

June 26, 2006



Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W. (HFS-450)
Washington, DC 20204

Dear Dr. Walker:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, DOX, LLC, Detroit, Michigan on its own behalf, wishes to notify the Food and Drug Administration that it will market a new dietary ingredient, 19-norDHEA, the 19-nor form of DHEA, a metabolite of DHEA, a dietary ingredient on the market prior to October 15, 1994. Accordingly, enclosed please find two (2) copies of this notification.

The dietary supplement that contains 19-norDHEA will consist of one hundred (100) mg of 19-norDHEA in a tablet or capsule that will be suggested to be taken up to three times per day.

Attached please find a summary and references which establish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe.

2006-5591-
AIMS

Section 1

- a) Scientific Wellness
120 North 4th Avenue
Ann Arbor MI, 48104
- b) Dennis Hayes
734-995-4646(Phone)

Section 2

- a) The name of the dietary ingredient is 19-nordehydroepiandrosterone

Section 3

- a) The dietary supplement that contains 19-norDHEA will consist of one hundred (100) mg of 19-norDHEA in a tablet or capsule that will be suggested to be taken up to three times per day.
- b) The label will contain the following instructions for use: "DIRECTIONS FOR USE: This product is for adults over the age of 21 only. Do not exceed recommended dosage. This product is not intended to diagnose, treat, cure or prevent any disease". KEEP OUT OF REACH OF CHILDREN

Section 4

- 4.1 Background: Dehydroepiandrosterone (DHEA) is a dietary ingredient that was marketed in the United States before October 15, 1994. DHEA is subjected to extensive metabolism forming a multitude of metabolites including but not limited to androsterone, epiandrosterone and etiocholanolone (2,3,5,6).

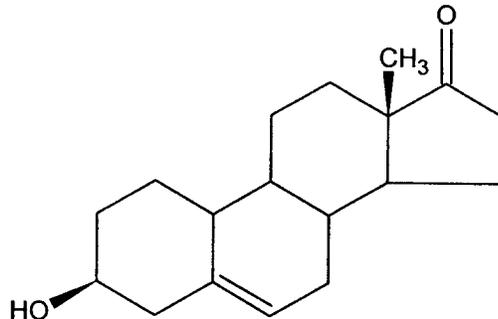
The endogenous formation of norandrostanes has been well documented with norandrosterone, norepiandrosterone, noretiocholanolone detected in healthy human and animal urine (7,8,9,10,11,12,13). The formation of 19-nor-metabolites has been suggested to be a byproduct of the incomplete aromatization of androgens to estrogens (12). DHEA is known to undergo aromatization to estrogens (1).

The presence of endogenous norandrosterone metabolites in urine strongly suggests the formation of 19-norDHEA through the incomplete action of aromatase in vivo.

19-norandrostanes are also present in the food chain (8,11,13). Consumption of a meal consisting of boar meat resulted in high plasma levels of both

norandrosterone and noretiocholanolone (8). Boar meat contains high levels of norandrostenedione which, when consumed has been shown to result in the excretion of 19-norDHEA in human urine (22).

4.1.1 Structure



4.2 Name of Ingredient: 19-nordehydroepiandrosterone

General extraction of Phytosterol Base

Product name: 5-androstene-19-Nor-3b-ol-17-one

Molecular Formula: C₁₈H₂₆O₂

Molecular Weight: 274

Physical state: powder

Appearance: white or off-white crystallized powder

Purity: >95%

Hazard symbols: None listed

Risk Phrase: None listed

4.2.1 Product Specifications

Physical state: powder

Appearance: white or off-white crystallized powder

Purity: >95%

Testing: HPLC & Mass Spectrometry

4.3.1 **Safety of Ingredient:** DHEA has a long history of use in healthy and diseased humans and has been shown to be safe in doses up to 200 mg per day for 24 weeks (20) and 2250 mg for 16 weeks (18) with minimal side effects. The side

effects that are encountered are due, in large part to the formation of estrogen and potent 5-alpha reduced metabolites (4,20,21). DHEA has been shown in the literature to convert via the aromatase enzyme to estrogens (1). In addition, DHEA has been shown to convert to more potent 5-alpha reduced metabolites. 19-norandrostanes, including 19-norDHEA, are known to convert to less potent metabolites through 5-alpha reduction. In addition, the lack of a carbon in the 19-position reduces affinity for the aromatase enzyme and results in reduce aromatization to estrogens (14,15). 19-norDHEA would therefore be expected to have a better safety profile than DHEA.

Dose Considerations

Selection of the dose of 19-nor-DHEA for human consumption was determined from reference to well tolerated doses of DHEA, up to 200 mg per day for 24 weeks in human clinical trials (20), on the rationale that 19-norDHEA has a higher level of safety in comparison to DHEA.

Section 5

Summary:

DHEA is known to be extensively metabolized in the human body into a diverse array of metabolites. 19-norDHEA is strongly suspected to be a direct metabolite of DHEA through incomplete aromatization of androgens to estrogens.

In addition, 19-norDHEA has been shown to be a metabolite of 19-nor androstenes which are present in the food supply from pork.

19-norandrostanes are considered to be safer than androstanes due to the formation of less potent 5-alpha reduced metabolites which reduces the risk of prostate as well as a decreased affinity for the aromatase enzyme.

Conclusion:

Considering the fact that 19-norDHEA is a metabolite of components found in the food supply as well as that it is a direct metabolite of DHEA which is currently sold on the U.S. market and the long history of the safe use of DHEA in a wide range of doses as a dietary supplement, it is believe that 19-norDHEA can reasonably be expected to be safe when used as in the manner outlined in this application and is expected to have an increased safety profile compared to DHEA.

References

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