REF. 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: February 23, 2001

From: Division of Product Policy, Scientific Support Branch (HFS-207)

Subject: Food Additive Petition 4A4419- Kuraray America Inc. (formerly Kurary International Corporation)/Keller & Heckman. n-Octanol, a currently cleared synthetic fatty alcohol produced by a new manufacturing process, for use as an ingredient in food. Submissions dated 4-7-1994 and 4-12-1994

To: Division of Product Policy, Regulatory Policy Branch (HFS-206)
Attn: R. Angeles, Ph.D.

Food Additive Petition: 4A4419

Kuraray America Inc./Keller & Heckman
1001 G Street, N.W., Suite 500 West
Washington, DC 20001

Keller & Heckman, on behalf of Kuraray International corporation, has submitted this food additive petition to seek an amendment of 21 CFR 172.864 (Synthetic fatty alcohols) to permit the safe use of n-octanol prepared by the hydro-dimerization of 1,3-butadiene. This synthetic n-octanol is intended to replace naturally derived and other synthetic n-octanol.

IDENTITY

CAS Name: octan-1-ol

CAS Number: 111-87-5

Common Names: n-octanol
1-octanol
caprylic alcohol

INTRODUCTION

n-Octanol is currently regulated for a number of direct (microcapsules, flavoring) and indirect (polymers) uses as food additives, which are described in details in Chemistry Memorandum (R. McDaniel to R. Angeles, May 3, 1994). The n-octanol prepared by the

proposed new manufacturing process, the hydro-dimerization of 1,3-butadiene described in this FAP, is intended to replace naturally derived and other synthetic n-octanol already regulated for uses as food additives. Therefore, the overall exposure to n-octanol is not expected to increase as a result of regulation of this FAP (R. McDaniel to R. Angeles, May 3, 1994). However, the toxic effects from exposure to the impurities in this synthetic n-octanol prepared by the new manufacturing process must be evaluated.

The toxicology section of this FAP contains an acute oral toxicity study report on n-octanol in rats and referenced toxicology information on the additive and one of the impurities, 3-octanol. This memorandum addresses and evaluates the toxicology information in this FAP.

ESTIMATED DIETARY EXPOSURE

Under the most conservative assumption that all regulated n-octanol used as food additives are replaced by the n-octanol prepared by the hydro-dimerization of 1,3-butadiene, the dietary exposure estimates of the additive and its impurities are calculated by CRB (R. McDaniel to R. Angeles, May 3 and July 26, 1994) and listed in the table below.

Substance (CAS No.)	EDI
n-Octanol (111-87-5)	1.9 mg/p/d
1,3-Butadiene (106-99-0)	1.9 ng/p/d
3-Octanol (589-98-0)	2.0 µg/p/d
Diethyloctylamine	1.8 µg/p/d
Dioctylether (629-82-3)	<0.02 µg/p/d
2-Hexyldecyloctalether	<0.02 µg/p/d

TOXICOLOGY EVALUATION

1. **n-Octanol Acute Oral Toxicity (limit) Test in Rats**

   This study report is very brief. GLP and QA statements are included in the report.

   After a 9-day acclimation, a single dose of n-octanol (5000 mg/kg bw), prepared by the hydro-dimerization of 1,3-butadiene, in maize oil (10 ml/kg bw) was gavaged to five male and five female Sprague-Dawley rats (6-8 wks age, 136-188g bw). The food and tap water were available *ad libitum* during the study, with the exception of the fasting of overnight prior to dosing and 4 h post dosing. Clinical signs were recorded frequently on the day of dosing and once daily for 14 days. Body weights were measured prior to dosing, 7 days post dosing and at death or sacrifice. Necropsy was performed at the terminal sacrifice or at death.

Reported clinical signs were limited to piloerection and increased salivation in all rats 0.5 -4 h after dosing, and recovered completely by 24 h. One female rat died 3 days after dosing for unknown reason. At the end of the study, no treatment-related abnormality was observed among study animals at necropsy. Food consumption and body weight gains were within normal range.

The study authors concluded that the median oral lethal dose (LD_{50}) of n-octanol in rats is greater than 5000 mg/kg bw. This reviewer concurs with this conclusion.

2. Toxicities of impurities

A. Dioctylether, 3-octanol, diethyloctylamine, and 2-hexyldecyloctylether:
These four impurities are present in the n-octanol prepared by the hydro-dimerization of 1,3-butadiene. This reviewer conducted an updated literature search on toxicity and carcinogenicity of these impurities since there was no information submitted with this FAP. The search results show that LD_{50}s for dioctylether and 3-octanol are greater than 1.1 g/kg and 5 g/kg bw, respectively. No toxicological information on other impurities can be found. No information indicates that any of these impurities are carcinogenic at the time of this review. The EDI for each of impurities in the n-octanol prepared by the hydro-dimerization of 1,3-butadiene is extremely low. We have no further questions for these impurities.

B. 1,3-Butadiene:
1,3- Butadiene is presumed to be a carcinogen. The Division of Health Effects Evaluation (DHEE, HFS-225) Memorandum of March 3, 2000 is an expedited worst-case estimate of human cancer risk from exposure to 1,3-butadiene as an impurity in food additives. The memo concluded that the exposure to 1,3-butadiene as an impurity in all regulated and petitioned uses of 1,3-butadiene-based polymers for all food contact applications is not expected to exceed 21 pptr, corresponding to an EDI 0.063 μg/p/d or 1.05×10^{-6} mg/kg bw/d. The carcinogenic unit risk for 1,3-butadiene is arrived at 1.4 $(mg/kg\ bw/day)^{-1}$ based on the results of the NTP study in mice. Thus, the worst-case, upper bound lifetime cancer risk from exposure to 1,3-butadiene from all regulated and petitioned uses of 1,3-butadiene-based polymers for all food contact applications will not exceed 1.5×10^{-6}.

The dietary exposure to 1,3-butadiene from the n-octanol used as a food additive in this FAP is 1.9 ng/p/d or 3.2×10^{-8} mg/kg bw/d, corresponding to a carcinogenic risk 4.4×10^{-8} as determined by multiplying the EDI (3.2×10^{-8} mg/kg bw/d) by the unit risk for 1,3-butadiene [1.4 $(mg/kg\ bw/day)^{-1}$]. That is far below the risk level 1.5×10^{-6}. We have no further questions for 1,3-butadiene as an impurity in this FAP.

SUMMARY

We have no further questions for this FAP.

Yan Gu, Ph.D.

INIT:
Linda S. Pellicore, Ph.D.

HFS-200 (Tarantino)
HFS-205 (Pauli)
HFS-206 (Angeles)
HFS-207 (Pellicore, Gu)
HFS-246 (Costantino)