NANO PORT (USA) INC.

317 W35th Street, Apt 3FE, New York, NY 10001, USA
Tel : 917-435-4423

November 18, 2002

Division of Standards & Labeling Regulations
Office of Nutrition Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety & Applied Nutrition
Food and Drug Administration
200 C Street, NW
Washington, D.C. 20204

Dear Sir,

New Dietary Ingredient Notification: Nano-Se

Nano Port (U.S.A.) Inc would like to introduce into the health food market of Nano Red Elemental Selenium (under the trade name of Nano-Se), following the 75 days waiting periods as provided by Law.

1. Distributor's name and address:
NANO PORT (USA) INC.
317 W35th Street
Apt 3FE, New York
NY 10001, USA

2. Name of dietary ingredient:
Nano red elemental selenium under the trade name Nano-Se

3. Description of the dietary supplement that contains the dietary ingredient:
Each bottle contains 72 capsules
Each capsule contains 45 mcg selenium (Nano red elemental selenium)
Other ingredients: Starch and dextrin
Suggested usage: Take one to two capsules 1 to 2 times daily or as directed by a health professional.

4. **Se and its Safety:**
Selenium (Se) is an essential trace element, it is metabolised within the human body into an array of selenoproteins: classical glutathione peroxidase (GPx1), gastrointestinal glutathione peroxidase (GPx2), extracellular glutathione peroxidase (GPx3), phospholipid hydroperoxide glutathione peroxidase (GPx4), thioredoxin reductase (TR1 and TR2), iodothyronine deiodinase (IDI, IIDI, and IIIDI), selenoprotein P, and selenoprotein W. It is well recognised that dietary selenium is important for a healthy immune response. There is also evidence that Se has a

protective effect against some forms of cancer [1].

There are several selenocompounds in tissues of plants and animals. Selenate is the major inorganic selenocompound found in both animal and plant tissues. Selenocysteine is the predominant selenoamino acid in tissues when inorganic selenium is given to animals. Selenomethionine is the major selenocompound found initially in animal given this selenoamino acid, but is converted with time afterwards to selenocysteine. Selenomethionine is the major selenocompound in cereal grains, grassland legumes and soybeans. Se-methylselenocysteine is the major selenocompound in selenium enriched plants such as garlic, onions, broccoli florets and sprouts, and wild leeks. Sodium selenite is the major inorganic form for comparison of bioavailability and toxicity among different forms of Se [2, 3].

The typical American diet provides the average adult with about 80 to 150 mcg of Se per day, which is more than the newly revised RDA for selenium of 55 mcg, but less than one half of the amount considered optimal for utilization of the protective potential of Se, especially for cancer prevention. Accordingly, extra dietary selenium supplementation is increasingly recommended by health professionals. As to the safety of Se, a supplemental dose of 200 mcg per day would cause the total daily Se intake of an average adult to increase to 280 to 350 mcg. This is a safe amount since it is below or equal to the Reference Dose (RfD) for selenium, which, for an adult of 70 kg, was set by the EPA at 350 mcg [4]. The RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. In line with this definition, studies have shown that prolonged daily selenium intakes of 750 to 850 mcg do not produce adverse effects [5, 6]. Sodium selenite, sodium selenate, selenomthonine, seleno-yeast and methyselenocystein have been used for Se supplementaion at the dose equal to or below 200 mcg Se daily. Long-term consumption of seleno-yeast (200 mcg Se daily, mostly in the form of selenomethionine) in 1312 persons for 4.5 years showed no toxicity and revealed a significant reduction in lung, prostate and colorectal cancer [7].

5. Nano-Se and its safety:

The efficacy of Se in inducing Se-containing enzymes and the pro-oxidative effect are determined by its chemical form. Normally, gray and black bulk particle of elemental Se (Se^0) has neither biological activity nor toxicity. It is known that particles of Se^0 formed from some bacterial strains and the redox system of glutathione or ascorbate and selenite has a very low bioavailability [8-10].We observed that red elemental Se, formed in the redox system of selenite and GSH or other reducing agents, was unstable and could further aggregate into gray and black Se^0 if there were no controlling factors. We further found that protein existing in the redox system could

affect the aggregation of red Se^0. The resulting Se^0 was bright red, highly stable, soluble and of nano define size. Nano-Se was prepared by the reaction of bovine serum albumin (BSA), sodium selenite, and GSH under the Chinese Patent [ZL97107038.5, attachment 1]. The final solution containing Nano-Se and BSA. X-ray photoelectric energy spectra (XPS) showed the binding energy of Se 3d was 55.3 eV indicating Se^0. Transmission Electron Microscopy (TEM) showed the size of red elemental Se was between 20~60nm [11, 12].

The Nano-Se shows totally different biological properties contrasting to the general concepts that elemental Se is inert. In HepG2 cells, Both Nano-Se and selenite have almost equal biological functions in increase of glutathione peroxidase (GPx), phospholipid hydroperoxide glutathione peroxidase (PHGPx) and thioredoxin reductase (TR), protection against free racial-mediated damage, and cell growth inhibition. Nano-Se has a 7-fold lower acute toxicity than sodium selenite in mice (LD_{50} 113 and 15 mg Se/kg body weight respectively). In Se deficient rat, both Nano-Se and selenite were efficient and generally equal in Se uptake and GPx biosynthesis [11].

Other toxicity investigations of Nano-Se are shown in two attatchments, in general Nano-Se's subchronic toxicity is near to sodium selenite and Se-enriched soybean, however, sodium selenite and Se-enriched soybean at 6 ppm in diet caused more overt growth inhibition, haematology changes and transaminases release from liver compared with Nano-Se at the same Se dose in diet [attachment 1]. Although these observations could not lead to consider Nano-Se's subchronic toxicity is definitely lower than sodium selenite and Se-enriched soybean, however, it is safe to conclude that this novel form of Se is not more toxic compared with inorganic and natural occuring Se. An independent research using Nano-Se at 1, 3, and 6 ppm in diet for subchronic toxicity evaluation showed Nano-Se did not cause obvious growth inhibition, being consistent with the results in attachment2 [attachment3].

Nano-Se, taken at the dose of 180 mcg Se daily, was granted as health care food by Ministry of Hygiene P. R. China in 1998 [attachment 4].

In summary, Nano-Se has comparable bioavailability of selenite, sharply lower acute toxicity, to less extent, lower subchronic toxicity at a dose therein other selenocompounds, such as selenite and Se-enriched soybean could cause serious toxic changes. Supplement at 180 mcg per day for adults is within the scope of RfD.

Dr. JS Zhang is our Research Scientist and would appreciate any comment you may have on the Nano-Se product prior to its introduce into the health food market.

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6. Signature of the distributor of this dietary supplement.

NANO PORT (USA) INC.

By:

Yu Har Fei
President

Enclosures

Reference

1. KM Brown and JR Arthur. Selenium, selenoproteins and human health: a review. Public Health Nutrition: ***49:***593-599, 2001.
2. GF Combs Jr. Review article: selenium in global food systems. British Journal of Nutrition. ***85:***517-547, 2001.
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4. BH Patterson and OA Levander. Naturally occuring selenium compounds in cancer chemoprevention trials: A workshop summary. Cancer Epidemiol Biomarker Prev ***6:***63-69,1997.
5. GN Schrauzer. Selenomethionine: A review of its nutritional significance, metabolism and toxicity. J. Nutr. ***130:***1653-1656, 2000.
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11. JS Zhang, XY Gao, LD Zhang, and YP Bao. Biological effects of a nano red elemental selenium. BioFactors. *15:*27-38, 2001.
12. XY Gao, JS Zhang, and LD Zhang. Hollow sphere selenium nanoparticles: their in vitro anti hydroxyl radical effect. Adv. Mater. *14:*290-293, 2002.

Attachments

1. Chinese Patent Certificate
2. Report on toxicity test of Xiwang capsule
3. REPORT ON QUALITY TEST by Analytic and Testing Centre of Nanjing Railway Medical College
4. Health Care Food Permit issued by Ministry of Hygience P. R. China
5. Reference 11
6. Reference 12

发明专利证书

证书号　　第 61223 号

发明名称：活性红色单质硒的制备方法

发明人：张劲松；高学云；黄镇；方宇澄

专利号：ZL 97 1 07038.5　国际专利主分类号：C01B 19/02

专利申请日：1997 年 7 月 8 日

专利权人：合肥经济技术学院

该发明已由本局依照中华人民共和国专利法进行审查，决定授予专利权。

本发明已由本局依照专利法进行审查，决定于 2000 年 9 30 日授予专利权，颁发本证书并在专利登记簿上予以登记。专权自证书颁发之日起生效。

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专利号

局长 姜颖

2000 年

专 利 登 记 簿 副 本

专利号：971070385　　（正　页）　　证书号：61223

I　著录项目

发 明 名 称：活性红色单质硒的制备方法

现 专 利 权 人：上海四通纳米技术港有限公司

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现专利权人国籍：　中国　上海

单 位 代 表 人：　高学云

现共同专利权人：

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方宇澄

主 分 类 号：　C01B 19/02

申 请 日：　1997.07.08　　公 开 日：1998.06.17

审定公告日：　　授 权 日：2000.09.30

II　登记事项

著 录 项 目 变 更

原专利权人及共同专利权人：中国科学技术大学

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原专利权人国籍：　中国　安徽

变更后专利权人及共同专利权人：上海四通纳米技术港有限公司

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变更后专利权人国籍：　中国　上海

著录项目变更登记日：2000.12.04

专 利 登 记 簿 副 本

专利号：971070385　　（附 1 页）　　证书号：61223

II 登记事项

专 利 权 的 转 让

原专利权人及共同专利权人：中国科学技术大学

原专利权人地址：安徽省合肥市金寨路

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转让登记日：2001.02.08

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