



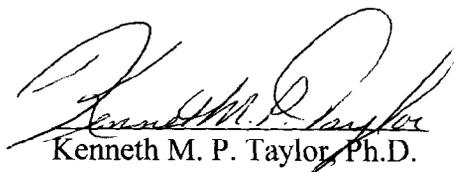
**Memorandum**

0437 '03 JAN 27 P2:25

Date: January 16, 2003  
From: Chemist, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821  
Subject: 75-Day Premarket Notification of New Dietary Ingredients  
To: Dockets Management Branch, HFA-305

Subject of the Notification: creatine ethyl ester (Cre-Ester™)  
Firm: Pro-Nutrient Technologies, Inc.  
Date Received by FDA: September 6, 2002  
90-Day Date: December 9, 2002

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

  
Kenneth M. P. Taylor, Ph.D.

Attachments

95S-0316

RPT154



NOV 22 2002

Samuel C. Augustine, Pharm. D.  
President  
Pro-Nutrient Technologies, Inc.  
11515 North 84<sup>th</sup> Street  
Omaha, Nebraska 68122

Dear Dr. Augustine:

This letter acknowledges receipt of a new dietary ingredient notification, dated September 6, 2002, submitted to the Food and Drug Administration (FDA) for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) [section 413 (a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)] and 21 Code of Federal Regulations (C.F.R.) 190.6. FDA received your submission on September 10, 2002. Your submission notified FDA that you intend to market creatine ethyl ester HCl and creatine ethyl ester bisulfate as a new dietary ingredient.

Your notification further states that creatine ethyl ester is intended for use in dietary supplements and will be marketed in 250 mg and 500 mg capsules under the trade name Cre-Ester™. The dosage range will be between 500 mg to 5 g, with a maximum daily intake of 30g.

In accordance with 21 U.S.C. 350b(a)(2), a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient must submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into commerce. This information must include the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the new dietary ingredient is deemed to be adulterated under 21 U.S.C. 342 (f)(1)(B), because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness and injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing creatine ethyl ester will reasonably be expected to be safe.

Your submission contains no information, nor provides evidence to establish historical use, if any, to reach a conclusion that your product, when used under the conditions recommended or suggested in the labeling will reasonably be expected to be safe.

Your submission contains 56 articles of references addressing creatine supplementation. These articles includes topics such as creatine and creatinine metabolism, creatine monohydrate supplementation in athletes, clinical pharmacology of creatine monohydrate, the role of creatine on human performance, the role of creatine on protein quality of meat products, potential health implications of creatine, and creatine deficiency. Reference 19 describes safety studies of Creapure™ (creatine monohydrate) and reference 21 provides a summary of more than 30 human studies of creatine use. Such information is likely of limited utility in evaluating the safety of creatine ethyl esters. The studies supplied with the notification do not appear to be relevant to an evaluation of the safety of the creatine ethyl ester product that is the subject of your notification. Your notification fails to explain the relationship between your substance and the substances used in the references submitted. Therefore, your notification does not meet the requirements establishing history of use or other evidence of safety when used as recommended or suggested as required by 21 CFR 190.6(b)(4).

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that creatine ethyl ester HCl and creatine ethyl ester bisulfate (Cre-Ester™), when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

If you decide to submit a new notification, it would be helpful if you would describe your basis for determining that the substance you identify as the new dietary ingredient is included in the definition of a dietary ingredient under 21 U.S.C. 321(ff)(1).

Your submission will be kept confidential for 90 days from the date of receipt, and after December 9, 2002, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public. Prior to December 9, 2002, you may wish to identify in writing specifically what information you believe is proprietary.

Page 3 – Samuel C. Augustine, Pharm. D.

Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Dockets.

Please contact me at (301) 436-2371, if you have any questions concerning this matter.

Sincerely yours,

A handwritten signature in black ink that reads "Felicia B. Satchell". The signature is written in a cursive style with a large initial 'F' and a long, sweeping tail on the 'l'.

Felicia B. Satchell

Director

Division of Standards

and Labeling Regulation

Office of Nutritional Products, Labeling

and Dietary Supplements

Center for Food Safety

and Applied Nutrition

**PRONUTRIENT TECHNOLOGIES, INC.**  
11515 NORTH 84<sup>TH</sup> STREET  
OMAHA, NE 68122  
(402) 573-6500

Friday, September 06, 2002

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD, 20740-3835  
Telephone Number: (301) 436-2371

Re: New Dietary Ingredient Notification – Creatine Ethyl Ester, (Cre-Ester™)

Please find enclosed an original and five copies of the “Notification of marketing of a new dietary ingredient – Creatine Ethyl Ester”, submitted pursuant to section 413 of the Federal Food, Drug and Cosmetic Act. We wish to keep the highlighted areas of the notification as proprietary information. Thank you for your attention to this matter.

Respectfully submitted,



Samuel C. Augustine, R.P., Pharm. D., BCNP, FAPhA  
President

encls



Friday, September 06, 2002

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD, 20740-3835  
Telephone Number: (301) 436-2371

Re: New Dietary Ingredient Notification – Creatine Ethyl Ester, (Cre-Ester™)

Please find enclosed an original and five copies of the Notification of marketing of a new dietary ingredient – Creatine Ethyl Ester submitted pursuant to section 413 of the Federal Food, Drug and Cosmetic Act.

**1.1 Name and address of the distributor and manufacturer**

The distributor of the creatine ethyl ester shall be:

Pro-Nutrient Technologies, Inc.  
11515 North 84<sup>th</sup> Street  
Omaha, NE 68122  
Phone: (402) 573-6500  
Fax: (402) 573-7646

Contact person:  
Sam Augustine, Pharm. D.  
President  
saugusti@unmc.edu  
Phone: (402) 573-6500  
Fax: (402) 573-7646

Creatine ethyl ester shall be manufactured for Pro-Nutrient Technologies by:

Mr. Mark Faulkner  
Vireo Systems, Inc.  
305 Williams Avenue  
Madison, TN 37115-2626  
Toll Free (800) 251-4166  
Local (615) 865-8310  
Fax (615) 865-8327

## **1.2 Name of New Dietary Ingredient**

The new dietary ingredient shall be:

**Creatine Ethyl Ester HCl (Cre-Ester™), CAS Registry Number 15366-32-2; Creatine Ethyl Ester bisulfate (Cre-Ester™), CAS Registry Number pending.**

The biological responses and safety considerations described below are the same for both salt forms.

### **1.3.1 Description of the dietary supplement or dietary supplements that contain the new dietary ingredient**

Cre-Ester™ will be manufactured under cGMP conditions by Vireo Systems, Inc, supplied, enclosed and contained in vacuum-sealed plastic lined PVC 20-kilo drums for use as a bulk raw material. All lots of Cre-Ester™ will undergo quality assurance testing prior to packaging and shipment. The raw bulk product will consist of at least 95% Cre-Ester™, with creatine and creatinine constituting the remaining material. The content of Cre-Ester™, creatine and creatinine will be determined using nuclear magnetic resonance (NMR) spectroscopy and/or high performance liquid chromatography (HPLC). A representative proton NMR spectra of Cre-Ester™ is shown in Appendix A. Additional proton NMR spectra are provided depicting the creatine ethyl ester (CEE), creatine (CRT) and creatinine (CRN) species to demonstrate the ability of the analytical analysis to discriminate between the three species (Appendix A).

In addition to the bulk raw material, Pro-Nutrient Technologies will produce and market Cre-Ester™ in 250 mg and 500 mg capsules.

### **1.3.2 Level of the new dietary ingredient in the product**

Recommended daily dosing of Cre-Ester™ shall be 500 milligrams to 5 grams per day, taken in a single or divided daily dose. Maximum daily exposure should not exceed 30 grams per day.

### **1.3.3 Conditions of use of the product**

Cre-Ester™ bulk powder is suitable for encapsulation; compression into tablets; or preparation as a powder for pre-mixed drinks, ready to mix drinks and consumable bars.

Pro-Nutrient Technologies will market Cre-Ester™ in 250 mg and 500 mg capsules.

Cre-ester™ is a dietary supplement that helps maintain muscular health. This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, mitigate or prevent any disease.

Cre-Ester™ should not be used by pregnant or lactating women; individuals diagnosed with, or at risk for, renal or hepatic dysfunction; individuals taking Antabuse™ (Disulfiram); or individuals with a known hypersensitivity to any component of the product. Cre-Ester™ should not be used by children under 18 years of age, unless directed by a physician or qualified health care professional.

**The following safety data applies to both salt forms.**

### **2.1.1 History of use or other evidence of safety**

Summary: Creatine ethyl ester (Cre-Ester™) is a pro-nutrient, serving as a source of creatine, a naturally occurring and endogenously synthesized phosphagen, present ubiquitously in mammalian, avian and marine tissue. Creatine is present in the human diet, particularly prevalent in red meat and fish. Creatine has also been supplemented as a variety of salts, including monohydrate, citrate and pyruvate.

Through a simple chemical modification, the acid moiety of creatine is converted to an ester. As a result of the ester modification, the creatine supplement has increased aqueous solubility, improved oral absorption and enhanced tissue delivery. Cre-Ester™ is de-esterified by esterases, present in most tissue and the serum, and the resultant creatine is identical to endogenous creatine formed through a two-step biosynthesis from the amino acids arginine, glycine and methionine.

### **2.1.2 History of use**

Creatine ethyl ester is a structurally related chemical analog of creatine. The difference between creatine and creatine ethyl ester is that the carboxylic acid group of creatine has been masked through the formation of an ester linkage. The masking of the carboxylic acid, results in a creatine-based compound with both increased aqueous solubility and enhanced membrane partitioning compared to the standard creatine monohydrate.<sup>1</sup>

Though creatine ethyl ester has not previously been introduced into the American diet, the constituent components and metabolic end products have long been present in the American diet and are accepted as being safe, when used as recommended within this text. Cre-Ester™ is a salt form (either HCl or bisulfate) of creatine ethyl ester. Creatine ethyl ester is metabolized by esterases, present in many human tissues and within the serum, into creatine and ethyl alcohol.<sup>1</sup>

Creatine is a guanidine compound, supplied to the human body through dietary sources<sup>2-4</sup> endogenous de novo production,<sup>4,5</sup> and supplemented as a variety of creatine salts.<sup>5-7</sup> Creatine plays a vital role as a phosphagen in cellular and sub-cellular bioenergetics.<sup>8-10</sup> Intracellular creatine supplies are not stable as creatine undergoes an irreversible, non-enzymatic degradation, and is excreted as the waste product creatinine.<sup>1,4</sup> The estimated daily turnover for creatine is approximately 2 grams.<sup>4,11</sup> Persons who suffer from rare disorders of failed creatine production or those with low dietary consumption (e.g.

vegans) have lower intracellular concentrations of creatine than those who consume a traditional American diet (omnivores).<sup>4,12-15</sup>

Ethyl alcohol is a byproduct of post-esterase endogenous processing of the Cre-Ester™ pronutrient.<sup>1</sup> A three gram daily dose of Cre-Ester™ yields less than one gram (0.707 g) of ethyl alcohol, a level recognized as safe for other food and health products, such as vanilla extract.<sup>16</sup> A single serving of an alcoholic beverage contains over ten times that amount of ethyl alcohol.<sup>17</sup>

Numerous studies have been published, evaluating the relative safety of creatine salts supplemented to healthy adults, specifically creatine monohydrate.<sup>18-26</sup> These human studies include both short term and long term studies, and have determined that supplementation with creatine monohydrate is not associated with any adverse health effects. No difference was noted in serum markers of liver or kidney function between creatine-supplemented groups as compared to placebo.<sup>19,27-30</sup> Two case reports of kidney dysfunction following creatine use exist within the medical literature, though neither was able to demonstrate a causative relationship with supplement use.<sup>31-33</sup> Creatine is an accepted ergogenic supplement in all major athletic organizations, including: IOC,<sup>34</sup> NCAA,<sup>35</sup> and other major sports organizations.

### **2.1.3 Safety of creatine**

The safety of creatine salts used as dietary supplements have been extensively studied and reviewed. However, anecdotal and media reports have raised concerns over the safety, especially long-term safety, of oral creatine supplementation. The safety of oral creatine supplementation is addressed in a review by Wyss and Schulze,<sup>20</sup> several other reviews worthy of note have been published.<sup>21,22,24,25,36-38</sup> The pyruvate salt of creatine has a pre-market notification on file as a dietary supplement.<sup>39</sup>

#### **2.1.3.1 Anecdotal reports of side effects of oral creatine supplementation**

Weight gain is the only consistent side effect of creatine supplementation, typically in the range of 1-2 kg, though increases as great as 5 kg have been reported.<sup>22</sup> Users have complained of gastrointestinal distress, muscle cramps, muscle strain, dehydration and heat intolerance. These complaints are felt to be due to acute water retention caused by the practice of “loading” creatine (using multiple doses daily for several days, often 20-30 g/day for 5-7 days) as well as the osmotic effect of unabsorbed creatine salts in the intestine, leading to fecal water loss.<sup>22</sup> Cre-Ester™’s markedly improved solubility and more moderate dosing should alleviate these complaints. Rare reports of rash, dyspnea, vomiting, diarrhea, nervousness, anxiety, fatigue, migraine, myopathy, polymyositis, seizures, atrial fibrillation<sup>22</sup> and acute quadriceps syndrome exist.<sup>40</sup> These rare reports represent isolated cases and are often associated with poly-pharmaceutical/nutraceutical use. There is no physiologic or chemical explanation linking creatine as the causative mediator of such effects and they likely represent effects related to other compounds, such as herbal stimulants, laxatives or pharmaceutical elements such as anabolic steroids. Further, such effects, other than weight gain, have not been scientifically proven in

appropriately designed double-blind studies.<sup>37</sup> Surveys of user have shown a higher frequency of certain complaints (e.g. nausea, diarrhea), again related to the osmotic nature of creatine salts.<sup>41</sup> These side effects may be easily avoided for most with proper hydration and an avoidance of excessive dosing schedules, in so far as creatine salts are concerned.<sup>20</sup> Again, Cre-Ester™ will avoid any osmotic related side effects due to its improved solubility.<sup>1</sup>

#### **2.1.4 Creatine supplementation and renal function**

Creatine's effect on renal function is less well established, though several studies have shown no impairment of renal function in healthy adults.<sup>23,27-29</sup> Increasing the body pool of creatine increases serum creatine concentration and urinary excretion rate, though not to a clinically significant degree.<sup>24,40,43,44</sup> Creatinine, a metabolic waste product of creatine, is metabolized, to a limited extent, to methylguanidine.<sup>22</sup> Both creatinine and methylguanidine have been implied as renal toxins, but no minimum toxicity level has been established and oral creatine supplementation is not felt to cause any increased risk in healthy individuals. In fact, creatinine has even been suggested to serve as a free radical scavenger and protect against oxidative stress.<sup>22</sup> A mouse study has reported a minor percentage of oral creatine, after a single dose of 50 mg/kg, is metabolized to methylamine, which is further metabolized to formaldehyde.<sup>45</sup> Formaldehyde favors cross-linking of proteins *in vivo* and chronic methylene administration has caused oxidative damage in rats, possibly being nephrotoxic.<sup>45</sup> Again, there is no evidence from published studies associating oral creatine supplementation with nephrotoxicity in persons with normal renal function.

Two isolated case reports have been published in the literature of renal function change in humans associated with creatine use. The first involved a patient with focal segmental glomerulosclerosis who experienced an elevation in serum creatinine and a decrease in glomerular filtration rate, which resolved upon discontinuance.<sup>32</sup> The second case involved the development of acute interstitial nephritis in a previously healthy young man.<sup>33</sup> A professional baseball player, hospitalized for renal dysfunction, publicly blamed creatine supplementation, but no causative relationship was established.<sup>21</sup> Lastly, an animal model for autosomal dominant polycystic renal disease has shown that oral supplementation of creatine salts resulted in greater cyst growth and renal impairment.<sup>46</sup> The consensus of reviewers is that the extreme rarity of reports, one in a patient with pre-existing renal disease, is insufficient to conclude that creatine adversely affects renal function in healthy individuals.<sup>20,36,37</sup> Creatine use in individuals with a history of renal disease or at increased risk due to genetic or familial factors should be discouraged until this issue is resolved.<sup>20,21</sup> All containers of Cre-Ester™ will bear a warning label advising against use of the product by any person diagnosed with, or at risk for renal dysfunction (see 1.3.3).

#### **2.1.5 Carcinogenic potential of creatine**

A report issued through the media raised concerns about the potential carcinogenicity of creatine.<sup>47</sup> To date, no studies have shown tumor growth stimulation by creatine, with

some studies displaying antitumor activity.<sup>22,48</sup> The possibility of creatine being a precursor to two classes of food mutagens was raised in the report, specifically aminoimidazo-azaarenes (AIA) and nitrosation products of creatine. AIAs are formed under conditions of high heat, temperatures achieved when cooking meat, and the formation of AIAs under physiologic conditions is extremely unlikely.<sup>20</sup> AIAs formation from creatinine *in vitro* at 37°C has been reported, but not corroborated nor confirmed.<sup>49</sup> Cre-Ester™ should be more resistant to creatinine formation, due to the masking of the carboxylic group, further reducing this theoretical risk.<sup>1</sup> Nitrosation of creatine within the stomach is believed to be insignificant to non-existent.<sup>20</sup> At this time, it is felt that there is no evidence attributing a cancer risk to oral creatine supplementation.<sup>20</sup>

### **2.1.6 Production material and supply safety issues**

The variety of sources, both domestic and foreign, have raised concerns regarding the purity of creatine salts and the risks associated with contaminants.<sup>20</sup> The main contaminants of synthetic creatine production, most processes using sarcosine and cyanimide, are dicyanimide, dihydrotriazines and creatinine.<sup>20</sup> These byproducts are toxicologic unknowns, with dicyanimide being known to release HCN gas when exposed to acidic conditions, such as the gastric environment. The impact of these contaminants upon the individual has not been studied and should be avoided to the greatest feasible degree. Cre-Ester™ is manufactured from Degussa Bioactives creatine monohydrate (Creapure™), which has the greatest and most consistent purity as well as the lowest levels of the aforementioned contaminants.<sup>50</sup>

### **3.1.1 Safety of Ethanol**

Ethyl alcohol (C<sub>2</sub>H<sub>5</sub>OH, CAS Registry number 64-17-5) is a product of fermentation or may be produced synthetically from natural gas or petroleum sources. Fermented ethyl alcohol is recognized as GRAS through prior sanction and synthetic ethyl alcohol has been accepted as a suitable alternative<sup>51</sup> Ethyl alcohol meets the “Food Chemicals Codex”, 4<sup>th</sup> ed. (1996, p. 136)<sup>52</sup> and is affirmed as GRAS in 21 CFR 184.1293.<sup>53</sup> Further, ethyl esters of fatty acids produced from edible fats and oils are allowed as direct food additives in 21 CFR 172.225.<sup>54</sup> Other ethyl esters are affirmed as a multi-purpose GRAS food substance, including Citrofol® brand Triethyl Citrate, 21 CFR 184.1911.<sup>55</sup>

## **4.1 Summary**

In summary, based upon the scientific evidence, oral Cre-Ester™ supplementation at the recommended doses should be regarded as safe.<sup>20</sup> No significant health concern has been identified in any controlled human study, nor has any acute or subacute toxicity of creatine in rats or mice, mutagenic activity in the Ames test or negative effects in tolerance tests using rabbits and guinea pigs.<sup>50</sup> Ethanol is a GRAS substance with a long history of common use in human consumption.<sup>56</sup>

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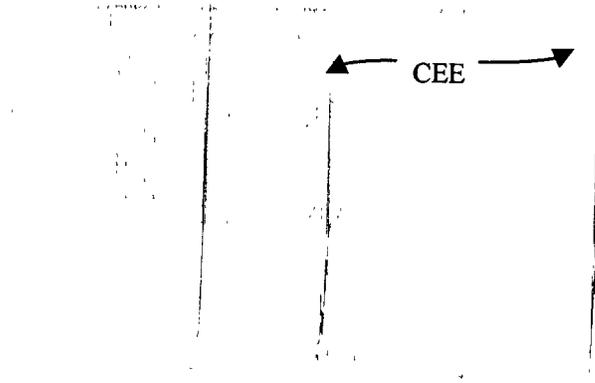
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## Appendix A

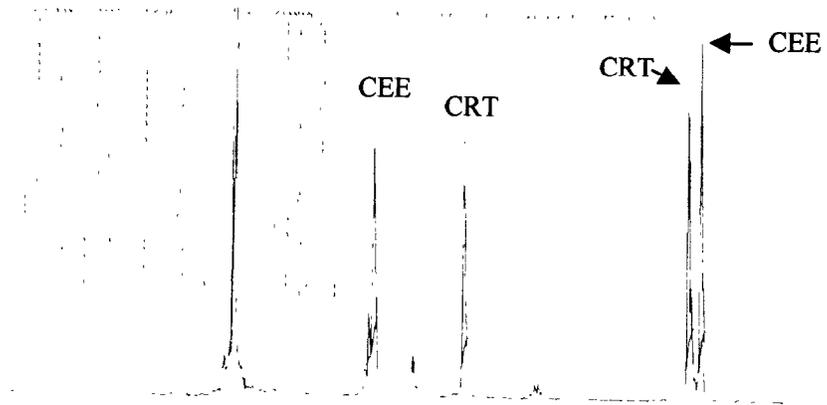
Proton NMR spectra from (a) creatine ethyl ester (CEE) alone, (b) CEE + creatine monohydrate (CRT) in a 1:1 volume ratio, and (c) CEE + creatinine (CRN) in a 1:1 volume ratio. All spectra were done in a D<sub>2</sub>O using a (blank). Creatine ethyl ester has characteristic triplet and quadruplet peaks occurring at 3.07 and 4.29 ppm respectively (Panel A). This can be distinguished from CRT which has triplet and quadruplet peaks at 3.04 and 3.9, respectively (Panel B) and from CRN which has triplet and quadruplet peaks at 3.08 and 4.09 ppm, respectively (Panel C).

APPENDIX A

A. CEE Alone



B. CEE + CRT



C. CEE + CRN

