



HUMANETICS

March 20, 2003

Constance J. Hardy
Center for Food Safety and Applied Nutrition
Food and Drug Administration

Dear Ms. Hardy:

It has come to my attention that there will be discussion about the issue of what constitutes a metabolite of a dietary ingredient or a natural substance. Unfortunately, I am unable to attend the meeting but I do wish to submit the following comments about this important topic.

I am a former pharmacist and now a board certified physician specializing in Internal Medicine. I have over 20 years of clinical experience and am currently the Chief Medical and Scientific Officer of Humanetics Corporation. Humanetics Corporation has spent the past 14 years in the research and development of new dietary ingredients, at least one of which is a metabolite of an existing dietary supplement ingredient.

On May 14, 1997, Humanetics Corporation in conjunction with General Nutrition Corporation filed a pre-market notification for 7-oxo-dehydroepiandrosterone (7-oxo DHEA), which is a metabolite of DHEA. DHEA is a dietary ingredient that was on the market prior to October 15, 1994. As part of that notification, appropriate documentation was presented to verify that 7-oxo DHEA was indeed a metabolite of DHEA. In addition, Humanetics Corporation performed rigorous toxicology studies to develop a safety profile for 7-oxo DHEA independent of that for DHEA.

Most available references agree on the definition of a metabolite; a metabolite is a product of metabolism. The defined explanation of metabolism is as follows:

“The sum of physical and chemical processes in an organism by which its substance is produced, maintained and destroyed, and by which energy is made available.”

Therefore, for the purposes of this discussion, a metabolite of a dietary ingredient would be a distinct entity produced as a result of the physical and/or chemical processes occurring in an organism. Metabolites of physiologic compounds tend to be derivatives of their parent molecules and are measurable or otherwise identifiable in the organism that produces it.

For example, 7-oxo DHEA as a metabolite of the parent molecule DHEA is measurable in the urine and serum of humans. Similar to DHEA, the concentrations of 7-oxo DHEA decline with age indicating a depletion of the parent substrate.

The issue of metabolites of natural compounds is an intriguing one because an organism may metabolize a parent molecule for a variety of different reasons; (1) it may metabolize it as part of its normal degradation and excretion process, (2) to maintain its activity by converting it to a different form, or (3) to convert it to a more active compound that may have activities completely different from the parent compound. For instance, cholesterol serves as the parent compound for the production of DHEA and DHEA serves as the parent compound for the production of testosterone, all three of which have markedly different physiologic responsibilities and activities. All three compounds are their own distinct entity, measurable in the bloodstream.

According to Section 3 of the DSHEA Act the term “dietary supplement”:

1. **means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:**
 - a. a vitamin;
 - b. a mineral;
 - c. an herb or other botanical;
 - d. an amino acid;
 - e. a dietary supplement used by man to supplement the diet by increasing the total dietary intake; or
 - f. a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause a, b, c, d or e.

Since “metabolite” is not defined in DSHEA, the issue of what constitutes a metabolite is at question. Under this existing definition, a dietary ingredient could be a metabolite of a vitamin, mineral, herb or botanical or an existing dietary supplement already in use.

In my opinion, the accepted scientific definition of metabolism and metabolite as I have described above would be a more than appropriate benchmark to apply to this issue. Using these principles as a guide, a metabolite of any of the compounds described above in Section 3 of the Act would be physical and/or chemical derivations of the parent compound occurring as a result of normal metabolism in a living organism. A metabolite produced in this manner should be measurable or otherwise identifiable in the organism that produces it. Since dietary supplements are products that are intended for use by humans, it would be appropriate that the living organism that creates the metabolite be human.

Furthermore, metabolites identified under this definition should be considered unique entities and have the appropriate toxicological safety evaluation with consideration given to the proposed use and dosage.

Thank you for allowing me to comment on this issue and I would be happy to discuss it with you or members of the Advisory Committee. I hope your meeting goes well and that you gain valuable advice and insight into this important question.

Sincerely,

A handwritten signature in cursive script, reading "John L. Zenk, MD". The signature is written in black ink and is positioned below the word "Sincerely,".

John L. Zenk, MD
Chief Medical and Scientific Officer