Analysis of the Efficacy and Safety of Novel Forms of Creatine

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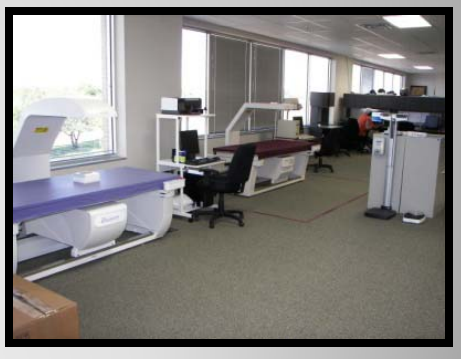

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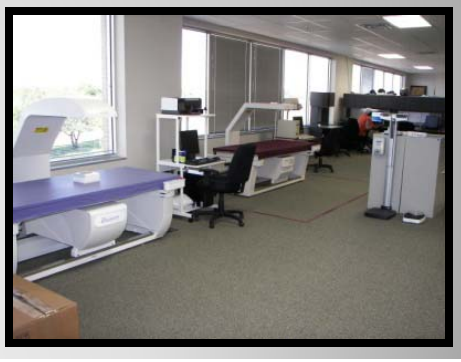

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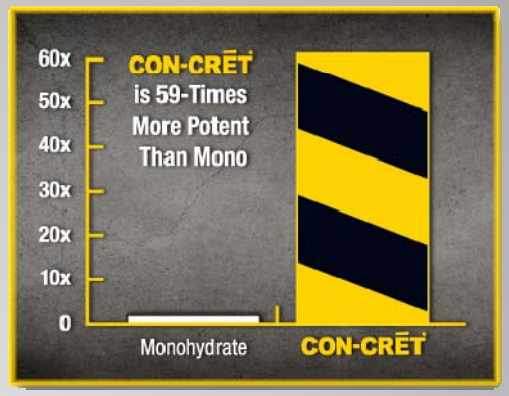
Introduction

- CM is the most common form of creatine found in dietary supplements
- In the US alone, creatine-containing supplements make up a large portion of the estimated $2.7 billion in annual sales of sports nutrition supplements (*NBJ 2009*).
- "New" forms have been marketed with claims of improved stability, solubility, bioavailability, efficacy, and safety
- Most new forms of creatine have not been well-studied and are more expensive than CM
- The legal and regulatory status of newer forms of creatine is at best uncertain.

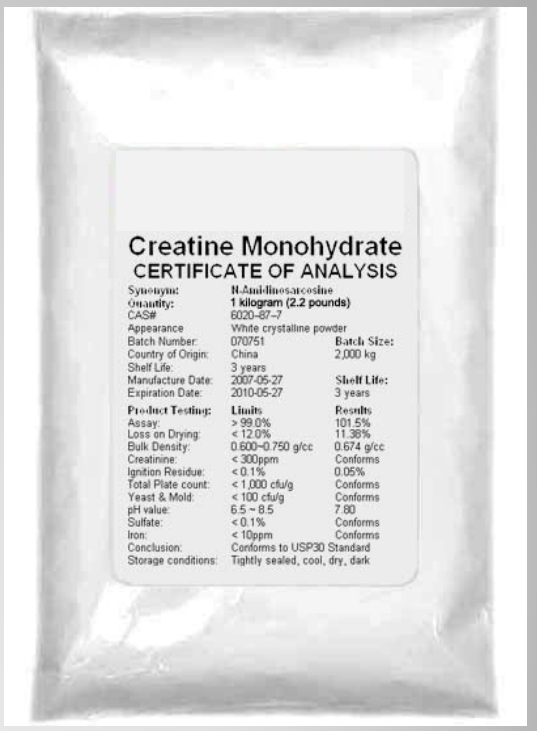


Analysis of the Efficacy and Safety of Novel Forms of Creatine

- Comparison of different forms of creatine
  - Physio-Chemical Properties
  - Bioavailability
  - Ergogenic Properties
  - Regulatory Status
- Bottom Line

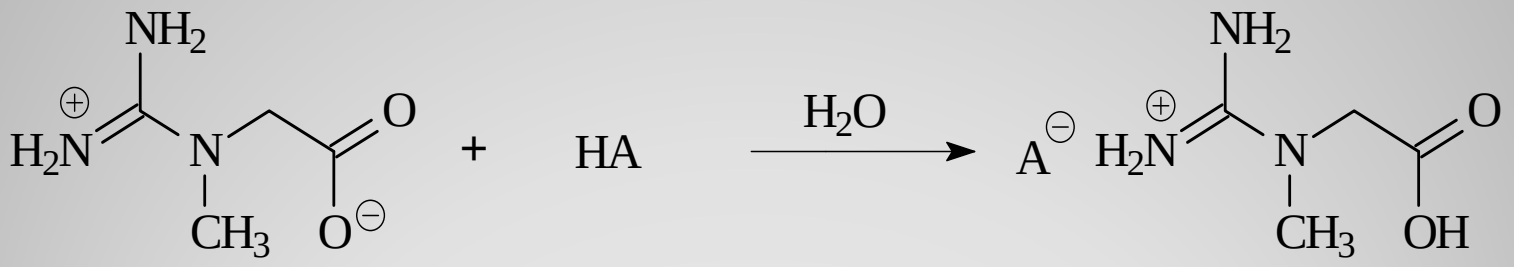
Physio-Chemical Properties

- Creatine crystallizes from water as monoclinic prisms holding one molecule of water of crystallization per molecule of creatine.
- Continued drying of CM results in a loss of the water of crystallization at around 100 °C, yielding in creatine anhydrous.
- Creatine is a weak base with a pk_b value of 11.02 at 25°C.
- As a result creatine can only form salts with strong acids, having a pk_a value of less than 3.98.



Physio-Chemical Properties

- Creatine forms salts by the protonation of its guanidine moiety.



Creatine **Strong Acid** **Creatine-Salt**

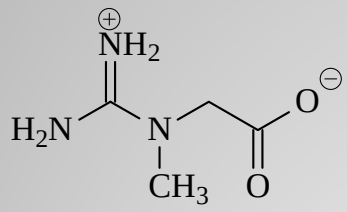
- Creatine is also able to act as a complexing agent.

Physio-Chemical Properties

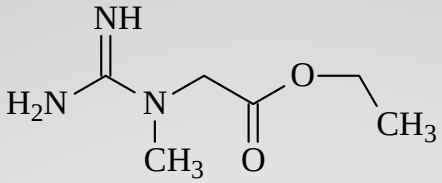
- Creatine salts such as citrate, maleate, fumarate, tartrate (*Negrisoli and Del Corona 1997*), pyruvate (*Pischel and Weiss 1996*), ascorbate (*Pischel et al. 1999*), and orotate (*Abraham and Jiang 2005*) were first introduced to the market place in the late 1990's.
- Creatine and acids with multiple acid moieties such as citric acid can form salts and complexation products.
- For example, the first acid moiety of citric acid is strong enough ($pk_a = 3.09$) to form a salt with creatine, however, the other two moieties ($pk_a2 = 4.75, pk_a3 = 5.41$) should only be able to form complexes with creatine.

Physio-Chemical Properties

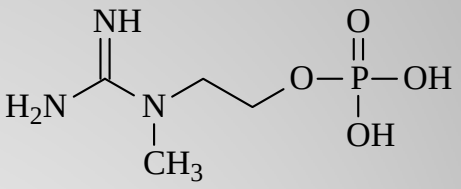
- In addition to creatine and its salts, derivatives of creatine such as creatine ester and creatine alcohols are marketed as dietary supplements in the US.



Creatine



Creatine Ethylester



Creatinol-O-Phosphate

- CE and COP are chemically-altered forms of creatine
- Assumed that the human body will transfer those molecules into creatine upon intake

Creatine Content of Different Forms of Creatine

Form of Creatine	Creatine Content	Difference to CM
Creatine Anhydrous	100.0%	+13.8%
Creatine Monohydrate	87.9%	0%
Creatine Ethyl Ester	82.4%	-6.3%
Creatine Malate (3:1)	74.7%	-15.0%
Creatine Methyl Ester HCl	72.2%	-17.9%
Creatine Citrate (3:1)	66%	-24.9%
Creatine Malate (2:1)	66%	-24.9%
Creatine Pyruvate	60%	-31.7%
Creatine α-Amino Butyrate	56.2%	-36.0%
Creatine α-Ketoglutarate	53.8%	-38.8%
Sodium Creatine Phosphate	51.4%	-41.5%
Creatine Taurinate	51.4%	-41.6%
Creatine Pyroglutamate	50.6%	-42.4%
Creatine Ketoisocaproate	50.4%	-42.7%
Creatine Orotate (3:1)	45.8%	-47.9%
Carnitine Creatinate	44.9%	-49.0%
Creatine Decanoate	43.4%	-50.7%
Creatine Gluconate	40.2%	-54.3%

Solubility

- One major limitation of creatine as an ampholytic amino acid is its rather low solubility in water.
- The solubility of creatine in water increases with temperature in almost a linear manner
- One liter of water dissolves:
  - 6 g of creatine at 4 °C
  - 14 g of creatine at 20 °C
  - 34 g of creatine at 50 °C
  - 45 g of creatine at 60 °C
- The solubility of creatine can be increased by lowering the pH of the solution (rational for creatine salts).

Solubility

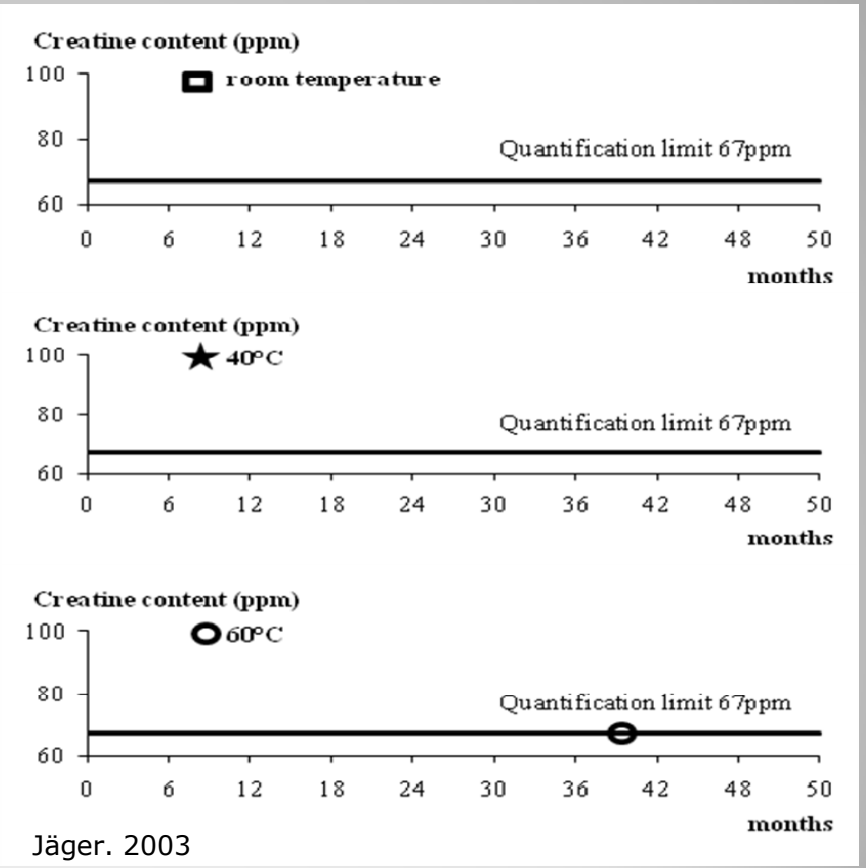
- CM dissolves at 14 g/L at 20°C resulting in a pH of 7.
- A saturated solution of tricreatine citrate (TCC) in water has a pH of 3.2 while a saturated solution of creatine pyruvate (CYP) has a pH of 2.6 (*pyruvic acid is a stronger acid than citric acid*).
- The decrease in pH results in an increase of solubility:
  - 14 g/L creatine monohydrate at 20°C (pH 7)
  - 29 g/L creatine citrate at 20°C (pH 3.2)
  - 54 g/L creatine pyruvate at 20°C (pH 2.6)

Solubility

- Normalized by the relative amount of creatine per molecule (*CM = 87.9%, citrate = 66%, pyruvate = 60%, etc*); solubility at 20°C would be:
  - Creatinol-O-phosphate 5.0 g/L
  - Creatine Monohydrate 12.3 g/L
  - Creatine Citrate 19.1 g/L
    (*1.55-fold better solubility than CM*)
  - Creatine Pyruvate 32.4 g/L
    (*2.63-fold better solubility than CM*)

Stability in Solid Form

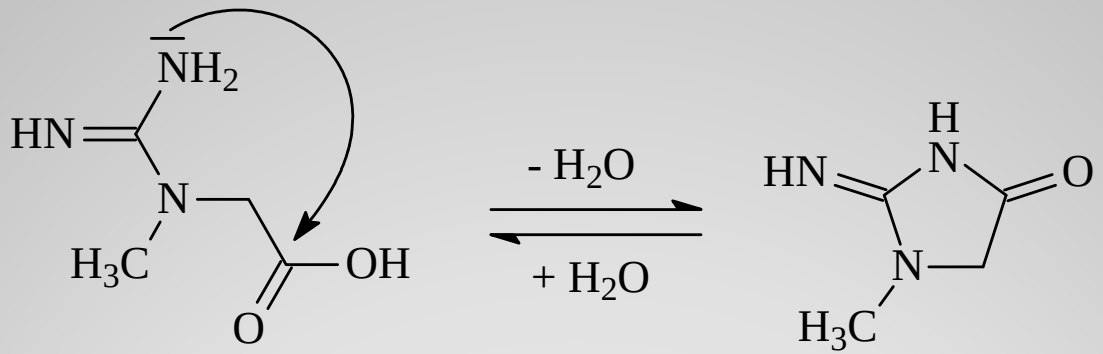
- CM is very stable even when stored at elevated temperatures for years.
- At room temperature and at an 40°C (104°F), CM shows no signs of degradation after more than three years.
- Even when stored at 60°C (140°F), creatinine (106 ppm) was only detected after a period of 44 months (*Jäger 2003*).



Jäger. 2003

Stability in Liquid Form

- Creatine is not stable in aqueous solution due to an intramolecular cyclization (*Howard and Harris 1999*).

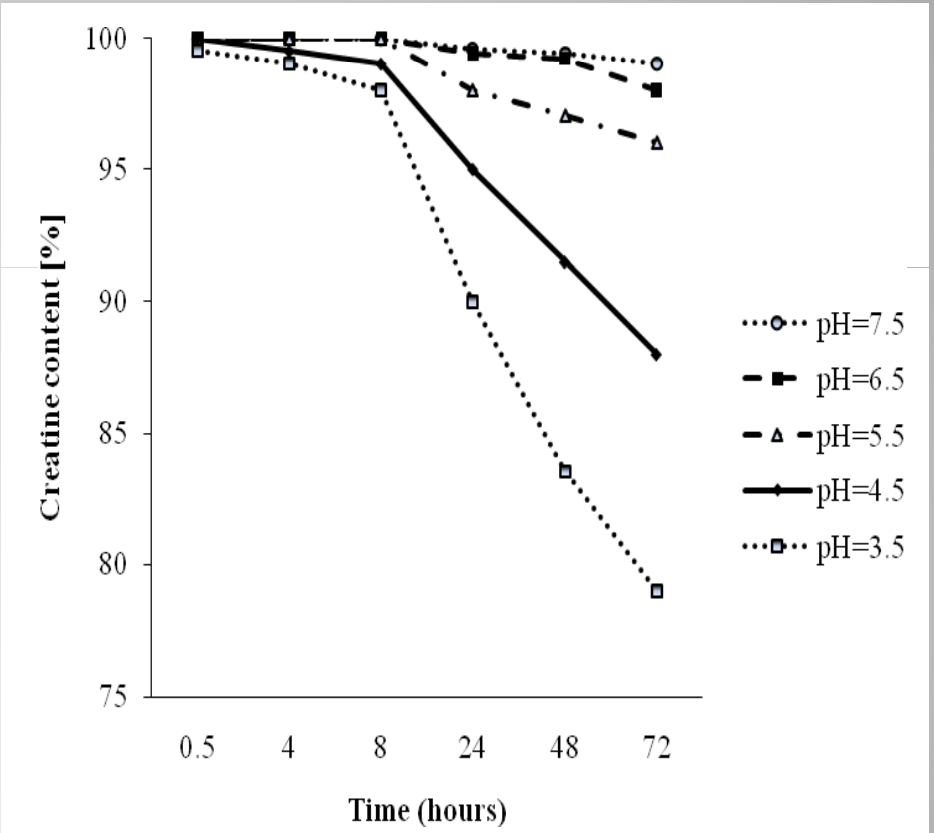


Creatine Creatinine

- The rate of creatine degradation in solution is not dependent on its concentration, but on pH.
- Generally, the lower the pH and higher the temperature the faster the degradation.

Stability in Liquid Form

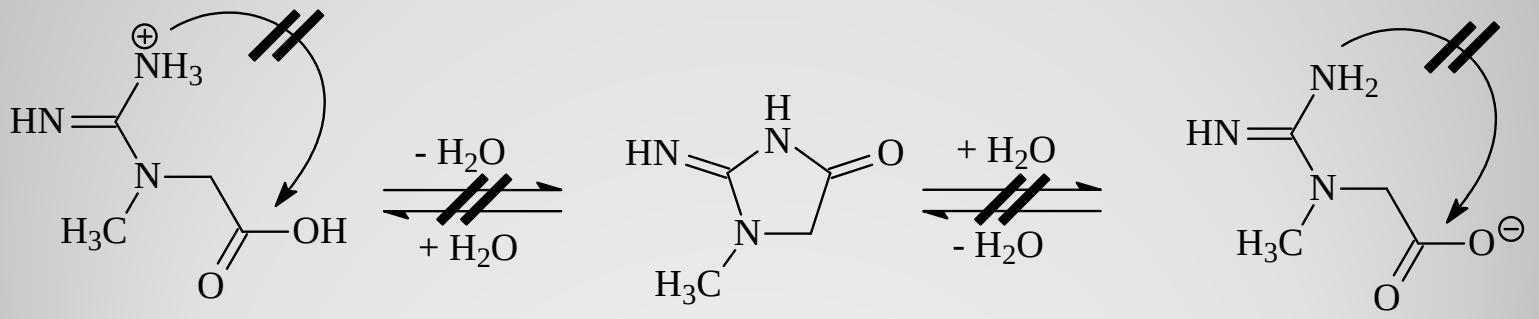
- After 3-d at 25°C, creatine degraded:
  - 4% at pH 5.5
  - 12% at pH 4.5
  - 21% at pH 3.5
- Rapid degradation in solution precludes the manufacture of shelf-stable standard acidic beverages containing efficacious amounts of creatine



Howard & Harris, 1999

Stability in Liquid Form

- The degradation of creatine can be reduced or halted be either lowering the pH under 2.5 or increasing the pH.
- A very high pH results in the deprotonation of the acid group, thereby slowing down the degradation process by making it more difficult for the intramolecular cyclization.
- A very low pH results in the protonation of the amide function of the creatine molecule, thereby preventing the intramolecular cyclization (as in the stomach)
- Digestion ***does not*** significantly degrade creatine into creatinine.



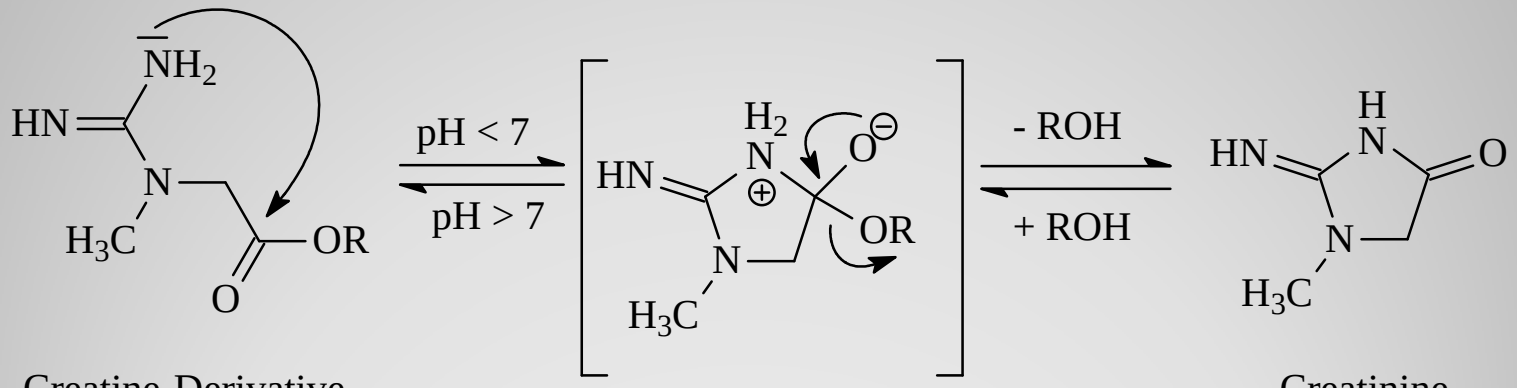
Creatine at very low pH | Creatinine | Creatine at very high pH

Stability of Other Forms

- Some creatine salts appear to be less stable when compared to CM.
- Tricreatine citrate results in creatinine levels of 770 ppm at 40°C (104°F) after 28-d of storage.
- Addition of CHO has been shown to increase stability of some creatine salts (*Purpura et al. 2005*).
- Creatine salts are not expected to have a greater stability in solution; however, the pH lowering effect of the salt might reduce stability compared to CM in the same environment.

Stability of Other Forms

- The degradation of creatine and creatine ester involves intramolecular hydrolysis of a carboxyl acid (*in case of creatine*) or carboxylic ester (*in case of creatine methy- or ethyl ester*) under acidic conditions and the rate of degradation depends on the leaving group



Creatine-Derivative

Creatinine

R = OH (Creatine)
R = OC_2H_5 (Creatine Ethyl Ester)
R = OCH_3 (Creatine Methyl Ester)

Stability of Other Forms

- It has been suggested that the methy ester or ethyl ester groups are better leaving groups than hydroxyl or water and that the degradation into creatinine would be accelerated.
- *Child and Tallon (2007)* reported that CEE was less stable than CM
- *Giese and Lecher* (2009b) investigated the stability of CEE at 37ºC in water and phosphate-buffered saline and the *in vitro* response of CEE to incubation in human plasma by H-NMR analysis
- The conversion of CEE to creatine by the esterases in human plasma was not detected while the only species detected after the incubation period was creatinine.
- It is concluded that CEE is mostly converted into creatinine under physiological conditions encountered during transit through the various tissues, suggesting no ergogenic effect is to be expected from supplementation of CEE.

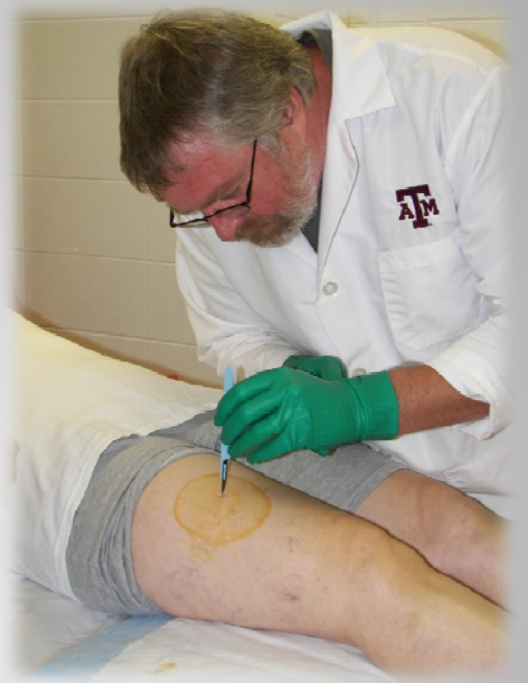
Physio-Chemical Properties

Summary

- The high stability of CM is well documented, whereas the stability of newer forms of creatine (salts, ester, etc) either has not been investigated or appears to be inferior.
- New forms of creatine contain less of the active principle creatine in comparison to CM
- Creatine salts can offer an advantage over CM in regards to solubility.
- Many "new" product claims of greater stability are unsubstantiated

Bioavailability

- Bioavailability refers to both the intestinal absorption and the use of a substance by the body's cells and tissues
- Conclusive proof of an increase in relevant bioavailability can only be gained from assessing the amount of creatine reaching the muscle, measured by muscle biopsy and/or whole body creatine retention assessed by measuring the difference between creatine intake and urinary creatine excretion



Bioavailability

Creatine Monohydrate

- Dietary creatine is presumed to have high bioavailability since intestinal absorption of CM is nearly 100% (*Deldicque et al. 2008*).
- The response to creatine supplementation is heterogeneous, due in part to some non-responders, which might be overcome by alternative forms of creatine and/or ingesting creatine with other nutrients (*Greenhaff 1997b; Greenhaff et al. 1993*).

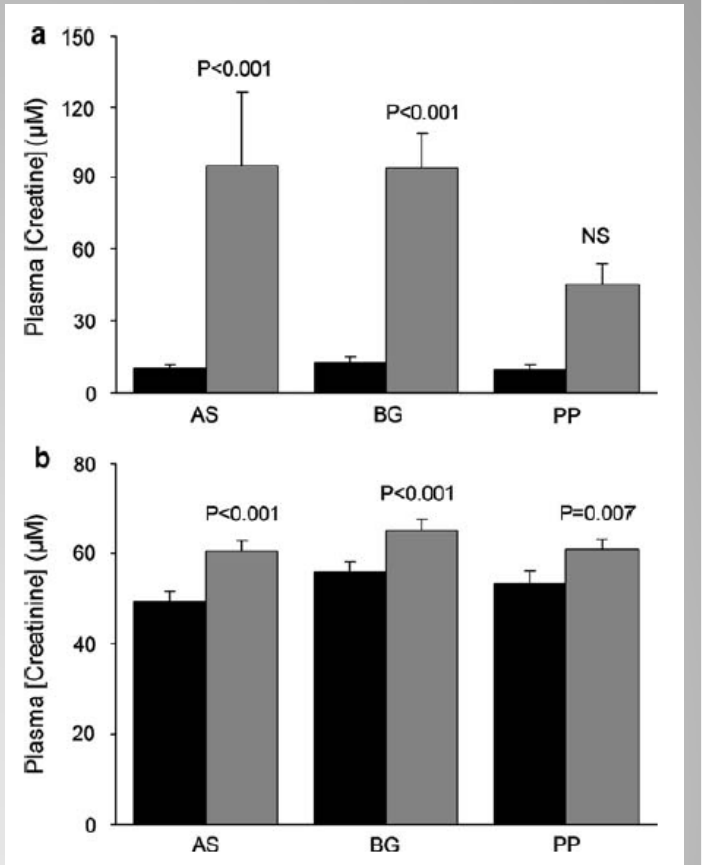


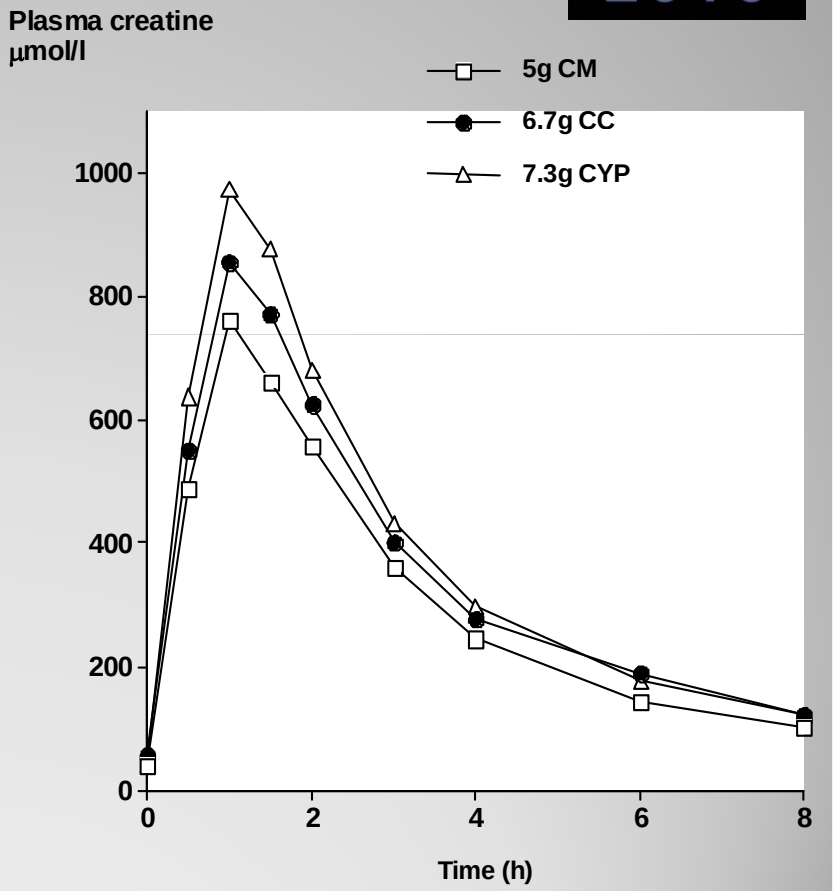
Fig. 5 Plasma creatine **a** and creatinine **b** concentrations measured before (*black*) and after 1 week (*grey*) creatine supplementation (3×2 g per day). *P* values above histograms depict statistical significances of differences between pre- and post- creatine supplementation. *AS* aqueous solution, *BG* beta-glucan-rich bar, *PP* protein-rich bar. The results are expressed as the means ± SEM ($n = 17$)

Deldicque et al. EJAP. 102:133-43, 2008

Bioavailability

Creatine Citrate & Creatine Pyruvate

- In a balanced cross-over designed study, 6 subjects were assigned to ingest a single dose of isomolar amounts of creatine (4.4 g) in the form of CM, tricreatine citrate (TCC), or creatine pyruvate (CPY) followed by measurement of the plasma creatine levels (*Jäger et al. 2007*).
- Mean peak concentrations and area under the curve (AUC) were significantly higher with CYP and TCC (17 and 14%, respectively) in comparison to CM



Jäger et al. J Int Soc Sports Nutr. 4/17, 2007

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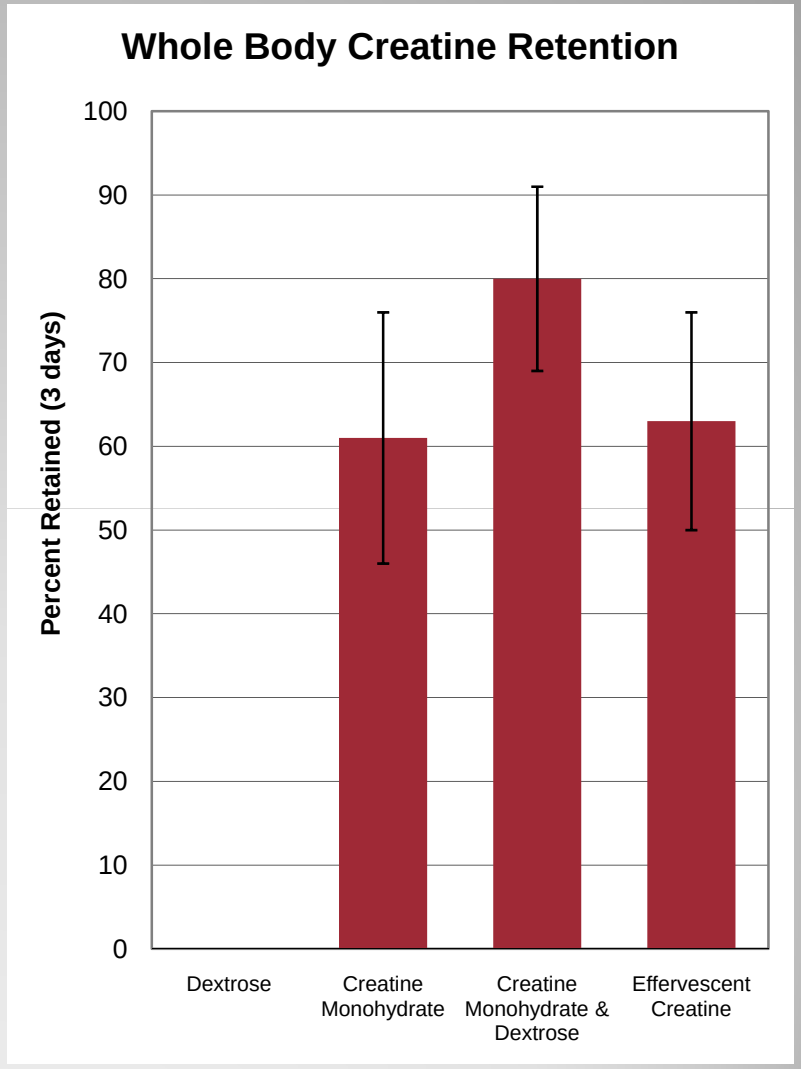
Transforming Lives...

Bioavailability

Effervescent Creatine

- *Greenwood et al. 2003* investigated how different forms of creatine affect whole body creatine retention.
- 16 males were assigned to ingest 5g of dextrose; 5g of CM; 5g of CM plus 18g dextrose; or, an effervescent form of creatine containing 5g of TCC plus 18g dextrose four times/day for 3 days.
- Whole body creatine retention was 61±15% (CM), 80±11% (CM plus dextrose), 63±13% (TCC)



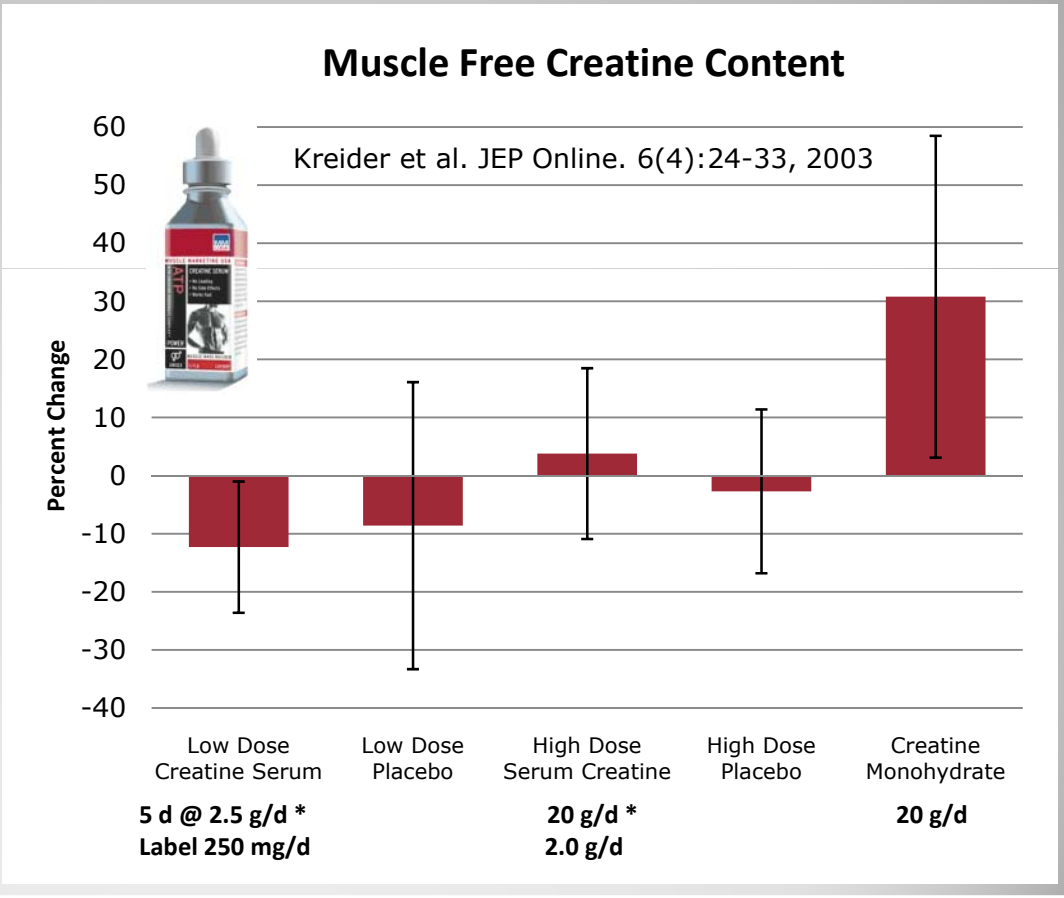
Greenwood et al. JEP Online. 6:37-43, 2003

Bioavailability

Serum Creatine

CM supplementation significantly increased muscle Free Cr content by 31±28 %

Serum Creatine had no affect on Free Cr, TCr, or PC



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Transforming Lives...

Bioavailability

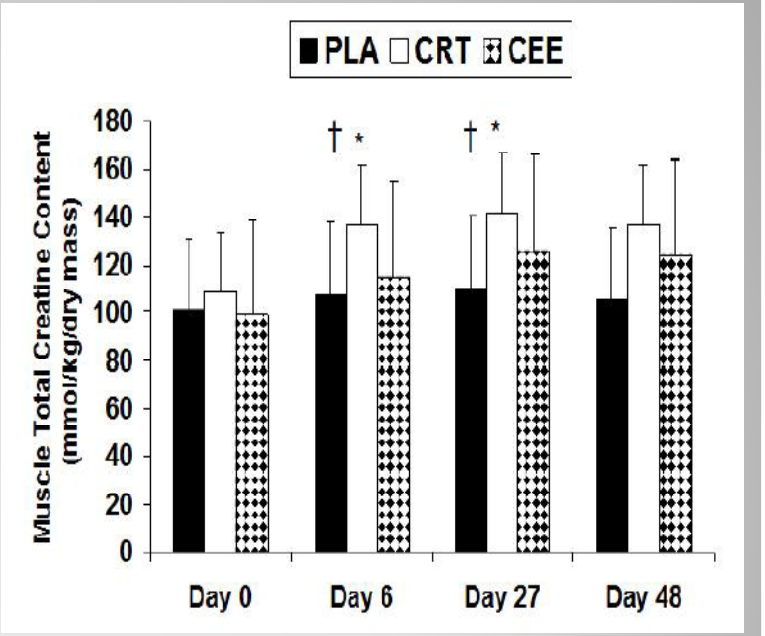
Colloidal CM

- An alternative dissolved form of creatine is colloidal CM.
- CM is dissolved in its own crystal water and dispersed into a stable protective polymer matrix containing carbohydrates (*Kessel et al. US 6,689,299 B2, 2004*).
- The product is claimed to be the only solubilized form of powdered creatine in the market, making it more bioavailable and stable.
- No evidence has been published to date to substantiate any benefit of this form of creatine.

Bioavailability

Creatine Ethyl Ester

- *Spillane et al. 2009* compared the effects of supplementing the diet with a placebo, CM, or CEE during 42-days of training.
- Serum creatinine levels were significantly increased in the CEE group after 6, 27, and 48 days of supplementation.
- While CEE supplementation promoted a modest increase in muscle TCr, it was less than the CM group.



Spillane et al. J Int Soc Sports Nutr. 6/6, 2009

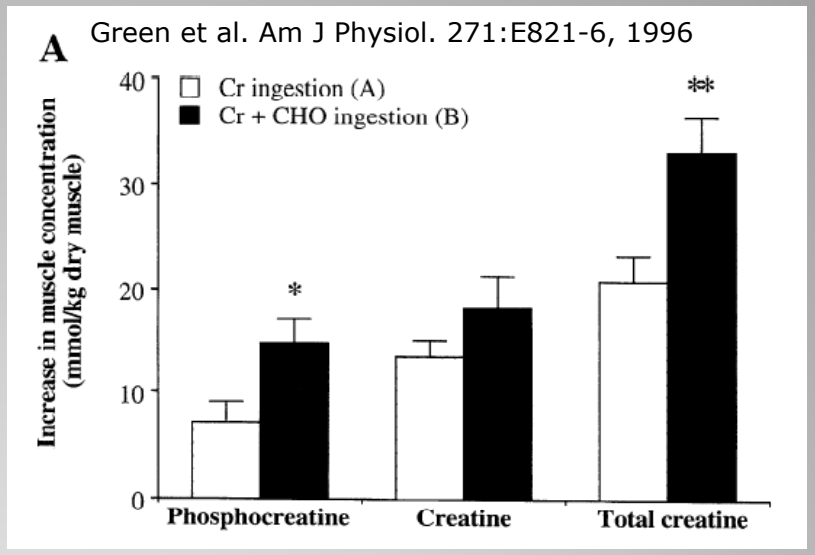
Bioavailability

CM with CHO and PRO

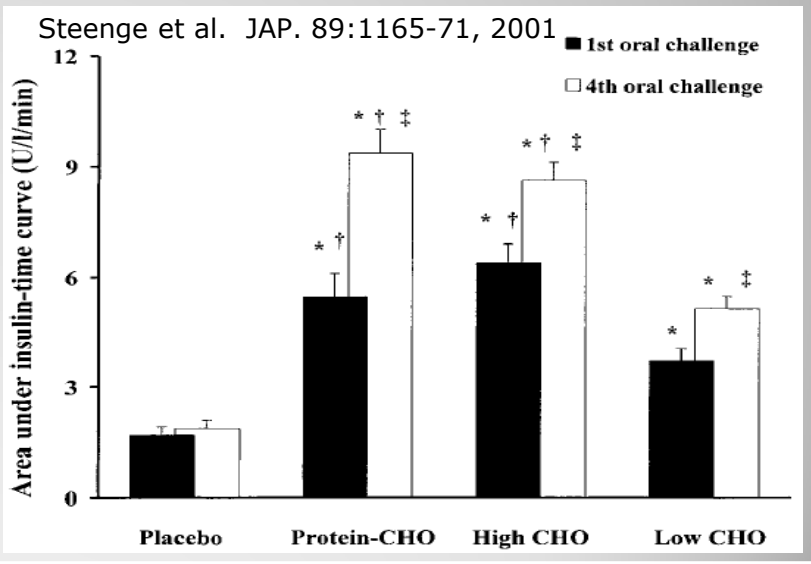
- *Green et al (1996a; 1996b)* demonstrated that co-ingesting creatine (5 g) with large amounts of glucose (e.g., 95 g) enhanced creatine and carbohydrate storage in muscle.

- *Steenge et al. (2000)* found ingesting creatine (5 g) with 47–97 g of carbohydrate and 50 g of protein also enhanced creatine retention.

Green et al. Am J Physiol. 271:E821-6, 1996



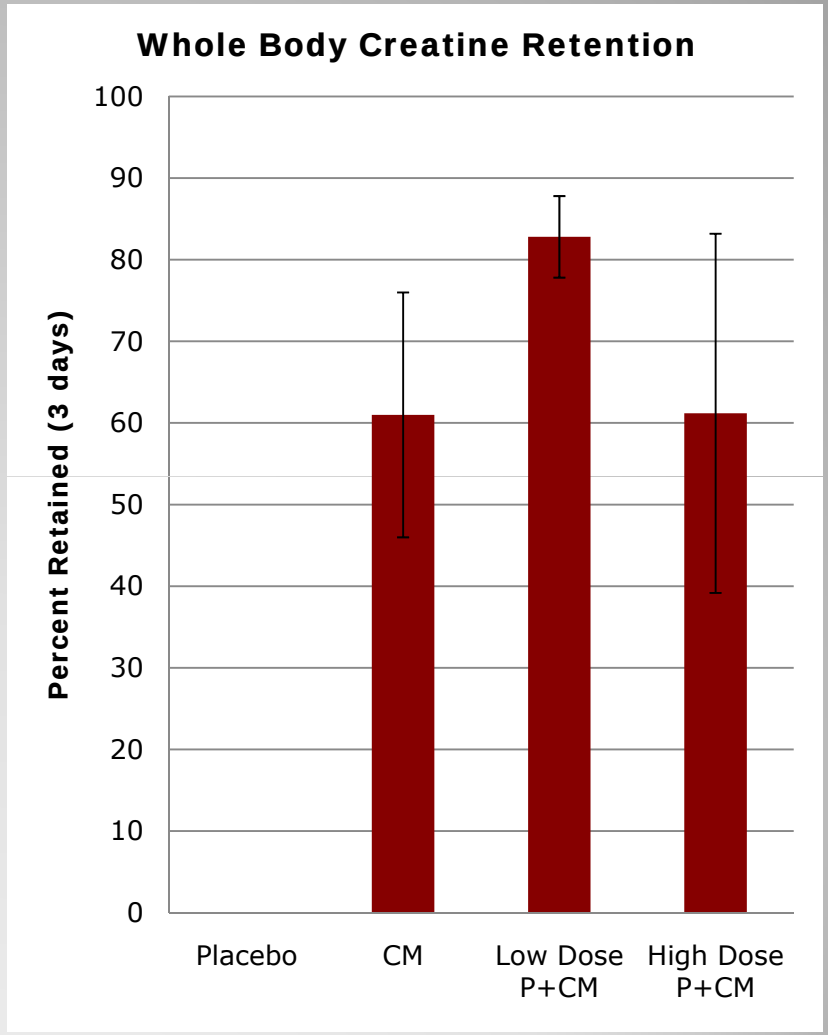
Steenge et al. JAP. 89:1165-71, 2001



Bioavailability

CM with D-Pinitol

- *Greenwood et al. 2001* examined whether co-ingesting creatine with D-pinitol influences whole body creatine retention.
- Results revealed that whole body creatine retention was significantly greater in the low dose D-Pinitol group in comparison to the group ingesting CM alone with no differences seen with higher dose of D-Pinitol.
- *Kersksick et al. 2009* did not find greater creatine retention or training adaptations with 4-wks of D-pinitol & CM intake

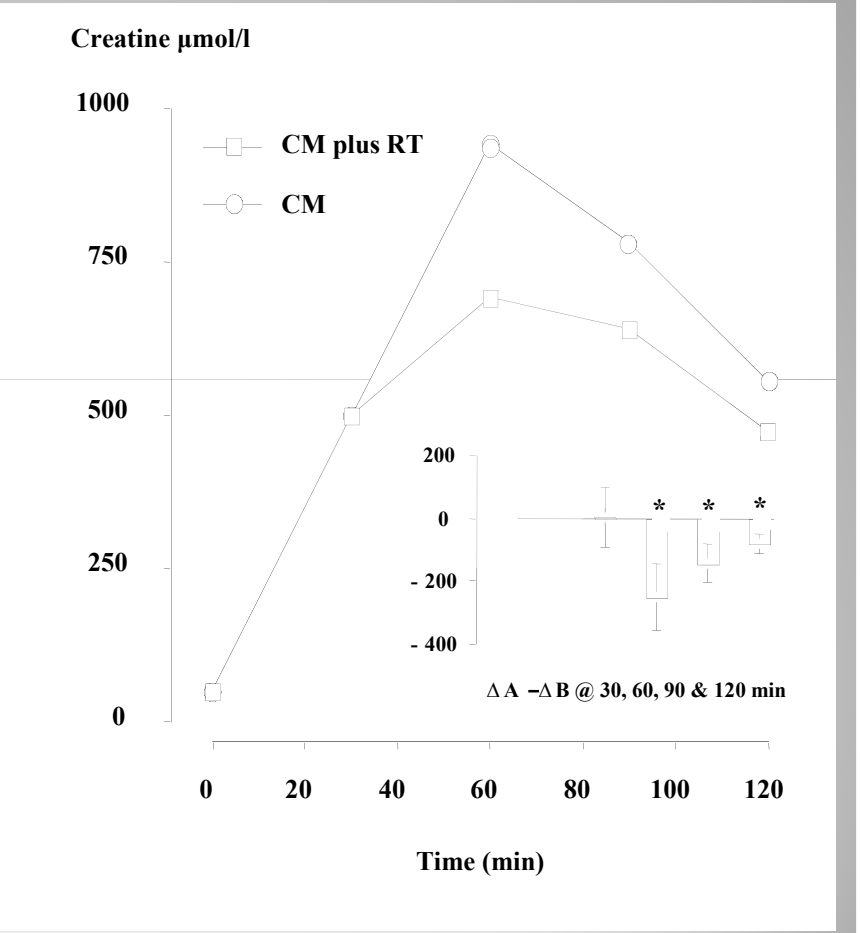


Greenwood et al. JEP Online. 4(4):41-47, 2001

Bioavailability

CM with Russian Tarragon

- Russian Tarragon (*artemisia dracunculus*) is an ethanolic extract that appears to have antihyperglycemic activity when combined with CM (*Jäger et al. 2008a; Wang et al. 2008*).
- *Jäger et al. 2008a* reported that RT influences plasma creatine levels during the ingestion of CM in a similar manner than glucose and protein.
- Further research is needed to evaluate the effects of RT on creatine uptake and retention in muscle before conclusions can be drawn



Jäger et al. 2008a

Bioavailability

Summary

- CM supplementation promotes significant increases in muscle creatine levels in most individuals.
- There is some evidence that co-ingestion of CM with various nutrients (e.g., carbohydrate, CHO/PRO) may enhance creatine uptake to a greater degree.
- There is no evidence that effervescent creatine, liquid creatine, and/or CEE promotes greater uptake of creatine to the muscle.
- Rather, there is some evidence that some of these forms of creatine may be less effective and/or be of greater clinical concern in terms of safety.

Ergogenic Properties

Creatine Monohydrate

- Numerous studies have found that CM supplementation increases muscle phosphagen levels generally by 10-40% (*Harris et al. 1992a; Hultman et al. 1996*).
- Acute and chronic supplementation of CM has been reported to improve performance primarily during high intensity, intermittent activities (*Greenhaff 1997a; Kreider 2003*).
- Numerous studies have shown that CM supplementation during training promotes greater gains in performance and/or fat free mass (*Cribb and Hayes 2006; Kreider et al. 1998; Volek et al. 1997; Willoughby and Rosene 2001; Willoughby and Rosene 2003*).
- The only clinically significant side effect has been weight gain.
- CM has proven to be one of the most effective, safe, and well-studied ergogenic aids.

Ergogenic Properties

Creatine Pyruvate

- Research on the ergogenic value of CYP is mixed
- *Van Schuylenbergh et al. (2003)* reported that ingesting 7 g/d of CPY for 7-d did not beneficially impact endurance capacity or intermittent sprint performance in well-trained cyclists
- *Nuuttilla (2000)* reported that 7.5 g/d of CPY for 5-days increased paddling speed and decreased lactate in Olympic canoeists.
- *Jäger et al. (2008b)* investigated the effects of 28-d of CPY (5 g/d) and Cr-Cit (5 g/d) on handgrip performance.
- Researchers found that CPY and Cr-Cit intake significantly improved performance during intermittent handgrip exercise of maximal intensity with some evidence that CPY may have more favorably affected endurance capacity.

Ergogenic Properties

Creatine Citrate

- Cr-Cit supplementation (4 × 5 g/d for 5-d) has been found to increase anaerobic working capacity (AWC) in healthy physically active women (*Eckerson et al. 2004*)
- Cr-Cit supplementation has been reported to delay the onset of neuromuscular fatigue during cycle ergometry (*Smith et al. 2007*).
- In a recent study, Cr-Cit supplementation increased VANT during intensity interval training (*Graef et al. 2009*).
- Although these studies are interesting, none of those studies compared Cr-Cit to CM and gains observed are similar to those reported with CM.
- More research is needed to compare Cr-Cit to CM before it can be concluded that Cr-Cit has any additional benefits.

Ergogenic Properties

Creatine Ester

- *Spillane et al. (2009)* studied the impact of CM and CEE on training adaptations in resistance trained individuals.
- 30 male resistance-trained athletes were randomly assigned to ingest in a double-blinded manner 0.30 g/kg/day FFM (about 20 g/day) of either a placebo, CM, or CEE for 42 days
- CEE did not promote greater increases in muscle TCr, body mass, FFM, strength, or sprint performance.
- CEE increased plasma creatinine levels to a greater degree suggesting it is degraded to a greater degree and may possess greater safety concerns.
- CEE has no apparent ergogenic value over CM

Ergogenic Properties

Creatine Containing Formulations

- Ingesting CM with vitamin/mineral fortified CHO and PRO supplements promote greater gains in strength and FFM than CHO or CHO/PRO supplements alone (*Kreider et al. 1996; Kreider et al. 1999; Cribb et al. 2007a; Kreider et al. 1998*).
- Co-ingesting CM with different types of PRO may have differential effects on gains in FFM and/or training adaptations (*Kerksick et al. 2007; Cribb et al. 2007b*).
- Co-ingesting CM with other potentially ergogenic nutrients like β-HMB (*Jowko et al. 2001*), beta-alanine (*Hoffman et al. 2006*), phosphates (*Eckerson et al. 2005*), and alpha-lipoic acid (*Burke et al. 2003b*) may have some additive effects.
- These studies and others support contentions that including CM in nutritional formulations may promote additive and/or synergistic effects on training and/or performance.

Ergogenic Properties

Summary

- The vast majority of peer-reviewed studies investigating the ergogenic properties of creatine have studied CM
- There is some data showing the efficacy of creatine salts (e.g., CYP, Cr-Cit) on performance but no studies showing greater benefits than CM
- There is no evidence that creatine serum, CEE, or other newer forms of creatine provide greater ergogenic benefit
- Adding CM to CHO/PRO can provide additive benefits
- Some evidence that co-ingesting CM with β-HMB, β-Alanine, phosphates, and alpha-lipoic acid may have some additive effects

Retail Cost of Different Types of Creatine

Type of Creatine	Creatine Content (%)	Cost / kg (USD)
Creatine Monohydrate (Creapure®)	**87.9**	**$29.99**
Creatine Monohydrate (China) *	87.9	$15.00 - $19.99
Micronized Creatine Powder	?	$18.99
Di-Creatine Malate (3:1)	74.7	$26.91
Creatine Ethyl Ester - HCL	82.4	$30.99
Creatine Ethyl Ester Malate	?	$38.99
Creatine Gluconate	40.2	$46.99
Magnesium Creatine Chelate	?	$49.97
Creatine AKG (2:1)	53.8	$54.15
Creatine Pyruvate	60	$61.16
Creatine Citrate	66	$129.00*
Kre-Akalyn "pH Correct" Creatine	"Concentrated"	$372.67
Conjugated Creatine (Concentrated Creatine HCL)	"Concentrated"	$833.17
Creatine Serum (250 mg/serving)	"Concentrated"	$4,132.00

Estimated cost per serving of available products extrapolated to 1 kg of CM
* Concern over dicyandimide, dihyrotriazine, and creatinine content

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Regulatory Status

United States

- The legal and regulatory status of CM is unequivocal.
- CM appeared on the US market in 1993 (*EAS 1993*) and was considered a "*Grandfathered*" nutrient.
- CM satisfies the statutory requirement of having been present in the food supply in a form that has not been chemically altered.
- Since 1994, a number of new forms of creatine have entered the marketplace with only a few subjected to the requisite 75-day New Dietary Ingredient (NDI) notification to FDA.
- These alternate forms of creatine include, but may not be limited to, Cr-Cit, CEE, COP, CPY, creatine malate (CML), creatine phosphate (CP), creatine-L-carnitinate, (CLC), and tricreatine orotate (TCO).
- A number of apparently unsubstantiated structure and function claims have been made which may be of concern to the FTC.

Regulatory Status

United States

- Only CEE, CPY, CLC and TCO have been the subject of an NDI, submitted to the FDA between 1998-2004 (*FDA 2005*).
- The FDA has objected to each notification (*with the exception of CPY where no decision has yet been posted*) citing one or more of the following reasons as the basis for their objection:
  - The form(s) of creatine may not be legal dietary ingredients as defined by the FD&C Act §201(ff);
  - Inadequate information to conclude that the form(s) of creatine is reasonably expected to be safe due to insufficient safety data and/or failure to establish a history of safe use; and/or,
  - Inadequate information about the chemical identity of the creatine form(s)
- Thus, with the exception of CM (and perhaps CPY), other forms of creatine appear to be on the US market without the proper sanction from FDA or without notification to FDA.

Regulatory Status

Canada

- Creatine is considered a natural health product (NHP) that is regulated by the Natural Health Products Directorate (NHPD) of Health Canada (*NHPD 2003*).
- The NHP regulation requires that all NHP products be licensed and approved by the NHPD, and each is assigned an eight digit numerical code.
- The NHPD has developed a compendium of monographs to assist with the review of the safety and efficacy of many commonly used NHP's (*NHPD 2007*).
- Only CM has been approved for use in NHPs and was recently assigned a monograph by the NHPD (*NHPD 2008*).
- At present there are 17 creatine-containing licensed and approved NHPs, all of which contain CM (*NHPD 2010*).

Regulatory Status

European Union

- In the EU, creatine is regulated as a food supplement, under the Food Supplement Directive (FSD) (EPC 2002) and the Directive on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (FPNU) (*EPC 2001*).
- In 2004 the European Food Safety Authority (EFSA) issued a positive opinion on CM for FPNU (*EFSA 2004*).
- No other opinions have been issued on any other creatine forms, either by EFSA or its predecessor (the Scientific Committee on Food, SCF).

Regulatory Status

Japan

- In Japan, dietary substances are legally classified as food, food additives or "non-drug" (food), and are subject to one of two regulations, both enforced by the Ministry of Health, Labor and Welfare (*MHLW*).
- CM is categorized as a "non-drug" (*MHLW 2009*), and is permitted for use as both a food ingredient and a food additive under the Food Sanitation Law (*MHLW 2001*), allowing it to be imported, distributed and produced as food in Japan.
- New forms of creatine must be approved by the MHLW before they can be imported, distributed and produced in Japan which requires documentation on the safety and similarity to CM.
- Currently two new forms of creatine (Cre-Cit and CPY) have been approved to be imported into Japan.

Regulatory Status

South Korea

- In South Korea, the category of dietary supplements was established through legislation in 2004, and is regulated by the Korean FDA (*Shimizu 2008*).
- New ingredients must be approved by KFDA and are required to have sufficient toxicological and human clinical trial data supporting the safety and efficacy.
- An application for registration of CM was filed with the KFDA in 2005 and was approved for use in dietary supplements in 2008, along with an accompanying health claim (*KFDA 2009*).
- At present, no other forms of creatine have been approved for use in South Korea.

Regulatory Status

Summary

- The legal and regulatory status of CM is unequivocal in the major global markets for dietary or food supplements.
- The status of other creatine forms present in the marketplace and/or subjected to pre-market notification is less clear.
- These alternatives to CM are prevalent in the market, yet don't appear to have met the necessary statutory or regulatory requirements in any of the countries examined.
- In countries where regulatory approval is required prior to use, with the exception of Japan (CC and CPY), none of these forms has achieved approval.
- At present, there do not appear to be any imminent or specific safety concerns associated with any of these alternate forms.
- However, the public health implications remain to be fully realized.

Regulatory Status

Summary

- The presence of newer and typically more expensive forms of creatine with misleading and/or unsubstantiated claims of greater bioavailability, efficacy, and safety sets a negative precedent.
- The reality that companies need not fulfill the necessary registration or notification requirements to satisfy regulatory authorities, but still feel free to market their ingredients without penalty establishes an "unlevel" playing field among competitors.
- This undermines any incentive to invest upfront resources to establish ingredients as safe and efficacious prior to reaching consumers.
- Inevitably, this will result in unintended and unforeseen consequences, which will serve to erode consumer confidence.

Bottom Line

- CM supplementation has been consistently reported to increase muscle phosphagen levels, improve performance, and promote greater training adaptations.
- CM has been found to be a stable form of creatine that is not significantly degraded during the digestive process.
- No medically significant side effects have been reported and the regulatory status of CM is well established.
- The efficacy, safety, and regulatory status of most of the newer forms of creatine have not been well-established.
- There is little to no evidence supporting marketing claims that these newer forms of creatine are more stable, digested faster, more effective in increasing muscle creatine levels, promote greater training adaptations, and/or are associated with fewer side effects than CM.

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