7-5-95

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: Case No. 813615. Re-registration
Case No. 4005. Chemical Code 079034.
Methyl Esters of Fatty Acids, C6; C8; C10; C12.
DP 207640.

From: Albin B. Kocialski, Ph.D
Risk Characterization Analysis branch
Health Effects Division (7509C)

To: Bruce Sidwell, PM 53, and
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Re-registration Branch
Special Review and Re-registration Division (7508W)

Thru: Karen Whitby, Acting Chief
Risk Characterization and Analysis branch
Health Effects Division (7509C)

Compliance Services International on behalf of the Cochran Corporation submitted scientific studies responding to the data call-in notice of August 10, 1993, in support of the subject compounds (i.e. straight chain saturated methyl esters of the fatty acids C6; C8; C10; C12). Of the supporting data and documentation submitted four of the studies were acute studies conducted in 1994 and accompanied by the raw data. These four studies were reviewed and found acceptable - they are:

* AOLD 50 (81-1) - MRID - 433345 -1

* ADLD 50 (81-2) - MRID - 433345 - 2

* Primary Eye Irritation (81-4) 433345-3

* Primary Skin Irritation (81-5) 433345-4

All other remaining data/registration support was found in one volume and identified as MRID No. 433345-5. These data were inappropriate and/or unacceptable. However, no additional testing is required based upon the rationale for each guideline and data requirement provided by this reviewer. The data submissions which are all found in MRID No. 433345-5 and which are for the most part reprinted articles from scientific journals (the exceptions being

the dermal sensitization study conducted on humans by the Proctor and Gamble Company as well as their acute inhalation toxicity study in rats and rabbits) were so grossly inappropriate and/or unacceptable with the respect to addressing and satisfying their intended regulatory data requirement that no written explanation of their inappropriateness or unacceptability was deemed necessary. However, after careful consideration, deliberation and discussion by knowledgeable and experienced scientists (i.e. Alberto Protzel Ph.D., Toxicology Branch; Joel Garbus, Ph.D., Chemistry Branch; and Albin Kocialski, Ph.D.) within the Health Effects Division there was agreement that no useful purpose would be served in requiring the registrant to conduct the obligatory studies for the purpose of satisfying the regulatory data requirements for re-registration for this technical material.

The reasoning for this position as developed from the deliberations and discussions referred to above is noted as follows: These straight chain and saturated methyl esters of caproic acid (hexanoic acid), caprylic acid (octanoic acid),capric acid (decanoic acid), and lauric acid (dodecanoic acid) when absorbed systemically are cleaved at the ester bond and metabolized as normal fatty acids and one carbon fragments with the fatty acids entering the beta-oxidative pathway with the generation of acetyl CoA and the carbon moiety being metabolized by alcohol dehydrogenase to be expired as carbon dioxide or incorporated into the carbon pool. There is also evidence in the literature which indicates that when fatty acids are fed as esters of other alcohols it is mainly as the esters of glycerol that they are present in the chyle thus further confirming that these straight chain saturated methyl esters are metabolized in a manner similar or identical to other neutral fats. It can therefore be concluded that no additional testing is required for the straight chain saturated methyl esters of caproic, caprylic, capric and lauric acid and that the product can be re-registered.

Conclusions/Comments:

1. Based on the reviews provided and the rationale contained herein this product can be re-registered with other considerations and disciplinary reviews permitting.

2. The acute inhalation study conducted by Proctor and Gamble although not supportive of re-registration has raised the possibility of chemical pneumonitis (chemical pneumonia) to the applicator when the product is applied as a fine spray (or mist). We are therefore requiring that either (1) a mask be used by the applicator (2) a new acute inhalation study conducted over the same time period and number of days as originally conducted by Proctor and Gamble with histopathological examination of the lungs or (3) the arguments presented in this review be clearly and definitely rebutted.

3. Although there is Food and Drug Administration (FDA) approval for some of these methyl esters as food additives the FDA approval which outlines strict limitations as to the use of these methyl esters is not in and of itself sufficient argument for waiving some of the data associated with this use and use pattern.

Attachments:

Acute Inhalation LC 50: Guideline No.81-3. The acute inhalation report submitted on four rabbits and ten rats is not acceptable and fails to satisfy this data requirement (guideline no. 81-3) However, it is our judgement that reconducting this study would not significantly add to our knowledge for a change of classification out of toxicity category III for acute inhalation. We are therefore initiating a data waiver for this data requirement while concurrently leaving the toxicity category for this information in category III for acute inhalation. However, we do have a concern with regard to the use of this product in greenhouses. The concern is with the particle size of the spray formulation which may be respirable during application and the possible treatment related to pneumonitis associated with perivasculitis which was suggested in the original transcript of the animal inhalation studies. We are therefore requiring that the labeling include a mask during application of the product or that spray droplets be shown to be large enough not to be respirable (greater than 15 micro meters) or that our assumptions are not correct with a successful rebuttal by the registrant, or a new acute inhalation study be conducted over the same time period and number of days as originally conducted by Proctor and Gamble with histopathology conducted on the lungs.

Skin Sensitization: Guideline No. 81-6. The dermal sensitization study conducted on humans is not acceptable and fails to satisfy this data requirement (guideline no. 81-6). However, it is our judgement that the reconduct of this study would not significantly add to our knowledge as to the original conclusion of these studies - i.e. that this formulation is not a sensitizer. We are therefore initating a data waiver for this study and concluding that the product is not sensitizer. We are basing our conclusion on the fact that there are no known reports of sensitization in either animals or man in the available published literature with regard to any of the formulations' individual compounds as well as the absence of known sensitizing moieties within each individual compound of the formulation.

21-Day Dermal Toxicity Study: Guideline No. 82-2

The dermal sensitization study conducted on humans to fulfill the data requirement for the 21-day dermal toxicity study is inappropriate, unacceptable and does not satisfy this data requirement (guideline no. 82-2) {The 21-day dermal toxicity study is normally a three dose study that determines a systemic no-observable-effect level as well as an observable toxic systemic effect as measured by various parameters}. However, when consideration is given to (1) the fact that the acute dermal LD 50 study tested at the limit dose of 2000.0 mg\kg was negative as measured by (i) the absence of clinical signs (ii) the absence of gross pathology and (iii) the absence of the loss of body weight, with body weight changes being viewed as a parameter that indirectly measures a multitude of systemic endpoints (2) the fact that methyl esters of fatty acids are not totally soluble in organic solvents (thereby limiting dermal penetration) and the fact that (3) these methyl esters when systemically absorbed are cleaved at the ester bond into their respective components and metabolized as normal fatty acids and one carbon fragments with the fatty acids entering the beta-oxidative pathway with the generation of acetyl CoA and the carbon moiety being metabolized by alcohol dehydrogenase to be expired as carbon dioxide or incorporated into the carbon pool, we conducting of this study would not add to our knowledge of the sytemic toxicity of these compounds and therefore we are initiating a data waiver for this study.

There is also evidence in the literature that with respect to isotopically labelled triglycerides, a majority are hydrolyzed to glycerol and fatty acids and some are absorbed directly as triglycerides, which would further indicate that systemically absorbed methyl esters of the subject fatty acids are not of concern when absorbed systemically by the dermal route thereby leading one to conclude that further testing of the subject methyl esters of fatty acids is not necessary.

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Teratology Study: Guideline No. 83-3.

The literature data submitted to fulfill the data requirement for the teratology study are inappropriate, unacceptable and do not satisfy this data requirement (guideline No. 83-3). However, in discussions with Health Effects Division scientists Alberto Protzel in Toxicology Branch and Joel Garbus in the Chemistry Branch there was agreement that these straight chain saturated methyl esters of fatty acids or their metabolic by-products should not be of toxicological concern. These methyl esters when absorbed systemically are cleaved at the ester bond and metabolized as normal fatty acids and one carbon fragments with the fatty acids entering the beta-oxidative pathway with the generation of acetyl CoA and the carbon moiety being metabolized by alcohol dehydrogenase to be expired as carbon dioxide or incorporated into the carbon pool. There is also evidence in the literature that indicates that when fatty acids are fed as esters of other alcohols it is mainly as the esters of glycerol that they are present in chyle thus further confirming that these straight chain saturated methyl esters are metabolized in a manner similar to or identical to other neutral fats. Therefore, based on the preceding one can reasonably conclude that these saturated straight chain methyl esters of fatty acids C6,; C8; C10; and C12 are not teratogenic.

Mutagenicity: Guideline No. 84-2. Gene Mutation;

Structural Chromosomal Aberration; Other Genotoxic Effects.

The literature data submitted to fulfill the data requirement for mutagenicity (guideline no. 84-2) are inappropriate, unacceptable, and do not satisfy this data requirement. However, in discussions with Health Effects Division scientists Alberto Protzel of Toxicology Branch and Joel Garbus in the Chemistry Branch there was agreement that these straight chain saturated methyl esters of fatty acids when absorbed systemically are cleaved at the ester bond and metabolized as normal fatty acids and one carbon fragments. The fatty acids enter the beta-oxidative pathway with the generation of acetyl CoA and the carbon moiety being metabolized by alcohol dehydrogenase to carbon dioxide or incorporated into the carbon pool. There is also evidence in the literature that indicated that when fatty acids are fed as esters of other alcohols it is mainly as esters of glycerol that they are present in chyle thus further confirming that these straight chain methyl esters of fatty acids are metabolized in a manner similar to or identical to other neutral fats.

Therefore, based on the preceding one can reasonably conclude that since these saturated straight chain methyl esters of fatty acids are structurally related and metabolized in a similar manner to other neutral fats with the production of similar metabolic by-products further testing of methyl esters for their genotoxic (mutagenic) effects is not necessary.

AOLD50-3

MEMORANDUM

SUBJECT: Acute Oral Toxicity (Limit) Test in Rats

Test Compound: CE-810 Methyl Ester [Methyl Esters of Straight Chaim Fatty Acids C6-C12] Quality Code: 803-213

Purity of Test Material: 99.6% [C_6=2.4%; C_8=58.3%; C_{10}=38.5%; C_{12}=0.4%]

Testing Facility: Inveresk Research International

IRI Project No.: 555719

IRI Report No.: 10481

Study Completion Date: August 3, 1994

MRID No. 433345-1

Guideline: 81-1

Five male and five female healthy young adult rats of the Spraque - Dawley strain [6-8 weeks old and weighing 130-150 grams] were gang caged and allowed to acclimate for seven days prior to treatment in an environmentally controlled setting. All animals had free access to standard laboratory rat chow and tap water.

The test material was administered at a single dose level of 5000.0 mg\kg body weightafter an overnite fast. Food was also withheld 3.5 hours past dosing. Animals were again weighed seven days post dosing and at sacrifice at the end of the 14 day observation period. Clinical signs were recorded frequently on the day of dosing and once daily for 14 days following dosing. All animals were sacrificed by carbon dioxide asphyxiation at the end of 14 days and necropsied.

No animals died and no abnormalities were noted at necropsy. Clinical signs were absent with the exception of piloerection in one female occurring two hours post dosing.

Conclusion: The acute oral LD 50 under the test conditions is greater than 5000.0 mg\kg body weight.

Toxicity Category: Category 4

Classification: Guideline

ADLD-50

SUBJECT: Acute Dermal Toxicity (Limit) Test in Rabbits.

Test Compound: CE-810 Methyl Ester [Methyl Esters of Straight Chaim Fatty Acids C6-C12] Quality Code: 803-213

Purity of Test Material: 99.6% [C6=2.4%; C8=58.3%; C10=38.5%; C12=0.4%]

Testing Facility: Inveresk Research International

IRI Project No: 555703

IRI Report No: 10482

Study Completion Data: August 3, 1994

MRID No. 433345-2

Guideline: 81-2

Five male and five female young healthy New Zealand White rabbits weighing 2.1 - 2.7 kg. were housed individually and allowed to acclimate for eight days in an environmentally controlled setting. All animals had free access to standard laboratory chow and tap water.

The back of each rabbit was clipped free of hair with care taken to avoid abrading the skin. The test compound was then administered dermally as a single application at a dose level of 2000.0 mg\kg of body weight in the following manner. The test material was applied onto a gauze dressing (10cm x 10cm) which was applied to the shaved back of each rabbit. Approximately 10% of the body surface area was in contact with the test material. The gauze was held in place with Elastoplast Elastic Dressing wrapped around the trunk of the animal. After a contact period of 24 hours following dosing the dressing was removed and the skin wiped with a water dampened tissue.

All animals were observed at least once daily for 14 days following dosing and frequently on the day of dosing. Animals were weighed prior to dosing at seven days post-dosing and at sacrifice at the end of the 14 day observation period.

All animals were sacrificed with an over dose of pentobarbitone administered intra-venously and then subjected to necropsy.

None of the animals died on study. There were no clinical signs and no abnormalities were detected at necropsy. Body weight gains were generally acceptable.

Conclusion: The acute dermal LD 50 under the test conditions is greater than 2000.0 mg\kg body weight.

Toxicity Category: Category 3

Classification: Guideline

PEI

SUBJECT: Primary Eye Irritation Test In Rabbits

Test Compounds: CE-810 Methyl Ester [Methyl Esters of Straight Chaim Fatty Acids C_6-C_{12} Quality Code: 803-213

Purity of Test Material: 99.6% [C_6 = 2.4%; C_8 = 58.3%; C_{10} = 38.5%; C_{12} = 0.4%]

Testing Facility: Inveresk Research International

IRI Project No: 555698

IRI Report No. 10484

Study Completion Date: August 3, 1994

MRID No: 433345-3

Guideline: 81-4

Six male healthy young adult New Zealand White rabbits were housed individually and allowed to acclimate for eight days in an environmentally controlled setting. All animals had free access to standard laboratory chow and tap water. Animals ranged from 2.20 to 2.60 kg in body weight at test time. Eyes were clear of any defects.

Approximately 0.1 ml of test material was inserted into the right eye of each rabbit with the left eye remaining untreated and serving as control. The eyelid was then gently held together for 1-2 seconds. All eyes were examined using a hand held magnifier and pencil type flash light and ocular reactions recorded at 1,24, 48 and 72 hours after instillation. Eyes were scored based on the system of Draize.

There was no involvement of the cornea or the iris at any time period. Redness and discharge were observed at the one hour reading but not at any other time period. Some slight redness was observed in 4 of 6 animals and discharge was observed in all 6 animals ranging from slight to moderate/severe.

Conclusion: The test material is considered a slight irritant to the eyes.

Category of Toxicity: Category 3

Classification: Guideline

SUBJECT: Primary Skin Irritation Test in Rabbits

Test Compound: CE-810 Methyl Ester [Methyl Esters of Straight Chaim Fatty Acids C_6 - C_{12}] Quality Code:803 - 213.

Purity of Test Material: 99.6% [C_6 = 2.4%, C_8 = 58.3%; C_{10} =38.5%; C_{12} = 0.4%].

Testing Facility: Inveresk Research International.

IRI Project No. 555682

IRI Report No. 10483

Study Completion Date: August 3, 1994

MRID No: 433345-4

Guideline: 81-5

Six male healthy young adult New Zealand White rabbits were housed individually and allowed to acclimate for seven days in an environmentally controlled setting. All animals had free access to standard laboratory chow and tap water. Animals ranged in weights from 2.06 to 2.60 kg. on the day of treatment.

Hair was clipped from the dorsal area of the test trunk of each rabbit one day prior to test material application. Care was taken to avoid abrading the skin. The test material [0,5 ml.] was applied to the intact skin on each rabbit and then covered with a 2.5 cm by 2.5 cm patch of gauze [6 cm sq]. The patch remained in place for four hours covered with micropore tape and the entire trunk loosely bound with Elastoplast Elastic Bandage. After four hours the patch was removed and the skin wiped with damp tissues to remove excess test material without altering the existing response or the integrity of the epidermis. Skin reactions were assessed at 1, 24, 48 and 72 hours then daily thru 15 days with the exception of day 8 which was inadvertently omitted. Scoring was based on the method of Draize.

A slight to well defined erythema was observed thru 72 hours and four days. Erythema was absent in 4 of 6 animals from days 5 thru 15. Erythema was not observed in the remaining two animals from days 9 thru 15. Edema was not observed at anytime period. However, evidence of desquamation (i.e. dry and flaky skin) was in evidence for four animals on day 5 with all animals showing this effect for days 9 thru 15.

Conclusion: The test material is a slight irritant to the skin.

Category of Toxicity: Category 4

Classification: Guideline

Memory PSI

CHEMICALS: 079034 Methyl esters of fatty acids C6; C8; C10; C12; [straight chain saturated fatty acids]

Case No. 813615
Re-registration Case No. 4005

Citation	Test Material	MRID No.	Results	Tox Cat.	Core Grade
81-1 Acute Oral LD 50 Species: Rat Inveresk Res.Labs Report No.10481 August 3, 1994	CE-810 Methyl Esters {Methyl esters of straight chain, saturated fatty aids C6;C8; C10;c12} Quality Code 803-213 Purity 99.6% [C6=2.4%; C8=58.3%; C10=38.5%; C12= 0.4%]	433345-1	LD50> 5000 mg/kg	4	Guideline
81-2 Acute Dermal LD50 Species: Rabbit Inveresk Res. Lab Report No. 10482 August 3, 1994	Same as for 81-1	433345-2	LD50 > 2000 mg/kg	3	Guideline
81-4 Eye Irritation Species: Rabbit Inveresk Res. Lab. Report No. 10484 August 3, 1994	Same as for 81-1	433345-3	Slight irritant	3	Guideline

81-5 Skin Irritation Species: Rabbit Inveresk Res. Lab. Report No. 10483 August 3, 1994	Same as for 81-1	433345-4	Slight irritant	4	Guideline
(81-3) Acute Inhalation LC-50		See Review	Data Waived	3	
(81-6) Dermal Sensitization		See Review	Data Waived	Negative	
(82-2) 21-Day Dermal		See Review	Data Waived		
(83-3) Teratology		See Review	Data Waived	Negative	
(84-2) Mutagenicity		See Review	Data Waived	Negative	