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RE: Scientific Details Related to SELECT Trial

To our valued customers:

In an effort to provide additional research details and answer many of the questions that have arisen as a result of the termination of the SELECT study, we have worked closely with many of the leading selenium research groups to develop an in depth response to key matters.

The SELECT study found no cancer risk reduction activity of one chemical form of selenium, namely selenomethionine (SeMet) used at a single dose. While the study did not add support to the earlier studies, we find that the SELECT study does not call into question earlier clinical trials that have been published in scientific journals. More importantly, the SELECT study does not shift the overwhelming scientific support that selenium has an important role in cancer risk reduction. Although SELECT results were thought initially to be convincing, one of the SELECT study's authors, Dr. Alan R. Kristal, stated in a recent editorial that the possibility remains that the decisions of SELECT on dose and formulation were wrong (Cancer Epidemiology Biomarkers & Prevention 17, 3289-3291, December 1, 2008). Furthermore, the SELECT authors, Lippman et al, quoted that "Potential limitations of SELECT include that it did not test different formulations or doses of selenium and vitamin E and that it did not definitively assess results in subgroups of men who may have responded differently than did the overall population" (JAMA, Dec. 9, 2008 online edition and JAMA, Jan. 7, 2009-Vol. 301, No. 1, print version).

At the recent American Institute of Cancer Research (AICR) conference, the SELECT results were thoroughly discussed and Dr. Karam El-Bayoumy of the Penn State Hershey Cancer Institute called the case against selenium far from closed (Oncology Times, Jan. 10, 2009-Vol. 31, No. 1). His research, which used high-selenium yeast instead of SeMet, has shown a benefit for selenium for cancer risk reduction. Moreover, Dr. El-Bayoumy found the mechanisms of prevention to be far-reaching, "Collectively, based on mechanistic studies conducted in our laboratory and others in preclinical systems, it appears that selenium can alter cellular and molecular targets implicated in prostate cancer progression, recurrence, and metastasis, and thus selenium compounds have the potential to promote prostate cancer survivorship" (Oncology Times, Jan. 10, 2009-Vol. 31, No. 1). He further quoted that, "Selenium compounds should be considered for further exploration as primary or supplemental treatment options for advanced prostate cancer in addition to their role as chemopreventive agents".

Furthermore, in the same publication, Dr. John A. Milner, Chief of the National Cancer Institute's (NCI) Nutritional Science Research Group stated that dietary supplements can differ in quality and vary from brand to brand.

We believe the SELECT results add clarity to the form and dose of selenium as critical determinants in cancer risk reduction. Clarity, by confirming that subjects with relatively high baseline levels of selenium will not benefit from supplementation. This is exactly what was found in the NPC trial of Drs. Clark and Combs (Clark et al, JAMA, Dec. 25, 1996-vol. 276, No.24) and is what Dr. Walter Willet suggested over 25 yrs ago from his cohort study (Willet et al, Lancet, July 16, 1983: 2[8342]:30-134). It remains very likely that a significant sub-group of subjects will benefit from selenium supplementation, namely, those with baseline plasma selenium levels below 120 ng/ml. The SELECT results showed that both the placebo and treatment groups to be above the 120 ng/ml level, where no further selenium supplementation was found to be effective. Whereas in the NPC trial, selenium supplementation was found to be effective in the sub-group with baseline plasma selenium levels below 120 ng/ml.

It is well documented in the University of Arizona and Cornell University Gold-Standard clinical trial that high-selenium yeast supplementation (at 200 micrograms per day) reduced the incidence of lung, colon and prostate cancers by as much as 63% (Clark et al, JAMA, Dec. 25, 1996-vol. 276, No.24). Researchers at the Penn State Hershey Cancer Institute found that supplementation with high-selenium yeast, reduced oxidative stress and serum PSA levels, risk factors for prostate cancer in humans (El-Bayoumy et al, Cancer Epidemiology Vol. 11, 1459-1465, Nov., 2002). In the SELECT study, it appears that SeMet had no effect on PSA levels (Lippman et al, JAMA, Dec. 9, 2008 online edition and JAMA, Jan. 7, 2009-Vol. 301, No. 1, print version). We emphasize that both the Clark et al clinical chemoprevention study and the El-Bayoumy et al pilot clinical study used high-selenium yeast and not SeMet.

A very extensive body of animal and cell culture data further provides strong evidence to support the human clinical results where high-selenium yeast has been shown to be effective in reducing the risk of certain types of cancer. In addition, the lack of effect of SeMet for cancer prevention in the SELECT study is consistent with the previous animal data. For example, Dr. McCormick at the Experimental Toxicology and Carcinogenesis Division, IIT Research Institute in Chicago found no effects with SeMet supplementation on the prevention of prostate cancer in rats (Eur Urol 1999;35:464-467). Furthermore, research at Purdue University found high-selenium yeast to be more effective than SeMet in the reducing DNA damage in canine prostate cells (Waters et al, J. Natl Cancer Inst (2003); 95:237-240).

We and many other selenium experts believe that the SELECT study should have included the standardized high-selenium yeast, which has been found effective in reducing cancer risk in animal studies and human clinical trials. High-selenium yeast is different from the single synthetic amino acid compound, SeMet, used in the SELECT study. High-selenium yeast contains several different natural anabolic and catabolic forms of organically-bound selenium in addition to SeMet, such as selenocysteine, methylselenocysteine, and several other selenium compounds, all organically bound. We suspect that the advantage of high-selenium yeast lies in its content of multiple forms of selenium, including some forms that are more effective than SeMet in anti-carcinogenesis.

More importantly, current research at Penn State Hershey Cancer Research Institute is aimed at comparing high-selenium yeast and SeMet on biomarkers of prostate cancer risk. This research was recently funded by the NCI. In addition, there are numerous other ongoing human clinical selenium trials listed at the CLINICAL TRIALS.gov website at <http://clinicaltrials.gov/ct2/results?term=selenium> . Many of these trials are funded by the NCI and have the sole purpose of studying the effectiveness of selenium on cancer prevention. Further research is currently ongoing to provide additional support that the form of selenium is of paramount importance in its effectiveness for cancer risk reduction.

The underlying mechanisms for selenium and anti-carcinogenesis were identified in a recent publication (Jackson & Combs, Current Opinion in Clinical Nutrition and Metabolic Care 208, 11:718-726). Besides the chemical form of selenium being a potential factor in selenium's effectiveness for cancer prevention, another scientific possibility that may account for the lack of effect of SeMet in SELECT study is that free-SeMet is not being used like protein-bound SeMet in high-selenium yeast. For example, free-SeMet may be more susceptible to oxidation (which then converts to selenomethionine selenoxide) than it is within a protein, due to some sort of protection because of the tertiary-folding of the protein itself. We know that SeMet is more sensitive to oxidation than its S-analogue and as a result of its oxidation it would reduce its bioavailability.

The undersigned,

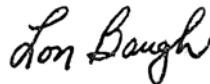
Dr. Mark Whitacre, COO and President of Operations, received his Ph.D. in nutritional biochemistry at Cornell University in 1983 under the direction of Dr. G.F. Combs, Jr., who is a world renowned selenium scientist and co-author of many of the studies reviewed above. His Ph.D. dissertation was on the biochemical role of selenium at the cellular level in the pancreas.

Dr. Lon Baugh, Director of Fermentation and Quality Control, received his Ph.D. in Anatomy & Physiology in 1974 at the University of Texas. He has been involved with high-selenium yeast research and production since 1980 when he co-developed the product.

Sincerely,



Mark Whitacre, Ph.D.



Lon C. Baugh, Ph.D.