasonable, the requirement can continue to be considered waived.

Acute dermal toxicity data can also be considered waived based on the very low pH of the product. (Corrosiveness to tissue is assumed.) In such a case, acute dermal toxicity Category I should have been assigned unless there was a compelling rationale to indicate some other Category as worst case. The VigorOx™ Citrus XA product label (EPA accepted 08/23/2001) implies that Category III was accepted. Can this be justified as worst case? Based on the dermal LD_{50}'s listed in the RED document for the technical grade active ingredients, and based on the results of the acute oral and acute inhalation toxicity studies now submitted for VigorOx™ Citrus XA, it appears that Category III is a *likely* representation and that Category II is a

good *worst case* representation. The differences between the active ingredients themselves and the subject product formulation are not expected to greatly alter the acute dermal toxicity, so assignment of Category I is arguably unnecessary.

The product label was accepted (08/23/2001) with precautionary statements that imply acute dermal toxicity Category III. PSB does not know what was the rationale for this acceptance. If we knew, we could comment further. Note, however, that the applicant is not proposing label changes right now.

It is in the Product Manager's discretion whether to require a rationale (or a supporting study) or not, for acute dermal toxicity Category III labeling at this time.

Skin sensitization

Because a skin sensitization waiver apparently was granted previously, and because it does appear reasonable, the requirement can continue to be considered waived.

Dermal sensitization studies were not required for Reregistration eligibility in the Peroxy Compounds RED document, which addresses both the subject product's active ingredients. Presumably the agency considered each of these chemicals to be a non-sensitizer, a property which would be unlikely to change based on differences between the active ingredients themselves and the VigorOx™ Citrus XA product formulation. PSB wonders if the stabilizer ingredient in the product (for which little acute hazard information is known) might make a difference. But the waiver was accepted previously, and the formulation differences were presumably considered, so PSB has no adverse comments.

Summary

The updated acute toxicity regulatory profile is tabulated below.

Table: Acute toxicity regulatory status for VigorOx™ Citrus XA

Data Requirement	Means of Support	Status
Acute Oral Toxicity	MRID 455238-01 (submitted)	Acceptable/ Tox Category III
Acute Dermal Toxicity	Waiver request	Waived/ Cat. II by PSB recommendation, Cat. III implied on accepted label
Acute Inhalation Toxicity	MRID 455238-02 (submitted)	Acceptable/ Cat. IV
Eye Irritation	Waiver request	Waived/ Cat. I
Skin Irritation	Waiver request	Waived/ Cat. I
Skin Sensitization	Waiver request	Waived/ Non-sensitizer

Product Labeling

The precautionary statements on the product labels – EPA Reg. No[s]. 65402-1, 65402-2, and the subject product 65402-6 – under the "Hazards to Humans and Domestic Animals" heading must be revised in accordance with the Label Review Manual. The following would be acceptable; note also the numbered notes for specific revisions:

> "DANGER. Corrosive. Causes skin burns and irreversible eye damage.[1] Harmful if swallowed or absorbed through skin.[2] Do not get in eyes, on skin, or on clothing. Wear goggles or face shield, rubber gloves, and protective clothing.[3] Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse.[4]"

[1] The wording "causes eye and skin damage" on the Reg. No. 65402-2 label must be edited.
[2] The phrase "or absorbed through skin" is missing (all three product labels).
[3] The phrase "and protective clothing," or specific protective clothing, is missing (all three product labels).
[4] This last statement is missing (all three product labels).

The additional statements on the current accepted labels (for all three products) regarding inhalation hazard are optional and acceptable.

If acute dermal toxicity Category II will be assigned (see discussion above), then the following additional revisions will be needed: "May be fatal if absorbed through skin" and "Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco."

The First Aid statements are not affected by the subject registration amendment (revised labels were not submitted, and all four routes of exposure are represented on the current accepted labels for the three products registrations), so First Aid statements are not being reviewed at this time. As with any product registration, the First Aid statements on the product label must be brought into compliance with Pesticide Registration (PR) Notice 2001-1 if this has not been done already.

2 Attachments

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING

Attachment to 04/17/2002 Memorandum Regarding Data Package D278991
(VigorOx™ Citrus XA, EPA Registration No. 65402-6)

Reviewer: W. Powell
Antimicrobials Division
MRID No.: 455238-01
Report ID: I97-2236 (Study Number)
Study completion: 04/09/1998 (Report Date)
Author: Christine Freeman

Conclusion:
LD_{50}: 1993 mg/kg Males (95% confidence limits 938-3048 mg/kg),
1859 mg/kg Females (95% C.L. 1056-2663 mg/kg),
1922 mg/kg Combined (95% C.L. 1342-2501 mg/kg)
Toxicity Category: III
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: None found

Testing Facility: FMC Corporation, Toxicology Laboratory, Box 8, Princeton, NJ 08543

Test Material: Peracetic acid, 5%, a clear liquid

Test Animal: Rat, Sprague-Dawley CD
Age: Young adult
Weight: 205-245 g (fasted)
Source: Charles River Laboratories

Test Method:

Fasted healthy male and female rats (5 per sex) were exposed orally to one of three single doses of a 25% w/v preparation of the test material in tap water. Doses of 1000, 2000, or 4000 mg/kg were administered orally by ball-tipped intubation needle. The 25% w/v preparation in water was used for avoiding severe irritation in the test animals. Because volumes administered were adjusted to compensate for the dilution, the stated dose values refer to the original formulation (containing 5% peracetic acid), not to the 25% preparation. Clinical observations were conducted several times on the day of dosing and daily thereafter for a 14-day observation period or until mortality. Body weights were recorded on Days 0, 7, and 14. Gross necropsy was conducted on all animals.

Results:

Based on the mortality data summarized in the table below, the following estimated median lethal doses were calculated:

(5)

LD_{50}: 1993 mg/kg Males (95% confidence limits 938-3048 mg/kg),
1859 mg/kg Females (95% C.L. 1056-2663 mg/kg),
1922 mg/kg Combined (95% C.L. 1342-2501 mg/kg)

The data place the test substance (formulation containing 5% peracetic acid) in Category III for acute oral toxicity (defined as 500 mg/kg < LD_{50} ≤ 5000 mg/kg). LD_{50} values were calculated at 910 mg/kg for the females (no confidence limits reportable), 970 mg/kg for the males (95% confidence limits 800 mg/kg to 1240 mg/kg), and 1000 mg/kg for sexes combined (no confidence limits reportable).

All mortality occurred between the Day 0 and Day 7 observations, with the exception of one female at 2000 mg/kg which died between the Day 7 and Day 14 observations.

Table: Mortality Results

Dosage (mg/kg)	Number Dead/Number Tested		
	Males	Females	Total
1000	0/5	0/5	0/10
2000	3/5	3/5	6/10
4000	4/5	5/5	9/10

Clinical signs included abdominal gripping, abdominal distension, loss of muscle control, squinting eyes, staggered gait, tremors, walking on toes, hypersensitivity to touch, splayed hindlimbs, hypothermia, abdominogenital staining, chromorhinorrhea, decreased (or no) feces, unkempt appearance, chromodacryorrhea, dehydration, decreased locomotion, lacrimation, mydriasis, oral discharge, unthriftiness, leaning to one side, recumbency, abnormal posture, and diarrhea. Necropsy findings included blanched stomachs and intestines, mottled blanched livers, distended stomachs with thin linings, darkened red adrenals, and white trachea. All surviving animals gained weight during the observation period.

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DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING

Attachment to 04/17/2002 Memorandum Regarding Data Package D278991
(VigorOx™ Citrus XA, EPA Registration No. 65402-6)

Reviewer: W. Powell
Antimicrobials Division
MRID No.: 455238-02
Report ID: 1444-001 SN1
Study completion: 07/05/2001
Author: Dennis M. Sullivan

Conclusion:
LC_{50}: > 5.7 mg/L (observed) (males, females, combined)
Toxicity Category: IV
Classification: Acceptable
Quality Assurance (40 CFR §160.12): Included
Deficiencies: Noted at end of *Results* section below

Testing Facility: IIT Research Institute - Life Sciences Operation -
10 West 35th Street, Chicago Illinois 60616-3799

Test Material: VigorOx Liquid Sanitizer and Disinfectant, a colorless liquid

Test Animal: Rat, Sprague-Dawley derived [Crl:CD®(CD)Br], 6/sex
Age: 55 to 57 days
Weight: Males 210 to 253 g, Females 159 to 188 g
Source: Charles River Laboratories (ordered from Wilmington, MA)

Test Method:

In each of two exposure levels, male and female rats (5 per sex) were exposed to a test atmosphere generated with a nebulizer. The rats were exposed nose-only for 4 hours (plus an atmosphere equilibration period). For each exposure level, concentrations at the breathing zone were determined once per hour: analytically for vaporized particles, gravimetrically for aerosolized particles. Predominant results were from the analytical analyses. Exposures were determined to be 3.9 and 5.7 mg per liter of air. Particle size distributions were obtained from cascade impactor analysis of the hourly exposure samples, and a Mass Median Aerodynamic Diameter (MMAD) was determined for each sample. Chamber airflow, temperature, and relative humidity were monitored at approximately every 30 minutes. Clinical signs were recorded at least once daily for a 15 day observation period (including the exposure day). Body weights were recorded prior to exposure and weekly thereafter. Gross necropsy was conducted on all rats.

Results:

Mortality results are tabulated below. With no deaths in the 3.9 mg/L exposure group and no more than 1 death in either sex in the 5.7 mg/L group, the results are considered sufficient to indicate LC_{50} > 5.7 mg/L (observed). This places the test material in acute inhalation toxicity Category IV (i.e., LC_{50} > 2.0 mg/L).

Table: Mortality Results

Concentration (mg/L)	Number Dead/Number Tested		
	Males	Females	Combined
3.9	0/5	0/5	0/10
5.7	1/5	1/5	2/10

Clinical signs considered to be exposure-related included salivation, red discoloration around nose and/or mouth, white foam around mouth, rales, rough hair coat, and labored breathing. Necropsy observations included gross lesions in the lungs of 4 females in the 3.9 mg/L exposure and in 1 male and 1 female in the 5.7 mg/L group. All surviving rats gained weight during the observation period.

Some exposure data from the study are tabulated below.

Table: Exposure conditions

Concentration (mg/L) (mean of 4 values)	3.9	5.7
Mass Median Aerodynamic Diameter (MMAD) (µm, mean of 4 values)	0.55	0.59
Geometric Standard Deviation (µm, mean of 4 values)	2.62	2.12
Nominal concentration (mg/L)	13.5	19.9
Chamber Airflow (L/min, mean)	51.0	42.0
Chamber Temperature (°C, mean)	20.0	20.0
Chamber Relative Humidity (%, mean)	37.3	45.4

For the particle size data, MMAD values were included in the study report, but distribution data were not reported for the individual cascade impactor filter stages. However, considering the low MMAD reported for each sample, the 4 such samples taken (2 is the required minimum) per exposure period, and the fact that the study report does not appear otherwise problematic, the study report can be accepted as it is (without the complete size distribution data).

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