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ORIGINAL SUBMISSION

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röhm enzyme finland oy
A Company of the Hüls Group

16 October 1998 1(1)

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Premarket Approval
200 C st., SW.
WASHINGTON, DC 20204
USA

FDA NOTIFICATION OF THE GRAS DETERMINATION

Dear Sir / Madam,

We would hereby like to notify of the generally recognized as safe (GRAS) determination of the enzyme preparation COROLASE LAP, an exo-peptidase produced by ***Aspergillus oyzae*** for use as a food processing aid.

The determination of the GRAS status of this product has been made by Dr Michael W. Pariza and Dr Joseph F. Borzelleca (Enclosure). Based on the information provided by the manufacturer, Rohm Enzyme GmbH, they have concluded that COROLASE LAP is safe for use as a food processing aid under current GMP as specified by the manufacturer and further that the available information supports GRAS status for this product.

Yours sincerely,

Kaarina Taimisto
Manager, Product Safety and Regulatory Affairs
Rohm Enzyme Finland Oy

Enclosures 1

cc. Mr Albrecht Höhn
Rohm Enzyme GmbH

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[redacted]

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Evaluation of the Safety of ***COROLASE LAP***

COROLASE ***LAP*** is an exo-peptidase product. The gene for the expo-peptidase activity was derived from a strain of Aspergillus soiae, and subsequently cloned into a strain of A. oryzae. *COROLASE LAP* is preferably used together with endo-peptidases (proteases) for the hydrolysis of proteins from animal or vegetable sources, for example casein, whey and soy proteins. Peptides formed by proteolytic activity are then further degraded by *COROLASE LAP*. *COROLASE LAP* is used at a concentration of up to 0.8% of a food product or ingredient.

We have been asked by ROHM ENZYME c/o HULLS AMERICA INC. (the manufacturer) to assess the safety of *COROLASE LAP* for use as a food processing aid. To assist us in this effort the manufacturer provided us with an appropriate search of the scientific literature on *Aspergillus*, the materials and procedures used in the genetic modification, and other relevant material including information relating to the production organism and its genetic manipulation, and manufacturing specifications. In reviewing this material and evaluating the safety of *COROLASE LAP* **we** employed the principles and procedures recommended by the International Food Biotechnology Council (Regulatory Toxicology and Pharmacolosv 12 [#3, part 2 of 2 parts]:S1-S196, 1990). We focused first on the production organism, and then on the information relating to the safety *of* the enzyme product.

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1. The Production Orsanism

Aspersillus soiae and A. oryzae are closely related harmless molds, both of which have long histories of safe use in food production, for example soy sauce manufacture. These organisms are not pathogenic and do not produce toxins. The manufacturer routinely assays the enzyme product for five common mycotoxins: aflatoxin B_1, ochratoxin A, sterigmatocystin, zearalenone, and T2 toxin. The data supplied by the manufacturer indicate that none of these toxins have been detected.

The manufacturer has provided information indicating that the production organism was prepared using materials and procedures that are appropriate for genetically manipulating an organism intended for the production of a food-grade product. These included the use of plasmid pKD23 and vector p3SR2. Plasmid pKD23 was prepared from *Escherichia coli* K12 strain DH5alpha. It consists of the 1.5 kb genomic DNA sequence for the leucine aminopeptidase gene from A. *sojae* RH 3782, combined with *0.6* kb alpha-amylase promoter sequence from A. *oryzae* DSM 63303, and cloned in the commonly used *E. coli* plasmid pUC19. Vector p3SR2 was prepared from E. coli K12 strain C600. It contains 5.0 kb A. *nidulans* VH1-TSRX6 DNA covering the amdS gene and amdl control region, and a 3.8 kb pBR322 EcoR1-Sall fragment for replication in E. coli.

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2. The Enzyme Product

COROLASE LAP is derived from A. oryzae, and will therefore

contain other proteins and metabolites of this organism in addition to the desired exo-peptidase activity (which was derived from A. soiae). Hence it is important to recognize the long history of safe use of both A. oryzae and A. soiae in food manufacture and the absence of toxins associated with these organisms. Accordingly it is appropriate to conclude that the proteins and metabolites of A. orvzae, including the exo-peptidase from A. soiae, which are present in *COROLASE LAP*, pose no food safety threat.

The manufacturing specifications for *COROLASE LAP* correspond **to** the recommendations given by FAO/WHO's Joint Expert Committee for Food Additives (JEFCA) and the Food Chemicals Codex (FCC) with regard to arsenic, lead, heavy metals, mycotoxins, antibacterial activity, and the absence of microbial pathogens. The manufacturing Process Description provided to us appears to be appropriate for the manufacture of a food processing aid. The Technical Information provided by the manufacturer describes conditions which appear to us to be appropriate for the use of *COROLASE* ***LAP.***

The recommended use level for *COROLASE LAP* is 0.02%-0.8% of a food product or ingredient, depending on protein concentration. The data supplied by the manufacturer indicate that 8% of the Total Organic Solids (TOS) in *COROLASE LAP* is derived from the production organism. Accordingly, the maximum amount of TOS from the production organism that will remain in a food product or ingredient is 0.00064%.

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Conclusion

Based on the foregoing, we conclude that *COROLASE LAP* is safe for use as a food processing aid under current GMP as specified by the manufacturer. The available information supports GRAS status.

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SUBMISSION END
Submission End

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