

Dear Editor,
Dear Reviewers,

We gratefully acknowledge your careful and kind evaluation of our manuscript and your constructive criticism, which really helped us to improve the overall quality of our manuscript. We have commented in detail to all your valuable suggestions and please find in the following a point-by-point response to your comments.

Yours sincerely
Lisa Schmölz

Reviewer: This review article provides an excellent coverage of Vit E metabolism, an important topic in biochemical research; some suggestions for revision are given below. Both the “abstract” and the “core tip” do not actually reflect the content of the manuscript. While the review covers many aspect of Vit E metabolism, more than half of the abstract is dedicated to the description of very specific biochemical reactions of Vit E degradation. There are some misspellings and errors throughout the manuscript (e.g. use of “principle” at pag 47, or “particularly” in the second line of the abstract), which will therefore benefit from professional editing.

We thank the reviewer very much for his kind evaluation and his very helpful suggestions. We have replaced the Abstract and Core Tip with new versions to address the recommendations of the reviewer see below. Furthermore, the paper has been professionally proofread. To remain good readability of the manuscript and to avoid confusion, the respective changes made during language editing have not been highlighted. Despite that, we have not made any changes to the content of the manuscript.

The new abstract reads as follows:

Bioavailability of vitamin E is influenced by several factors, most are highlighted in this review. While gender, age and genetic constitution influence vitamin E bioavailability but cannot be modified, life-style and intake of vitamin E can be. Numerous factors must be taken into account however, *i.e.* when vitamin E is orally administrated, the food matrix may contain competing nutrients. The complex metabolic processes comprise intestinal absorption, vascular transport, hepatic sorting by intracellular binding proteins, such as the significant α -tocopherol-transfer protein (α -TTP), and hepatic metabolism. The coordinated changes involved in the hepatic metabolism of vitamin E provide an effective physiological pathway to protect tissues against the excessive accumulation of, in particular, non- α -tocopherol forms. Metabolism of vitamin E begins with one cycle of CYP4F2/CYP3A4-dependent ω -hydroxylation followed by five cycles of subsequent β -oxidation, and forms the water-soluble end-product carboxyethylhydroxychroman (CEHC). All known hepatic metabolites can be conjugated and are excreted, depending on the length of their side-chain, either via urine or feces. The physiological handling of vitamin E underlies kinetics which vary between the different vitamin E forms. Here, saturation of the side-chain and also substitution of the chromanol ring system are important. Most of the metabolic reactions and processes that are involved with vitamin E are also shared by other fat soluble vitamins. Influencing interactions with other nutrients such as vitamin K or pharmaceuticals are

also covered by this review. All these processes modulate the formation of vitamin E metabolites and their concentrations in tissues and body fluids. Differences in metabolism might be responsible for the discrepancies that have been observed in studies performed *in vivo* and *in vitro* using vitamin E as a supplement or nutrient. To evaluate individual vitamin E status, the analytical procedures used for detecting and quantifying vitamin E and its metabolites are crucial. The latest methods in analytics are presented.

The new core tip reads as follows:

Several factors influence vitamin E bioavailability. Gender, age and genetic constitution cannot be modified but life-style and vitamin E intake can be. Physiological handling of vitamin E involves intestinal absorption, vascular transport, hepatic sorting by intracellular binding proteins, and hepatic metabolism. These processes involve kinetics which vary between the different vitamin E forms. The coordinated metabolism of vitamin E is an effective physiological pathway to prevent excessive accumulation of non- α -tocopherol forms. Interactions with other nutrients or pharmaceuticals occur. To evaluate vitamin E status, analytical procedures to detect and quantify vitamin E and metabolites are crucial. Current state-of-the-art analytics are presented.