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REPORT

How Congress Is Being Misled to Think That DHEA Is an “Anabolic Steroid”

No organization in the world has studied DHEA longer than the Life Extension Foundation. Since 1981, we have:

1. compiled and analyzed volumes of published DHEA studies;
2. performed and analyzed thousands of human DHEA blood tests;
3. published advanced DHEA safety-dosing protocols;
4. and in recent years have maintained a database that compiles real-world information showing what DHEA does in the human body.

We have witnessed firsthand the unique benefits that DHEA can bestow on aging humans. We know that DHEA does not cause the dramatic fat-loss and muscle-bulking effects of anabolic steroid drugs. If DHEA did contour muscular physique the way anabolic steroid drugs do, this would be truly miraculous, in as much as DHEA is virtually free of side effects.

The bottom line is that DHEA does not produce the effects associated with anabolic steroids and is in fact not an anabolic steroid drug. More than 30 years of peer-reviewed published research substantiates this. How then can some members of Congress say that DHEA is now an “anabolic steroid drug”?

GENE EXPRESSION ASSAYS: A LITTLE-UNDERSTOOD TECHNOLOGY

When we inquired to the Congressional office leading the assault on DHEA, we were sent one study that used gene expression assays to compare the effects of DHEA to dihydrotestosterone (DHT), a potent testosterone metabolite.¹

Gene expression studies assess the level of changes in response to the introduction of an external agent such as a drug, hormone, or nutrient. Comparing the status of gene activity before and after treatment provides a description of the genomic effect an external agent has on analyzed tissue.

According to this study being used to attack DHEA, extremely high DHEA doses caused some of the same gene expression changes as DHT in a hybrid group of mice. Since few doctors are able to interpret gene expression assay studies, a technology that virtually no one can comprehend is being used to discredit DHEA.

The Life Extension Foundation is a pioneer in the development of gene expression assay technology.^{2,3} We were the first organization to use gene expression assays to identify potential anti-aging therapeutic agents. We currently fund aggressive gene expression assay research aimed at finding calorie-restriction mimetics (such as metformin and resveratrol) that aging people can use today to slow or reverse the effects of aging in their bodies.

Based on Life Extension’s analysis and opinion, the gene expression study being circulated in Congress contains many serious flaws that render its findings meaningless.

GUESS WHO AUTHORED THIS QUESTIONABLE STUDY?

Before we reveal the failings of the study being used to attack DHEA, readers should understand that the lead scientist who authored this study (stating that DHEA is an anabolic steroid) is also listed on patents that could turn DHEA into lucrative prescription drugs!

That’s right. The lead author of the DHEA-anabolic steroid study circulating in Congress today is the inventor of patents that would enable DHEA to be used in synergistic combination with various drugs to improve their efficacy.⁴



It would appear that Congress may base its decision to ban DHEA on a study whose author stands to make a fortune if DHEA supplements are outlawed.

In the gene analysis study being used to attack DHEA, the lead author makes legal conclusions that DHEA should be removed from the OTC (over-the-counter) market and re-classified as an anabolic steroid. This of course would pave the way for patented DHEA prescription drugs that offer the same benefits as low-cost DHEA supplements do today.⁵

These kinds of legal interpretations, by the way, are quite unusual to see in peer-reviewed scientific studies. Even more curious is the statement at the very end of this study, where the authors declare that:

“There is no conflict of interest that would prejudice the impartiality of this scientific work.”¹

Based on the patents issued in the name of the lead author of this study, it would appear that a significant economic “conflict of interest” exists as it relates to the “impartiality of this scientific work.”

THE FLAWED STUDY

The study being used in efforts to ban DHEA measured the effects of very high doses of DHEA that were injected into a hybrid strain of castrated mice.¹ The study used DNA microassays to compare the genomic effects of DHEA, DHT, and placebo (control) on prostate tissues. At autopsy, prostate tissues of the various groups of mice were weighed to assess anabolic stimulatory growth.

Compared to the DHT group, the prostate tissues of mice injected with very-high-dose DHEA weighed 33% less. Even more revealing was the finding that the prostate tissues of an intact control group that received neither DHEA or DHT weighed 24% more than the DHEA group—suggesting that DHEA may have had an anti-anabolic effect in the tissues weighed.

Since huge doses of DHEA were injected into the mice, bypassing normal digestive-absorption-limiting barriers and the liver degradation that occurs when humans swallow DHEA supplements, the genomic findings—which are themselves highly questionable—have no relationship whatsoever to what occurs in a human being taking 15-75 mg of DHEA daily.

To expose some of the specific defects in the gene analysis study in the simplest terms, we present the following observations:

1. In the four-week arm of the mouse study, the amount of DHEA injected daily was 30 times greater than the DHT dose (0.1 mg of DHT compared to 3 mg of DHEA). In the one-week arm of the study, the amount of DHEA injected daily was 62 times greater than the DHT dose (0.1 mg of DHT compared to 6.25 mg of DHEA). Since the dose of DHEA was 30-62 times greater than the dose of DHT, the effects shown on the gene expression assays are not comparable. This has not stopped certain members of Congress from stating that DHEA exerts the same effects as DHT—a statement that is invalidated by the grossly higher amounts of DHEA used in this study compared to DHT.



2. The mice were given extremely high doses of DHEA that exceed what any human would ever take. For example, in the four-week portion of the DHEA-DHT study, the numerical human-comparison dose of DHEA based on weight alone was 5,832 mg, whereas in the one-week study, the numerical human-comparison dose was 16,200 mg.

When calculating the correction factor that extrapolates the conversion value of mice to humans, and then computing the mode of administration given to the mice (i.e., injection), the human-equivalent DHEA dose if taken orally would be about 15,800 mg a day. Typical human doses of DHEA are only 15-75 mg a day, a vastly smaller amount than used in this mouse study being used to discredit DHEA.

In other words, the mice in this study used to attack DHEA were given a human-equivalent dose that was a startling 316 times greater than what health-conscious people are taking today to restore DHEA to youthful ranges.

To put this in perspective, if one were to evaluate the genomic effects of a human taking one standard aspirin tablet daily (325 mg)—but the equivalent of 316 aspirin tablets (102,700 mg) were given to lab mice to measure the gene expression effects—the findings would have no meaning, since humans do not take 316 tablets of aspirin in a day.

The DHEA dose was even higher in the one-week arm of the study, where the extrapolated human-equivalent dose of 43,910 mg of DHEA was administered to mice. To elaborate, when DHEA is injected, it bypasses normal absorption barriers and degradation by the liver, thus becoming much more potent to the organism.

Based on the egregious overdoses of DHEA used in this mouse study, the findings have no genomic relevance to the 15-75 mg a day of DHEA that humans take. Yet certain members of Congress have been led to believe that this study somehow changes the status of DHEA to that of an anabolic steroid.

3. The experiments were performed on gonadectomized (testicles removed) animals. The effect of DHEA on the gene expression of normal (non-gonadectomized) animals is not described (neither by itself, nor compared to the effect of DHT on normal animals). The use of this flawed animal model further renders the findings meaningless to humans.

DHEA: WHAT YOU NEED TO KNOW

- For more than 25 years, the Life Extension Foundation has exhaustively researched DHEA's benefits for promoting human health and longevity. Currently, DHEA is readily available as a low-cost dietary supplement.
- Due to the recent publication of a flawed study, the US Congress is considering whether DHEA should be reclassified as an anabolic steroid. If this occurs, DHEA will no longer be readily available to health-conscious consumers.
- The study being used in this attempt to ban DHEA is full of flaws regarding dosage, route of administration, and interpretation of data, rendering its findings practically meaningless.
- Concerned citizens can help protect their access to this crucial dietary supplement by alerting members of Congress that DHEA should not be reclassified as an anabolic steroid.



4. When comparing the prostate weight of the mice receiving DHT, DHEA, or control, the DHEA group showed smaller growth in the prostate gland and surrounding tissues than the DHT and the intact control group, suggesting that DHEA may have impeded undesirable prostate growth in animals that were not castrated. The prostate tissues of DHT mice weighed 33% more than those of the DHEA group, whereas prostate tissues in the intact control group (receiving neither DHT nor DHEA) weighed 24% more than the DHEA group. This finding showed that DHEA did not exert anabolic steroid effects, yet this study is being used as evidence to re-classify DHEA as an anabolic steroid drug when the only tissues weighed show DHEA administration resulted in lower prostate weight than seen in normal control animals.

5. Microarray gene studies often yield a large number of differentially expressed genes that may require validation depending on study design and statistical methods used. Some researchers suggest that the expression changes in a subset of genes should be confirmed by independent methods (such as real-time polymerase chain reaction, or RT-PCR).^{6,7}

6. The findings of the study used to attack DHEA contradict other recent side-by-side gene comparison studies. In fact, studies show the risk of prostate cancer in men is clearly associated with increases in gene expression involving insulin-like growth factor-1 (IGF-1). Rigorous scientific studies recently conducted at the National Institutes of Health (NIH) with human prostate cells (in contrast to the aforementioned mouse study) show that unlike DHT, DHEA does not stimulate IGF-1 in human prostate cells, and this determination has been made by assessing for cell proliferation, mRNA expression, and quantitative real-time polymerase chain reaction (PCR).⁸ Furthermore, studies using human prostate cancer cells show that DHEA has a delayed and reduced effect on cancer cell proliferation compared to testosterone or DHT.⁹ Researchers at NIH concluded that DHT promotes prostate growth partly via modulation of the stromal cell IGF axis, while DHEA did not have this effect.⁸ These studies refute the notion that DHEA is an "anabolic steroid", but were not even mentioned in the conclusion of the one biased study being used as evidence that DHEA should be outlawed. It is customary to mention contradictory research in the conclusions of scientific studies in order to provide the reader with a glimpse of other research findings that show different outcomes.



7. The DHEA-DHT study showed that several genes were modulated by both DHEA and DHT in the mouse prostate and seminal vesicles.¹ However, simply because a number of mouse genes are modulated by both DHEA and DHT does not in any way provide information as to favorable or unfavorable changes in gene expression. Gene expression in response to an agent can be up-regulated, down-regulated, or unchanged. The gene expression study being circulated in Congress describes only those genes that are, per the authors, "commonly modulated," i.e., up-regulated in both DHEA and DHT treatments, or down-regulated in both treatments.

The authors do not comment on the numbers and identities of genes that are:

- a. up-regulated in one, but not in the other treatment,
- b. down-regulated in one, but not in the other treatment,

- c. up-regulated in one, but down-regulated in the other treatment.

It is our opinion that, without the data above, it is impossible to compare the effects of DHEA to those of DHT. Simply noting the “common modulation” of a certain number of genes does not establish a “genetic signature,” or “proof of androgenic anabolic activity.” Such a study would require verification using qualitative genomic analysis of commonly and separately affected genes to assess a genomic relationship between DHEA and DHT. Their relationship to biological anabolic activity needs to be further investigated using sophisticated molecular biological techniques like quantitative real-time PCR. Furthermore, due to known species-specific responses exhibited by DHEA, interspecies extrapolation to humans (with an experimental species of mice that was used in this study) needs to be cautioned.

DON'T LET CONGRESS BE FOOLED

Despite these serious flaws that invalidate the findings and conclusions of this DHEA-DHT study, Congress may unwittingly use this biased DHEA-DHT gene expression study to outlaw DHEA.

The reason Congress may be misled is that gene expression technology is incomprehensible to those who are not directly involved in the field. We doubt that anyone in Congress will figure out that the author of this study is listed on patents that could become enormously valuable if DHEA became a prescription-only drug.

Since members of Congress are unlikely to see the blatant flaws that exist in this study, but are likely to be besieged by pharmaceutical lobbyists, it is critical for concerned citizens to alert their Congressional members today to the fact that DHEA is not an anabolic steroid.

The information provided at the end of the previous article enables health-conscious Americans to easily inform their members of Congress that DHEA should not be banned!

HOW WE CALCULATED HUMAN EQUIVALENT DOSING

The amount of DHEA (3-6.25 mg, or 83.3-231.5 mg/kg) injected daily into these hybrid, castrated mice might appear to be small by human standards.

When one considers, however, that the mean weight of these mice was 1.26 ounces, then the magnitude of the high dose of DHEA used becomes apparent. The average person weighs 2,464 ounces—about 1900 times more than the average mouse in this study.

When extrapolating doses used in animal studies to what the human-equivalent dose (HDE) would be, factors in addition to weight have to be considered (such as the body surface area of lab mice compared to humans). We considered this and used recognized scientific tables to reduce the human equivalent dose by 12.3 times. Even with this large percentage reduction, the human-equivalent dose of DHEA was still very high compared to what humans supplement with.

When we saw that the mice were injected with the DHEA instead of having it added to their food, we had to adjust the human equivalent dose much higher, since the natural limitations relating to digestion-absorption and liver degradation in response to oral ingestion would not occur.

We found a study showing that relative to subcutaneous dosing of DHEA, oral dosing of DHEA is only approximately 3% as potent.¹⁰ Since the mice were injected with DHEA, we calculated an equivalent potency dose for oral ingestion.

The numbers came in showing that the human-equivalent dose of DHEA used in this gene expression study was 15,800 mg in the four-week arm, and an astounding 43,910 mg in the one-week arm.

Since typical human doses of DHEA are 15-75 mg a day, the outlandish doses of DHEA (316-878 times more) used in the one- and four-week arms of this mouse study discredit its application to humans.

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