



## Letter to the editor

**Comment on “toxic hepatitis in a group of 20 male body-builders taking dietary supplements” by Timcheh-Hariri et al. (2012)****1. Creatine is an approved, effective and safe dietary supplement that is NOT causing toxic hepatitis!**

In their recent publication in “Food Chem. Toxicol. July 15th 2012 (Timcheh-Hariri et al., 2012) on: “Toxic hepatitis in a group of 20 male body-builders taking dietary supplements”, Timcheh-Hariri et al. report a dramatic picture of 20 body-builders presenting with toxic hepatitis after self-prescribing a number of “dietary supplements which are lesser known”. The subjects ingested a total of three such supplements for a time period of one year. These were: first Phosphagen (Timcheh-Hariri et al. Fig. 1) containing pure creatine-monohydrate, second a formulation called “T-BOMB” with 903 mg of an ingredient called “Optimone 5TM: Five Phase Hormone Optimizing Blend” as one of the main constituents, including some herbal extracts etc. (Fig. 2) and third a supplement with amino acids, a creatine-formulation, sugar, salts and vitamins, as well as an unspecified product called “Insulo Drive!” (Fig. 3). No information is given on any daily dose level of either of these supplements neither on other nutritional or behavioral habits of the body builders.

It is to be greeted that the authors of this paper stress the fact that dietary supplements are not generally under serious investigation for their efficacy and safety and that therefore people consuming certain preparations may expose themselves to more or less severe health risks. Often, products with a high scientific and regulatory data backup are put into the same basket with products for which a similar documentation is lacking, making it difficult for the consumer to decide upon what product to choose. However, in the discussion of their work, the authors themselves apparently have not checked the available safety and regulatory information for creatine-monohydrate and they specifically include and discuss creatine-monohydrate as one of the possible culprits for the reported cases of toxic hepatitis. Already in the introduction they state that “For example, creatine supplementation may cause renal dysfunction and hepatotoxicity” and quote Bizzarini and De Angelis, 2004 as a reference. Bizzarini and De Angelis, however, refer to one single study (Kreider et al., 1998) reporting moderate increases in selected blood parameters in 28 subjects. The dosing in this study (15.75 g/d of creatine-monohydrate for 28 days) does not reflect standard recommendations and prompted the same group to conduct a 21 month study applying a more general supplementation regime (15.75 g/d creatine-monohydrate during 5 days, followed by 5–10 g/day of creatine-monohydrate thereafter) in 116 subjects. None of the serum markers for liver were altered in this comprehensive study (Kreider et al., 2003). Also other groups have investigated this topic and showed that medium to high-dose (5–20 g/day) of creatine

supplementation has no detrimental effects on kidney and liver (Mayhew et al., 2002; Schröder et al., 2005). These results are supported by a number of other publications. In fact, a vast amount of literature with more than 1'000 publications on creatine supplementation does not hint towards any negative health effects of creatine, specifically to any that would affect the liver.

This prompted the “International Society of Sports Nutrition” to a position stand that stated that creatine supplementation is effective and safe, if chemical purity of the substance is guaranteed and guidelines of consumption are followed (Buford et al., 2007). Furthermore worldwide, tens of millions of professional and recreational athletes ingest creatine-monohydrate on a daily basis and no scientifically proven serious side effects of creatine have been reported.

Creatine is a substance naturally found in the diet. The commercial product creatine-monohydrate is a grandfathered dietary ingredient under the US Dietary Supplement Health and Education Act as it has been on safe use on the market even before October 15, 1994 (see CRN list of dietary supplements grandfathered under DESHA from September 1998, <http://www.fda.gov/ohrms/dockets/dockets/05p0305/05p-0305-cr00001-04-Council-For-Responsible-Nutrition-vol1.pdf>). Hence, creatine-monohydrate is not subject for approval as a new dietary ingredient. Daily recommendation values of this nutritional supplement are not established, therefore label information “percent daily value” have to be given with a disclaimer.

The European Association for Food Safety (EFSA) has officially approved a serving of 3 g creatine-monohydrate as safe for all age groups in 2004 as a daily intake of 3 g creatine-monohydrate is similar to the daily creatine turnover rate of 2 g/d (see: <http://www.efsa.europa.eu/de/efsajournal/pub/36.htm>).

The Norwegian Scientific Committee for Food Safety published an assessment of creatine in sports products in December 2012 (see: <http://www.vkm.no/dav/3178aba783.pdf>) confirming the EFSA Opinion, 2004 and recommending that only individuals with impaired kidney function should refrain from creatine.

It is difficult to understand why Timcheh-Hariri et al., 2012 would still point out creatine as the possible culprit for liver toxicity. Instead, they should have looked more closely at the mixed formulations “T-BOMB” and “Insulo Drive!” containing numerous and poorly defined ingredients or even anabolic steroids and other hormones, as suggested by the name of these preparations. Liver toxicity of anabolic drugs and androgenic steroids is well documented (see Neri et al., 2011) and the potential danger of a number of plant-derived nutritional supplements that may act in a toxic way or alter the body's hormone level has been recognized (Borri-  
one et al., 2012).

Also it is hard to understand that the authors did not ask the manufacturer for full and transparent disclosure of what kind of hormones and/or hormone-activating factors are contained in the ominous “Optimone 5TM: Five Phase Hormone Optimizing Blend”.

Knowing this information, it would have been much easier to assign the potential danger, instead the authors mainly concentrated on herbal substances that also were composites of the T-BOMB.

It is also difficult to explain why the reviewers of the work by Timcheh-Hariri et al., 2012 did not request that the hormones and hormone-activating factors most likely to be present in T-BOMB would have to be fully disclosed to give this work and the conclusions drawn a higher scientific significance. This way, one is left with an uneasy feeling and an unsatisfactory situation that did not clarify the issue of which of the compound(s) in the three dietary supplements or supplement mixtures did in fact cause liver toxicity. Looking at the data, however, it is obvious that creatine cannot be the culprit here. By contrast, considering the fact that an adult person, depending on body weight, harbors a total of about 100–150 grams of creatine in the body, mostly in skeletal, heart and smooth muscles, as well as in the brain, nervous tissue, retina, inner ear, gonads, sperm, egg etc., it is hard to imagine any toxicity of creatine-monohydrate for the human body. The daily turnover of creatine, depending on body weight, is between 2 and 4 g per day and this creatine has to be replaced. Approximately 50% of creatine are replaced by endogenous synthesis in the kidney and liver and the other 50% have to be acquired by dietary sources (meat and fish, or by supplementation with creatine-monohydrate (Wyss and Kaddurah-Daouk, 2000)). In the body, creatine exerts a plethora of pleiotropic physiological effects, not only working as a cellular energy booster but also as a cell protectant against a number of stressors (Wallimann et al., 2011; Tokarska-Schlattner et al., 2012). In fact, creatine-monohydrate is already used as a valuable dietary supplement for muscle, bone and neuronal health, especially by the elderly, and as an adjuvant therapeutical intervention for muscular, neuromuscular and neurodegenerative diseases (Wyss et al., 2007; Harris, 2011; Gualano et al., 2012; Wallimann et al., 2011). Finally, creatine-monohydrate seems to exert a rather specific anti-cancer activity (Patra et al., 2012).

The notion by the authors that for many dietary supplements on the market there is insufficient reliable information is to be supported. But we are certain that creatine-monohydrate, as one of the most thoroughly investigated dietary supplements with its excellent, scientifically proven safety record certainly cannot be made responsible for the cases of toxic hepatitis reported by Timcheh-Hariri et al., 2012, and this certainly should have been stressed more clearly in their publication.

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