DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

·March 8, 2002

REF 2

Toxicology-Group 1, Division of Food Contact Substance Notification Review (DFCSNR)

Final Toxicology Memorandum FAP No. 8A4610

Division of Petition Review
Attn: Martha Peiperl

Through: Garfield N. Biddle, Ph.D. Garfield N. Biddle
Director, Division of Petition Review

FAP No. 8A4610

Related FAPs:
SFAE:
1A3564 9A4166
2A3590 0A4183
3A3708 2A4321
5A3839 5A3859
6A3914
Higher esters: 6T3900
Olestra: 7A3997

Keller and Heckman, LLP
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Suite 500 West
Washington, D.C. 20001

On behalf of: Mitsubishi Chemical Co.
Tokyo 100, Japan

BACKGROUND

Mitsubushi Chemical Co. is requesting a regulation for the use of sucrose fatty acid esters containing principally tetra-, penta-, hexa-, and hepta-esters, collectively referred to as SOE, for use as an emulsifier in chocolate and low fat spreads at a maximum use level of 2.0%. Sucrose fatty acid esters containing principally the mono-, di-, and tri-esters (SFAE) have previously been regulated under CFR §172.859 and those containing principally hepta- and octa-esters (Olestra) have been regulated under CFR § 172.867.

EXPOSURE

The Chemistry Review Team estimated in their October 13, 1998 memorandum (M. DiNovi) that a consumer at the 90th percentile would have an exposure of 110 mg/p/d (1.83 mg/kg bw/day) to SOE from the petitioned uses. The specifications for SOE

presented in the petition indicated that, "mono- thru tri-esters would comprise ≤ 45%, tetra thru hepta-esters would comprise ≥ 50%, and octa-esters would comprise ≤ 40% of the total SOE product. Based on these specifications the Division of Health Effects Evaluation (DHEE) met with Dr. DiNovi on August 4, 2000 to discuss the "Theoretical Worst Case Exposures" for the tetra-, penta, hexa, and hepta-ester components of SOE. It was determined that in the most extreme case up to 100% of the final SOE product could be either the tetra-, penta-, hexa, or hepta-ester. This information was discussed in more detail in the DHEE memorandum dated March 15, 2001.

In a continuing effort to further refine the potential exposure to SOE and its component esters a more detailed evaluation was conducted using data from approximately 50 samples of SOE that was submitted in the petition (Appendix 3, "SOE Product Analysis"). Based on these data and in consultation with Chemistry, the average percent of the tetra- thru hepta-esters as well as the average total percent for these combined esters have been calculated. These averages were then used in calculating new exposure estimates for the various sucrose ester components in SOE that is proposed for commercial use. Dr. DiNovi has concurred with these revised exposure calculations and has also provided new cumulative exposure estimates for the various sucrose esters in his e-mail dated March 6, 2002 (attached). This information is summarized in the following table.

Percent Contribution to SOE Product
from: "SOE Product Analysis"

Ester	% Range		% Average	Exposure from Proposed Use mg/p/day	Exposure from Regulated Uses mg/p/day	Cumulative Exposure mg/p/day
	Low	Hi				
Tetra	6	23	14	15	12	27
Penta	9	27	19	20	47	67
Hexa	13	30	23	25	70	95
Hepta	6	31	20	22	1400	1422
Total	52	85	75			

TOXICOLOGICAL ASSESSMENT

The Petitioner submitted a number of study reports and publications in support of their assessment of safety under Tabs 16 - 40, 42 and 43 in the FAP, however none of these studies used the SOE product as the test compound. This information has been reviewed and discussed in our memoranda of July 10, 2000, October 13, 2000,

January 12, 2001, February 2, 2001, February 7, 2001, March 1, 2001, and March 15, 2001. The petition did contain a combined chronic and carcinogenicity study in male and female rats[1] where rats were orally dosed with Ryoto Sugar Ester S-570, a blend of sucrose fatty acid esters, including tetra- and higher esters. Additional information was submitted by the petitioner for our consideration on June 13, 2001 and September 19, 2001. This information included analytical data for the percentages of tetra- and higher esters in 5 lots of Ryoto Sugar Ester S-570.

Toxicology has considered the nature of the petitioned SOE product and its constituents, the current regulated uses of sucrose fatty acid esters, available related toxicological data, and exposure estimates for the sucrose fatty acid esters. Based on the totality of this information, Toxicology determined that the safety assessments for the mono-, di-, and tri-ester components and the hepta- and octa-ester components of SOE were made during reviews for SFAE and Olestra regulations, respectively. The food additive petitions related to these regulations are provided on page 1 of this memorandum. Those safety determinations remain unchanged. The focus of the safety assessment for the current petition, FAP 8A4610, would therefore be the tetra-, penta-, and hexa-ester components of SOE.

Toxicology has considered the revised exposure estimates for the tetra-, penta-, and hexa-esters and the breadth of information about sucrose fatty esters, including pharmacokinetic studies. A metabolism study that was submitted under tab 34 in the petition[2] and evaluated in our memorandum dated March 1, 2001, provided evidence that labeled material was absorbed following administration of tetrastearate, and that this material may bioaccumulate. The biological significance of this potential bioaccumulation was explored and is discussed in the following paragraph. The metabolism study also indicated that the higher esters administered, hexa- and octa-stearates, were absorbed to a lesser extent and that they did not raise any particular concern related to bioaccumulation.

The data provided in the combined oral chronic (52 weeks) and carcinogenicity (104 weeks) rat study, mentioned above, was used to investigate the potential biological significance of the absorbed tetra-ester component of SOE. The study report indicated that male and female rats received Ryoto Sugar Ester S-570 in their diet at target concentrations of 0, 1, 3 and 5% for the specified times. No significant biological effects were noted at any of the dose levels and the no effect level (NOEL) was determined to be the highest dose tested, 5%. The mean quantity of test article

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[1]"Combined Chronic Oral Toxicity/Carcinogenicity Studies of Sucrose Esters of Fatty Acids in Rats"

[2]Metabolism of 14C-Labeled Sucrose Esters of Stearic Acid in Rats" (Study No. SRI-BIO 92-148)

consumed at the 5% dose level was reported to be 1970 and 2440 mg/kg/day for male and female rats, respectively. The concentration of tetra-ester in the test article, based on the analytical data submitted, was 9.3%. Multiplying the dose for males by the percent contribution of tetra-ester provides an intake of 183 mg tetra-ester/kg bw/day. An acceptable daily intake (ADI) of 110 mg/p/day for tetra-ester was determined by dividing the intake (183 mg/kg bw/day) by the safety factor (100) and multiplying the result by 60 kg (the reference body weight). Based on the comparison of the ADI, 110 mg/p/day, with the revised exposure estimate for tetra-ester, 27 mg/p/day, Toxicology has no safety concerns regarding the potential intake of sucrose tetra-ester in SOE.

CONCLUSION

Based on our reviews of available information related to the sucrose fatty acids which are the subject of this petition, and the absence of any overt toxicity, we have no safety concerns regarding the proposed regulation of SOE as described in this food additive petition.

Carolyn Young

Carolyn Young, Ph.D.

attachment: DiNovi e-mail

cc: (Lin, Roth, DiNovi, Edwards, Biddle, Varner, Zajac)
c:petit\ dir\SOE\final2.wpd

Young, Carolyn

From: Dinovi, Michael J
Sent: Wednesday, March 06, 2002 12:20 PM
To: Young, Carolyn
Subject: Recalculation of EDI's for SOE 8A4610

Carolyn

I have reviewed the table of percentages for the various sub-esters of SOE and concur with your conclusion that their use in estimating the exposure for these esters is appropriate. The worst-case estimates that were discussed in August 2000 should be replaced by these new EDI's. Additionally, using these new EDI's allows a recalculation of the cumulative EDI's for the sub-esters based on their presence in sucrose fatty acid esters and olestra combined with the new estimates. The tetra-ester changes from 122 mg to 27; the penta- from 157 to 67 mg; the hexa- from 180 to 95 mg; and the hepta from 1510 to 1422 mg. All of these are per person per day. you have my concurrence with your draft memorandum. Please call me if any more is needed to complete your memo.

Mike

Michael DiNovi, Ph.D.
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