

Current understanding of the efficacy and safety of alkoxyglycerides and the refined fraction of Ecomer shark liver oil. Publication 1: Analysis of the results of preclinical studies

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Modern views on the efficacy and safety of alkylglycerols (AKG) and purified shark liver oil Ecomer®. Publication 1: analysis of the results of preclinical studies

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SUMMARY

From an array of bibliographic sources of varying degrees of reliability, we identified and analyzed the results of preclinical studies of alkoxyglycerides (AKG), crude and purified Ecomer shark liver oil - Ecomer® (Natumin Pharma, Sweden).

The results of toxicological studies confirm the absence of toxicity and mutagenicity of Ecomer® and its scientifically based composition. Based on the study, the experimental evidence base on the immunomodulatory and antitumor types of action of the standardized product from the liver oil of deep-sea sharks of the northern seas "Ecomer" can be considered sufficient. The results of experimental studies that we have found necessitate a similar information and analytical study to justify therapeutic and toxic doses in the clinic separately for each specific product from shark liver oil of various degrees of purification and AKG fractions.

The extrapolation of the evidence we have identified cannot be considered legitimate. base in terms of immunomodulatory, hypocholesterolemic, antineoplastic action and lack of toxicity of AKG and standardized product "Ecomer" for a cheaper line of dietary supplements for food from shark liver oil of various degrees of purification and quality.

Key words: alkoxyglycerides, alkylglycerides, shark liver oil, Ecomer, Ecomer, toxicity, mutagenicity, immunomodulatory effect, antitumor effect.

RESUME

Pre-clinical researches of alkoxy glycerides (AKG) crude and purified shark liver oil Ecomer® (Natumin Pharma, Sweden) were analyzed basing on bibliographic sources of various reliability.

Results of toxicological researches confirm absence of toxicity and mutagenicity of Ecomer and its scientifically proven formula. Existing data provide sufficient experimental

confirmation of immune modulating and anti-inflammatory action of standardized product from liver oil of deep water sharks of northern seas Ecomer. Found data show necessity of analytical research of therapeutic and toxic doses for each certain product made of liver oil of shark AKG of various purification degree. Revealed data supporting immune modulating, hypocholesterolemic, anti-inflammatory action as well as non toxicity of AKG and standardized product Ecomer can't be extrapolated to low price food supplements with different degree of purification and quality.

Keywords: alkoxy glycerides, alkyl-glyceride, shark liver oil, Ecomer, toxicity, mutagenicity, immune modulating action, anti-inflammatory action.

In connection with the colossal sales volumes (in the world market - more than 250 tons annually) of products based on shark liver oil, our attention was attracted by the problem of the scientific substantiation of the declared wide spectrum of its biological action. The urgency of the problem is obvious, since in accordance with a number of provisions of the Law "On Advertising", today advertising related to the spectrum of therapeutic action or clinical efficacy of dietary supplements to food is illegal [11-13]. Now such advertising is present on a large number of sites on the global Internet, including Russian ones. Shark Liver Oil, Shark Oil 100%, Shark Liver Oil, "Orihiro squalene / Deep-sea shark liver oil" and many other similar dietary supplements for food of various qualities and degrees of purification are supplied with detailed information about the "unique biological properties discovered by scientists" and the widest range of indications for use. At the same time, there are no references to any scientific research and reliable publications.

It is reported that dietary supplements for food, for example, from the company "Coral Club", "delays the aging process, restores the body after a course of radiation therapy, helps to heal the body, cope with many diseases", and "taking the product stimulates the immune system, protects the body from the effects of adverse environmental conditions, development of diseases "[3]. The list of indications for the use of this dietary supplement on the same website (at the time of this writing) is as follows: "allergic rhinitis; bronchial asthma; eczema; diabetes; chronic infections, long-term recurrent infection; congenital heart failure; active chronic hepatitis; nephritis and other kidney diseases; phlebeurysm; sickle cell anemia; post-alcoholic cirrhosis of the liver "[3].

Another site, for example, for the dietary supplement for food "Deep-sea shark liver oil" (Orihiro, Japan) states the following spectrum of its action: "inhibits the growth of cancer, reduces side effects during radiochemotherapy, against radiation substances (removal of mercury from the body), prevents the development of diabetes mellitus, inhibits the development of atherosclerosis, normalizes blood pressure, reduces the likelihood of heart attacks and strokes, protects against respiratory tract infections, chronic fatigue syndrome, fibromyalgia, pain relief in

arthritis, strengthens the immune system, against allergic sinusitis, lowers blood cholesterol, against various fungal and bacterial infections, for quick healing of wounds, in the complex treatment of eczema, psoriasis, improves the condition of the skin, hair, nails, improves vision "[4]. There are many similar Internet publications that do not withstand scientific criticism, but we have not found any scientific substantiation or links to original articles with the results of scientific research on these (and similar) sites.

At the same time, the history of using shark oil goes back hundreds of years. Professor Ingemar Näslund of the Karolinska Institute in Stockholm discovered a page describing the beneficial properties of shark liver oil in a medical reference book published in Iceland as early as 1830 [8, 20, 37]. First by Scandinavian fishermen [37], and then throughout the world, it has traditionally been used for therapeutic purposes externally for minor skin problems and internally for the prevention and treatment of the so-called. small infections - colds and flu [8, 20], as a general tonic and in eye diseases to stimulate the growth of lactic acid bacteria [21] and activate immunity [8, 20, 22, 24]. There is also information about the traditional use of shark liver oil products in the treatment of cancer, skin diseases, respiratory infections, and aphthous stomatitis, to prevent radiation damage and increase fertility [37, 53]. Since the 60s of the twentieth century, oil has been used to stimulate the production of antibodies [22, 24], to prevent the development of leukopenia and thrombocytopenia that arose as a result of radiation [25].

At the first stage, we conducted a screening information and analytical study of available bibliographic sources in terms of studying the spectrum of biological action of various products based on shark oil. The vast majority of the reliable results of preclinical and clinical studies that we found were obtained on isolated fractions of alkoxyglycerides (AKG) "AT 18" (AB Astra) or on liver oil samples from deep-sea shark species[one] the northern seas of special purification "Ecomer" (Natumin Pharma AB) [8, 22, 23, 25, 29, 30]. Only a small part of the published research results were devoted to dietary supplements, consisting of crude shark oil or without specifying the degree of purification and product quality characteristics [9, 10]. Toxicological studies were carried out on both purified AKG fractions from various animal raw materials and on crude shark liver oil and on samples of standardized refined Ecomer® oil.

Alkoxyglycerides, or alkylglycerides (alkylglycerols, AKG) are glycerolipids with an alkyl bond and the general formula $CH_2O \cdot CHOH \cdot CH_2O \cdot R$, where R are long-chain aliphatic radicals, that is, alkylglycerol esters, fatty acids C, 0 C 18: 1 at the α -position. Compounds of this group of various structures were found in a limited number of natural products - in the liver of fish (shark, burbot, catfish), meat, natural cow's milk [1, 21-23, 25, 29, 30, 47] (Table 1). Relatively many of them accumulate in the organs of hematopoiesis (hemopoiesis) of mammals [1, 25, 47] and in the milk of nursing mothers (about 0.1%) [25]. Highest content

Alkylglycerol esters of various structures were found in the liver oil of certain shark species - up to 50% by weight [1, 21–23, 25, 29, 30, 47]. For example, the liver oil of the Greenland shark contains 3-4% methoxy-substituted alkoxyglycerides [31, 33]. For the first time these compounds were clinically studied in the 50s of the twentieth century. by the Swedish physician Dr. Astrid Brohult, who used bone marrow in the treatment of children with leukemia and proved that the immunomodulatory effect is associated with the presence of AKG [8, 20].

Table 1

Content of individual alkoxyglycerides in various natural sources (according to Hallgren and Larsson [22–23, 26, 29, 30]), in% of the total alkoxyglycerides

Алкoксиглицериды ³	Костный мозг человека	Женское грудное молоко	Жир печени гренландской акулы
14:0			2,0
15*			0,7
16:0	29,4	23,9	9,1
16:1		Следы	10,8**
17*	7,6	3,6	3,6
18:0	24,6	22,8	2,8
18:1	16,7	33,8	59,4**
18:2		1,4	1,6
18:3			7,0
19*	6,1	2,4	1,5
20:0	2,9	1,6	
20:1	3,2	2,3	6,2
22:0	0,7	0,7	
22:1	5,1	3,4	2,2
24		2,1	

* Both branched chains and linear molecules are present: C15, C17, C19.

* * Greenland shark liver oil contains 3-4% methoxy-substituted alkoxyglycerides [31–33].

³ The number before the colon denotes the number of carbon atoms in the long-chain component of the molecule; the number after the colon is the number of double bonds in the molecule.

"Ecomer" (Ecomer®) is by myself highly purified a standardized product from the liver oil of deep-sea sharks of the northern seas, which is characterized by a significantly high content of the sum of hydrolyzed AKG (20–22%) [25, 41, 44]. Each Ecomer® gelatin capsule sold in any country in the world complies with the internal manufacturing standard of Natumin Pharma AB (Natumin Pharma AB, Sweden) and all applicable EU regulations.

In accordance with these documents, one capsule contains 250 mg of refined shark liver oil with an amount of AKG of at least 50 mg [8], and its quality is standardized for the content of dioxins and polychlorinated biphenyls in accordance with EU Directive 199/2006 (<2 µg per 1 ton fat, or <2 Toxic Equivalent Quantity / g) [2, 8][2]... —

Ecomer® has been present on the world market since 1986 [8], on the Russian market - since 2010 - as a dietary supplement for food ("Ecomer" - Ecomer®, no. RU.77.99.11.003.E.001390.09. 10) in gelatin capsules weighing 386 mg, packed in a blister pack. The fundamental difference between Ecomer and similar products based on shark liver oil present on the world market is its almost complete release from heavy metals, toxic impurities and squalene (<1%) as a cholesterol precursor [eight].

The purpose of this work is to collect, summarize and analyze the results of scientific studies of the spectrum of pharmacotherapeutic action and biological activity of AKG and the standardized purified fraction from shark liver oil "Ecomer" (Ecomer®). In this article (Publication 1), we have made an attempt to generalize information about preclinical (pharmacological and toxicological) studies of these biologically active objects.

Materials and methods

At holding this study applied methods: information and analytical, historical, content analysis, systematization, grouping, ranking, comparative and structural analyzes. As objects of research, we used bibliographic sources of a high level of reliability of three categories: domestic and foreign publications in scientific periodicals, abstracts of dissertations and monographs.

Results and discussion

We found it expedient to systematize the results of toxicological and preclinical studies that we found in reliable bibliographic sources according to the types of biological action and toxicity identified separately for the AKG fraction (shark liver oil and other natural sources), a highly purified fraction of liver fat of deep-sea sharks of the northern seas "Ecomer" (Ecomer®), as well as for shark oil of unknown degree of purification and composition, if data published by representatives of serious scientific schools were found for them.

1. Toxicity

Hajiyeva Z.M. and Kulakova S.N. (2014) studied the effect of AKG from the liver of the Commander squid (*Berytenthis magister*) on the structure of internal organs (rat liver) [1]. It was shown that in rats fed various amounts (7 and 50 mg / day) of AKG in the peripheral zones of the hepatic cells, the number of reticuloendothelial cells, containing polysaccharides in the cytoplasm and forming thin cords along the hepatic tracts, increased (compared to the control) ... In the middle and central zones of the hepatic

lobules more often (2.3 and 2.1 times, respectively) than in the control, foci of proliferation of the reticuloendothelium were detected, which contained 1.7 and 1.6 times more cells, and the number of animals with foci of proliferation of the reticuloendothelium doubled compared with control. In addition to the cells of the reticuloendothelium, lymphocytes and the contours of disintegrating hepatocytes were found in the proliferation foci. It is important that in rats receiving a lower dose of AKG, the lumens of the central veins and intralobular sinusoidal capillaries differed little from those in the control group.

B. Hallgren et al. (1978) conducted a toxicological study on two species of animals synthetically obtained 1-0- (2methoxyhexadecyl) glyceride (MGE), which is naturally found in shark liver oil.

In the study of subacute toxicity, MGE was administered orally to rats at a dose of 2 g / kg body weight, to dogs - 700 mg / kg body weight, daily for 4 weeks. As a result of the experiment, degenerative changes in the spleen and lymph nodes were revealed. An involution of the lymphocytic component occurred in the thymus. Also revealed degenerative changes in the epithelium of the renal tubules and urinary bladder, in the testes and ovaries of animals, atrophy of the uterus and prostate. The death of animals was not recorded [32].

Based on the results obtained, Natumin Pharma (Sweden) scientifically substantiated the quantitative content of MGE (and AKG in general) in Ecomer (100 times less than the dose administered to experimental animals), which makes it possible to characterize it as a product with a high safety factor [8, 20, 37]. The amount of AKG in Ecomer is strictly standardized and amounts to no less than 20% and no more than 22% of the mass of refined shark liver oil (50 mg per 1 capsule) [8].

In 2002, the subacute toxicity of shark liver oil was studied by S.N. Kulakova et al. on rats fed for a month a food consisting of 23% shark liver oil, enriched with polyunsaturated omega-3 fatty acids, also obtained from polar shark liver oil. Investigation of the histological structure of the internal organs of laboratory animals revealed fatty liver infiltration, moderate hyperplasia of the lymphoid tissues of the spleen, and an increase in the number of megakaryocytes in the spleen [6]. At the same time, keeping rats on a diet for 1 month, the fat component of which (23% by calorie content) was half squid fat, did not have a damaging effect on the histological structure of internal organs. Only in the liver was an insignificant fatty infiltration of the periportal, less often intramedial, type found. She,

There have been no specific studies on the effect of shark liver oil or AKG on the reproductive function of animals, but none of the experiments with pregnant mice and pigs have shown a negative effect on pups [41, 44], but there is evidence of the ability of shark liver oil to increase fertility animals [53].

Mutagenicity. Possible presence of mutagenic impurities in fat (oil) shark liver became the subject of close attention of researchers after the discovery of high levels of polychlorinated biphenyls in crude shark liver oil [17] and a number of commercial preparations of shark liver oil [51, 53, 54]. In particular, in 30 samples of dietary supplements produced in various countries, selected in 2005-2007. in the Canadian trade network (Vancouver), polychlorinated biphenyl derivatives (PCBs) and organic chlorine-containing insecticides (OCs) were found. The largest amount of PCB - 10,400 ng / g and DDT (1,1,1-trichloro-di- (4-chlorophenyl) ethane) - 3310 ng / g, was found in shark liver oil. In samples from oil of mixed origin (anchovies, mackerel, sardines), this amount was significantly lower - PCB - 0.711 ng / g and DDT - 0.189 ng / g [51].

Guided by the results of published studies and consumer safety, the manufacturing company included several stages of special purification of the raw material of shark liver oil in the technological scheme of production of Ecomer to the maximum permissible limit of dioxins and polychlorinated biphenyls content in it not more than 2 µg per 1 ton of fat (<2 Toxic Equivalent Quantity / g) [8].

Ecomer was tested for mutagenicity in accordance with the Organization for Economic Cooperation and Development (OECD) guidelines. The absence of mutagenicity was confirmed using the Ames test with *Salmonella typhimurium* (OECD 471), the mouse bone marrow test, the L5178Y mouse lymphoma test, and the mammalian erythrocyte micronuclear test (OECD 474) [8, 48-50].

A very interesting from a toxicological point of view, a preclinical study, indirectly related to the toxicity of the discussed shark liver oil products, was initiated by Natumin Pharma (Sweden) in 2002, since there were publications confirming that crude shark liver oil containing squalene increases the level of plasma cholesterol in animals and humans [39, 40, 52]. Especially high concentrations of squalene are found in the oil of a giant shark (English - Basking shark, Latin - *Cetorhinus maximus*) [53]. In addition, cases of lipoid pneumonia in humans and pigs, caused by shark liver oil [53], which was inhaled through the nose to treat upper respiratory tract infections, have been reported in Southeast Asia. It was assumed that squalene was the cause of the disease [16, 39, 40].

In the experiment, 0.05% of crude shark liver oil was added to the diet of hamsters as a feed additive [64]. As a result, there was a significant increase in cholesterol levels (by 19%) compared with the control, associated, according to researchers, exclusively with the content of squalene in

shark liver fat. Therefore, with the help of special technological stages, the initial shark liver oil during the production of "Ecomer" was freed from this compound as much as possible, and the quantitative content of squalene was strictly normalized (no more than 1%).

In a similar study conducted for Ecomer, there was no increase in blood cholesterol levels and no side effects [8]. According to the developers, the release from squalene makes it possible to take Ecomer for a long time without increasing blood cholesterol levels and toxic side effects on the liver, which is extremely important for cancer and immunodeficient patients. The risk of lipoid pneumonia while taking Ecomer is also excluded. In further clinical studies, there were no side effects from taking this product [5, 8, 20].

2. Pharmacological research

Immunomodulatory action. Today it can be considered proved that a number of the most important components of the immune system are directly or indirectly activated by AKG from shark liver oil or AKG of synthetic origin [8–10] due to the fact that AKG enhances the production of more than 50 factors of the body's defense against infections [9, 10].

In 1978-1999, a number of researchers using a sensitive prognostic and functional method for the detection of immunomodulatory substances "Method of plaque formation in mice (T-dependent immune response to ram erythrocytes)" has reliably shown that AKG significantly enhances the response of a plaque-forming cell to erythrocytes [15, 19, 28]. The introduction of AKG into the body of mice for seven days significantly increased the content of granulocytes and increased their activity [55].

A scientific review by Pugliese et al. (1998) indicates that AKG activated peritoneal macrophages in a range of studies in vivo and in vitro [46]. It was found that this activation is secondary, dependent on the activation of lymphocytes and the secretion of a signaling factor that activates macrophages [34, 42, 43, 59–63].

According to Oh SY and Jadhav LS (1994), the addition of AKG to the diet of pregnant rats (from fertilization to delivery) has been shown to increase the level of immune defense in nursed pups. The level of AKG in milk during lactation was significantly increased even when the rats subsequently received a standard diet without added AKG. At the same time, the content of lymphocytes in pups did not increase, but the content of granulocytes increased significantly and the level of plasma immunoglobulin increased [44].

In 2005, similar results were obtained by R. Miter et al. with AKG fraction and dietary supplement containing 32 g of shark liver oil on pregnant pigs fed from 80 days of gestation until weaning. The pigs were vaccinated against Aujeszky's disease, herpes virus infection, miscarriages and stillbirths. Blood sampling was carried out before the start of complementary feeding, during childbirth and 14 days after childbirth, in piglets - on the 2nd,

21st and 36th days of life. As a result, it was shown that pig colostrum contained a significantly higher concentration of IgG and Aujeszky antibodies compared to the control, and piglets - a higher concentration of leukocytes, IgG and Aujeszky antibodies, that is, they had a significantly higher immune status than the control group [41].

Experimental studies carried out at the Research Institute of Nutrition of the Russian Academy of Medical Sciences also established an activating effect of shark liver fat on humoral and cellular immunity and an increase in the functional activity of rat T-lymphocytes [9, 10].

Hypocholesterolemic action. Experimental studies on rats (Research Institute of Nutrition, Russian Academy of Medical Sciences) confirmed the hypocholesterolemic effect of shark liver fat [9, 10], however, we did not find specific data characterizing the qualitative indicators of the test product, as well as a description of the experiment in the available literature.

Antineoplastic action. V1999 The American Society of Clinical Oncology R. Firshine (et al.) Reported the results of a study (1998) of both direct action of AKG on sarcoma and mammary gland tumors in mice, and combined with standard chemotherapy. AKG was introduced into the diet of mice without any immunodeficiency conditions. The AKG dose was calculated according to the proportion of body surface area in humans and mice (corresponding to a 300 mg daily dose for humans). The cells of tumor cultures were injected subcutaneously, measurements of the tumor size in animals (in cubic mm) were carried out three times a week. In the experimental and control (received the usual food) series, there were 48 animals. As a result of the experiment in the experimental series, a significant inhibitory effect of AKG on the growth of cancer cells in mice was revealed, including when used together with chemotherapeutic agents - doxorubicin, fluoruracil and others. In all cases, the cytotoxic effect of chemotherapeutic agents against the background of AKG was significantly lower, and the survival rate of the animals increased significantly [20, 27]. It was found that when added to the food of mice, AKG exhibit antitumor activity by themselves, and also enhance the effect of chemotherapy and reduce the rate of tumor growth. Stimulation of tumor growth against the background of AKG was not detected in any case. It has also been shown that the bone marrow on the background of ACG is reliably better restored with a higher level of leukocytes, which persists until the next course of treatment [20, 27]. and the survival rate of animals increased significantly [20, 27]. It was found that when added to the food of mice, AKG exhibit antitumor activity by themselves, and also enhance the effect of chemotherapy and reduce the rate of tumor growth. Stimulation of tumor growth against the background of AKG was not detected in any case. It has also been shown that the bone marrow on the background of ACG is reliably better restored with a higher level of leukocytes, which persists until the next course of treatment [20, 27]. and the survival rate of animals increased significantly [20, 27]. It was found that when added to the food of mice, AKG exhibit antitumor activity by themselves, and also enhance the effect of chemotherapy and reduce the rate of tumor growth. Stimulation of tumor growth against the background of AKG was not detected in any case. It has also been shown that the bone marrow on the background of ACG is reliably better restored with a higher level of leukocytes, which persists until the next course of treatment [20, 27].

The report and scientific publications of Marcin Krotkiewski (MD, PhD) from the Institute of Clinical Neurology of the Sahlgrenska Academy at the University of Gothenburg (Sweden) [20, 36, 38] presents the results of studies carried out in various scientific institutions in Poland [55, 56] devoted to the study of mechanisms antitumor action. In particular, it has been shown that the antitumor effect is mainly due to methoxy-derivatives of AKG, while the immunomodulatory effect is due to unmethylated AKG [36, 56].

In experiments on mice and on cell cultures, the antiangiogenic effect (as a mechanism of the anticarcinogenic effect) of Ecomer was studied. The possibility of inhibiting the formation of new blood vessels was studied in

models of sarcoma, kidney and urinary bladder cancer in humans, transplanting tumor cells onto the inner surface of the skin of mice, in the diet of which 12.5 mg of "Ecomer" was injected for 3 days. The second group of mice "Ecomer" was injected locally - at the site of inoculation of cells. The control group of animals received water. As a result, in both experimental groups of animals, cutaneous angiogenesis was significantly less pronounced than in the control. The mechanisms of antitumor action were studied in a special series of experiments. According to the authors' conclusion, the research results allow us to consider Ecomer as an active antiangiogenic agent in the growth of tumor cells of three types of cancer: human sarcoma, kidney cancer, and bladder cancer [55]. Similar experiments were performed on human lung cancer cells that were injected into mice. Established

The original study looked at the role of squalene in the anti-tumor effect of shark liver oil. In addition to "Ecomer" mice were injected squalene and studied the antiangiogenic effect of the mixture (252 mice) and its effect on tumor mass (250 mice) in the L-1 sarcoma model. The results were evaluated after 3 days and 14 days, respectively. A significant decrease in angiogenesis and tumor mass was obtained both against the background of Ecomer monotherapy and with its combined use with squalene.

At the same time, the use of squalene as monotherapy did not give a positive result, and the tumor mass was fixed at the control level (with water) [57].

In the Department of Cell Biology of the Oncological Institute (Poland, Warsaw), to study the effect of Ecomer on the proliferation of prostate cancer cells, 3 types of human prostate cancer cells were used: DU145, PC-3, PCa-2b. In different series of the experiment, all cells were distributed in the minimum necessary medium (MEM) and evaluated by the method by counting the number of derived colonies. It was found that the number of colonies in the medium decreased in proportion to the increase in the Ecomer concentration in it. The number of colonies dropped to 0 at an Ecomer concentration of 1 mg / ml for all three types of cancer cells. For DU-145 and PCa-2b cells, a significant decrease was observed at a concentration of 0.1 mg / ml, for PC-3 - even at a concentration of 0.05 mg / ml [20, 38].

3. Biopharmaceutical research

We have not found data on the bioavailability of AKG and Ecomer® in the available literature. A number of studies have shown that AKG is well absorbed [18, 32], therefore, according to experts, there is no reason to expect problems associated with bioavailability that could affect the safety or efficacy of Ecomer® [8, twenty].

Thus, the analysis of preclinical studies of shark liver oil and AKG allowed to establish a reliable positive impact standardized products in the form of purified AKG fraction and refined Ecomer® shark liver oil for various components of the immune system with extremely low toxicity. As a result of experimental

Studies have revealed that squalene in crude shark liver oil samples increases cholesterol levels, which has led to the emergence of a scientifically substantiated stage of removing this component from the feedstock in the Ecomer® production process. According to experts [8], this fact gives reason to believe that prolonged use of Ecomer® as a dietary supplement to food to enhance immune protection will not expose the user to any risk, including increased blood cholesterol levels.

conclusions

1. As a result of the conducted information and analytical research We have identified the evidence base for the immunomodulatory and antitumor biological activity of the alkoxyglyceride fraction (AKG) and the Ecomer® food supplement (Natumin Pharma, Sweden), which is a purified standardized liver oil of deep-sea shark species of the northern seas in gelatin capsules.

2. The results of toxicological studies confirm the absence of the toxicity and mutagenicity of Ecomer®, its scientifically proven composition, and necessitate clinical studies to justify the therapeutic and toxic doses of purified AKG and each specific shark liver oil product of varying purity.

3. The results of experimental studies allow us to consider proven immunomodulatory and antitumor effects of purified AKG fractions and standardized shark liver oil product Ecomer®.

4. Extrapolation of the evidence base identified by us in part Immunomodulatory, hypocholesterolemic, antitumor effect and absence of toxicity of purified AKG fractions and standardized product "Ecomer" for a much cheaper line of dietary supplements for food from shark liver oil of various degrees of purification and quality cannot be considered legitimate.

5. The results of this information and analytical study determine the feasibility of conducting a similar study to identify and analyze the evidence base in terms of the clinical efficacy of products based on shark liver oil (shark liver oil) of various degrees of purification.

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[one] Shark liver oil (fat) is obtained from several species of sharks, including deep sea shark (Latin *Centrophorus squamosus*), short-finned spiny shark, or katrana (English Dogfish shark, Latin *Squalus acanthias*) and giant shark (English Basking shark, Latin *Cetorhinus maximus*) [53].

[2] Directive 199/2006 / EC: Commission Regulation of 3 February 2006 and amending Regulation (EC) No 466/2001 set maximum levels for a variety of contaminants in food for dioxins and dioxin-like polychlorinated biphenyls [2].

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