Reason for this handbook

Marine oils and similar ingredients containing omega-3 long-chain polyunsaturated fatty acids (omega-3 LCPUFA) have become very popular in recent years due to the health benefits relating to human nutrition. Hence, the quality and stability of omega-3 LCPUFA oils has also gained in importance. Control over oxidation is a most important aspect of the production and shelf-life of dietary supplements, functional foods, and pharmaceutical preparations containing omega-3 LCPUFA. Omega-3 LCPUFA of relevance to GOED members are eicosapentaenoic acid (EPA; C20:5 n-3) and docosahexaenoic acid (DHA: C22:6 n-3), as well as several other omega-3 LCPUFA such as stearidonic acid, docosapentaenoic acid, heneicosapentaenoic acid, eicosatetraenoic acid and alphalinolenic acid. These fatty acids are very reactive with molecular oxygen present in air, and oxidation of polyunsaturated fatty acids can occur rapidly via free-radical-propagated lipid peroxidation reactions under uncontrolled conditions. Oxidation will result in not just rancidity, but also can affect the nutritional value of these ingredients.

For EPA/DHA oils and products that fall within the scope of GOED’s monograph, GOED members adhere to maximum limits of primary and secondary oxidation levels, i.e. a Peroxide Value (PV) < 5 meq O₂/kg oil and a p-Anisidine Value (p-AV) < 20. In general terms, experienced GOED members estimate that in order to guarantee an end-of-shelf-life oxidation level that is within the maximum allowable oxidation limits specified by GOED, a bulk oil used for the manufacturing of a finished product is strongly recommended to have a PV below 3, to accommodate any increases in oxidation during manufacturing and product shelf-life.

All processes involved in the production, refining and formulation of EPA/DHA-containing oils as well as during their shelf-life could in theory introduce inadvertent oxidation by atmospheric oxygen. The site of attack by oxygen is normally the unsaturated portion of the fatty acid moieties of triglycerides and other lipids (Stansby, 1988). Due to the high content of polyunsaturated fatty acids, including EPA and DHA, marine oils are highly susceptible to oxidation, which is significantly different than other oils (Boran et al, 2006; Pak, 2005). A large number of saturated and unsaturated aldehydes, ketones, acids and other products have been isolated from oxidized oils, and have been shown to contribute to undesired flavors and odors.

The rate of oxidation can be controlled by suitable technologies to limit the extent of the oxidation that can occur during processing and storage. Specific points in the process are currently considered to impart higher risks of oxidation than others if not carried out under controlled conditions, for example blending or the encapsulation of oils.

Many of the EPA-DHA-containing oil producers and processors globally are members of GOED and have a profound knowledge in management of oxidation. However, this is not the case for all parts of the process and formulation steps. For example, many encapsulators and marketers are not GOED members and are used to handling ingredients which are less susceptible towards oxidation. Therefore, they are either not bound to the strict GOED oxidation limits or they do not have the in-depth knowledge or understanding of control of oxidation. Ideally, clients of GOED members and consumers would require that producers of omega-3 LCPUFA-containing oils and finished products offer products that are within specific limits of oxidation, such as GOED limits, in order to guarantee a sufficient level of product quality with respect to oxidative status. In practice, this is often not the case. In order to improve the control over oxidation by GOED members, as well as provide information to non-GOED member companies, it is not only important to set maximum limits on oxidation of EPA/DHA-containing oils, but also provide guidance on how to achieve the best control over oxidation during storage and over their entire shelf-life.

This handbook aims to systematically point out best-practice guidelines to the omega-3 industry for both members of GOED and non-members, to minimize and limit oxidation.

Factors determining oxidation

Given a specific oil type containing one or more types of omega-3 LCPUFA, several factors are known to affect the rate and extent of oxidation.

- Exposure to air

Air contains 21% molecular oxygen. It is very important to protect against air exposure at all stages of processing and/or when formulating oils. Nitrogen gas is often used to displace air, but oxygen is about twice as soluble in triglyceride oils as is nitrogen gas, and it is nearly impossible to completely displace oxygen with nitrogen gas from
oils, because nitrogen has a lower density (1.25 kg/m³) compared to oxygen (1.43 kg/m³). It is recommended that oils are stored with as little headspace (remaining volume in a container that is not occupied by the oil) as possible. If headspace appears due to oil use, it is recommended to flush the headspace carefully with nitrogen or alternatively with argon (density 1.78 kg/m³) or to store the remaining oil in smaller containers without headspace. Transfer of oil from one container to another should be done with specific oil pumps that restrict the backflow of air into the donor container. In order to guarantee that nitrogen protection is effective, it is important to design a nitrogen flow process that is adapted to each transfer line, and that nitrogen level is under control and persisting during storage. Not having a fully sealed storage container will result in loss of nitrogen, leading to a reduced, or complete loss of, oxidation control.

Different chemical mechanisms, autoxidation and photosensitized oxidation, are responsible for the oxidation of edible oils during processing and storage depending upon the types of oxygen. Two types of molecular oxygen (O₂) can react with edible oils. One is called triplet oxygen, ³O₂, the form of oxygen that is normally found in the atmosphere. The other is singlet oxygen, ¹O₂, a chemically highly-reactive and unstable form of oxygen that can be produced in the presence of light, sensitizers, and atmospheric oxygen. ³O₂ reacts with lipid radicals and causes autoxidation, which is a free radical chain reaction. Photosensitized oxidation of edible oils can involve the additional formation of singlet oxygen (Eunok, 2006).

• **Temperature**

In the presence of oxygen, oxidation reactions occur faster at higher temperatures. An increase by 10°C. increases the speed of oxidation by a factor of 2-3 comparable to other exogenic reactions. If possible, work under as cool conditions as possible (≤25 °C.). If this is not completely possible, it is highly recommended to take all other preventive measures to avoid as much as possible the onset of oxidation (e.g. use of inert atmosphere, suitable antioxidants, etc).

• **Time**

The longer the exposure to air and oxidation reactions are allowed to occur, the higher the extent of oxidation. Hence, keep steps that carry a risk of oxidation as short as possible.

Appropriate storage conditions and type of containers used for storage will play an important role when holding the oil for extended periods of time.

• **Light**

Photo-oxidation is the process whereby photons excite molecules, increasing the possibility for these to lose a hydrogen atom, thereby creating free-radical sites in PUFA where oxygen can react. Simple double bonds, such as in EPA/DHA, absorb UV light at a wavelength of around 185 nanometer (nm). Hence, they are sensitive to photo-excitation only by UV radiation close to or approximating that wavelength. One precaution to avoid UV-induced photo-oxidation is not using actinic light, i.e. UV light of 365 nm (which is UVA; 315-400 nm). Actinic lighting is rarely used indoors today and can come only from certain fluorescent light bulbs, which are very easy to eliminate from the workplace. UVB (280-315 nm) and UVC (100–280 nm) do not exist indoors. All glass and plastic containers block 100% of UV light below 400 nm. No demonstration is known that normal room illumination with visible light (VIS; 390-700 nm) directly excites EPA/DHA to accelerate oxidation. The influence of light on directly promoting oxidation of PUFA with simple double bonds may be less relevant than other factors that promote oxidation. General recommendations to handling of EPA/DHA oils in dim or dark conditions may be overrated. Exposure of unprotected oils to deep UV should always be avoided.

Light exposure should be controlled, however, when other substances are present in oils that act as photosensitizers. For example, if colored substances are present care should be taken to limit UV/VIS lighting intensity. Simple precautions to reduce any risk for photo-oxidation reactions are avoiding direct incident lighting (also to avoid heating) of unprotected oils (especially samples taken for analysis), and employing indirect lighting instead. Finished EPA/DHA products that also contain light-absorbing substances should be stored in containers that keep out light (for example using amber-colored
Containers, or other suitable packaging). In the case of a softgel product, another possible countermeasure might be to formulate in an opaque shell.

- **Transition metals**
  Transition metals, particularly iron and copper, catalyze oxidation reactions. Trace levels of transition metals can never be entirely avoided, but can be reduced by limiting the contact of oils with blank (non-stainless steel) metal surfaces, and using chemicals used in oil refining that are low in transition metal content. Chelators such as citric acid (typically up to 50 ppm) or EDTA might be used to control the reactivity of such transition metals. If possible, avoid using iron or copper salts in complex formulations together with omega-3 LCPUFA. However, as differences in reactivity between different mineral sources may exist, a specific study is always recommended to identify the best formulation and manufacturing conditions.

- **Water**
  In formulated products, water is often a required ingredient (for example, water is essential in the gelatin capsule composition), and water content or water activity should be controlled to the ranges permissible with oxidative stability for each particular formulation. Excessive water content, either as liquid or gas phase, can however have a detrimental effect on oxidative stability. Controlling excessive exposure to humidity or excessive water content are therefore targets to achieve better stability of PUFA oils to oxidation. In neat oils, nanoscopic water droplets promote the formation of association colloids, which may constitute sites of initiation of lipid peroxidation reactions in case suitable preventive measures are not taken. Lowering of water content in oils is achieved during bulk oil processing steps carried out at reduced pressure. The displacement of head-space with inert gas with as low water content as possible, the use of air-tight packaging, and the use of humidity absorbents can be useful to lower humidity and excessive water contamination.

- **Antioxidants**
  Antioxidants are typically used in the stabilization of bulk oils and finished products to reduce the rate of oxidation. The most important natural antioxidants today are: tocopherols, spice extracts (e.g. rosemary extracts), ascorbates and citric acid and their salts (Hraš et al. 2000, Tsimidou et al. 1995). For example, alpha-tocopherol or mixed tocopherols are commonly added to bulk oils (typically up to 0.2% wt/wt). Tocopherol inhibits free radical oxidation by reacting with peroxy radicals to stop chain propagation, and with alkoxyl radicals to inhibit the formation of additional hydroperoxides and decrease the subsequent formation of secondary oxidation products such as aldehydes (Frankel 1996). Ascorbic acid can work as an antioxidant, a pro-oxidant, a chelator, a reducing agent and oxygen scavenger. Citric acid can chelate ions by forming bonds between metal and the carboxyl and hydroxyl groups of the citric acid molecule. Citric acid is very effective in retarding oxidative deterioration. The use of specific types and concentrations of antioxidants can define whether a finished product is stable or unstable during its shelf-life, in combination with other measures taken such as adequate packaging for the conditions of the market that the products is targeted for.

  It is important that manufacturers know the content of antioxidant in the oil ingredient they purchase and handle. During handling and processing, e.g. distillation, a certain part of antioxidants might be removed or might be reduced by oxidation. In such cases, it might be necessary to restore the original levels of added antioxidants. It is a common misconception, however, that antioxidants could revert oxidation. Many tests have proven that adding antioxidants to already oxidized oils does not have significant benefits as the chain reaction of oxidation has already been initiated. Antioxidants are preferably added as early as possible in the process chain of fats and oils.

- **Other factors**
  In theory, certain oxidative enzymes (fatty acid oxygenases and oxidases) can accelerate the oxidative deterioration of polyunsaturated fatty acids. This may be of relevance in complex formulations in which oils come in contact with biological tissues, of vegetable or animal origin, containing intact protein with (remaining) enzymatic activity.

**Oxidation reactions specific to certain omega-3 LCPUFA oil types**

Crude fish oils have an intrinsic protection from oxidation by phospholipids and/or by certain protein residues. Properly stored under nitrogen or with low headspace or with an
unstirred layer, there is only limited oxidation in such oils. The reactivity for oxidation in refined omega-3 LCPUFA, however, depends mainly on the level of polyunsaturated fatty acids and the degree in polyunsaturation. Higher levels of EPA and DHA automatically will lead to faster oxidation which can be noticed by the change in the peroxide value. Therefore, it is essential to exclude air/oxygen or other oxidation-promoting factors even more strictly in higher concentrated omega-3 LCPUFA products.

Control of oxidation in bulk oils

• **Processing**
  Control temperatures, control exposure to air, use closed tank systems where possible, use inert gas during blending, and flush pipes/lines and vessels by inert gas prior to production.

• **Storage**
  In general, as cool as possible. Store all drums and tanks of oil at room temperature (≤25 °C.), or colder when achievable, practical and possible. Stability testing of bulk oils is carried out at 25°C, and in practice most producers and contract manufacturers have no capacity to store under actively-cooled conditions (such as at 10°C.). A distinction is made between drums for transport, and tanks used in product formulation. Producers of oil cannot use stainless steel drums as this is too expensive. They typically use new drums. If steel containers are used for storage, a type of stainless steel should be used that gives the least contamination of iron, for example coated stainless steel. Aluminum coated foils with minimal possibility for air migration are an alternative solution to metal containers. In production (e.g. blending) tanks are reused, and stainless-steel tanks must be used to avoid rust and oxidation. It is critical to have fully sealed tanks during storage where possible. If proper storage cannot be achieved, a re-test for oxidative parameters needs to be performed before the use of the oil.

• **Sampling**
  Employ sampling protocols. Sampling should only be carried out by experienced staff who have been trained in sampling of specialized products and specifically on the handling of oxidation-sensitive products. Samples should be immediately protected against oxidation by inert gas or close to zero headspace. In case that samples of received goods cannot be protected in the warehouse they should be treated or refilled as soon as possible in the QC lab. Oxidation values should be tested as close as possible to the time of sampling. Bulk containers should also be blanketed with nitrogen after completion of sampling and sealed immediately.

• **Weighing**
  Oils should ideally be weighed in the container in which they will be kept (knowing the weight of the empty container) rather than volume measured with exposure to air.

• **Oil transfer and dispensing**
  For dispensing of oil, a drum pump is recommended to be used. The lid should have one large bung hole and an atmospheric vent hole. Attach a food-grade dispensing valve (spigot, faucet) to the bung hole. Using a drum dispensing stand, tip the container from vertical to horizontal position (i.e. 90 degrees), with the dispensing valve at the lowest point of the container.

  Pouring out oil from a container without simultaneously filling the headspace with nitrogen is not advisable as air will flow back into the container. If the headspace is already filled with air, merely replacing it with nitrogen is useless, as nitrogen does not effectively completely remove oxygen already dissolved within the oil. It is recommended to de-aerate the oil under mild vacuum and then replace the headspace with nitrogen/argon. Sparging an air-exposed oil with nitrogen from the bottom or underneath the oil layer to remove dissolved oxygen may help to bring oxygen tension down.

• **Use of bulk oils**
  Oils should be allowed to gradually warm up to room temperature. If a drum heater is used, the drum should be agitated frequently and the temperature of the heater should be kept at 35°C-40°C or less if possible, and should be removed as soon as the oil is no longer solid, if applicable. Batches should be formulated so that complete drums of oil are used. This eliminates the need for storage of partial drums. If this is not possible,
Partial drums should be purged with nitrogen for at least 5 minutes, sealed and stored as cool as possible/frozen until they can be used again. The PV and p-AV of all drums (including partials) should be analyzed before use. For partial drums, this means that the PV and p-AV may be measured on the same drum multiple times.

- Notes on specialized processing technologies that can reduce and limit oxidation

**Filtration**

Specialized powdered filtration materials have been developed that may be useful during filtration steps employed in oil processing. Such materials can remove peroxides and secondary oxidation products, significantly lowering oxidation values of EPA/DHA-rich bulk oils.

**Deodorization**

Deodorization can be done using heated nitrogen gas instead of steam. Although during steam distillation air pressure is kept very low, lower exposure to oxygen may be achieved using nitrogen as stripping gas.

**Concentration**

Concentration of EPA- and DHA-ethyl esters in the absence of oxygen can be achieved using molecular distillation (mostly used), or by specialized technologies involving extraction and chromatography with carbon dioxide in its supercritical fluid state as mobile phase.

**General indications for control of oxidation and reporting of oxidative quality during formulation**

A diversity of formulated products containing EPA/DHA exist. Diversity refers to dosage form (encapsulated, bottled, emulsified, etc), as well as chemical composition. Each formulated product type requires a case-by-case development and evaluation of the individual components and formulation steps in order to create a product that is stable towards oxidation. In practice, a proper product development will allow stable products to be designed and manufactured that are oxidatively stable for the intended shelf-life and the atmospheric conditions that apply in the target market. General statements for finished product are often difficult to be made, since stability depends on many factors. It is important to understand that these guidelines that aim to indicate which factors that promote oxidation can be better controlled should not take away from the fact that a proper formulation currently already provides stable products. These guidelines should help eliminate formulations that are unstable under the market conditions they were developed for, or reduce instability for stable formulations that are unstable in markets they were not designed for with more extreme conditions (for example, markets with higher temperatures and high humidity conditions).

A number of critical points and useful guidelines for the successful manufacturing of finished products containing EPA/DHA are provided below.

- **General principles for proper finished product development**

  Develop an appropriate development plan considering the Quality Target Product Profile (QTTP), taking the following factors into consideration: a suitable gelatin formula, quality of the supplied oil, and a manufacturing process to limit oxygen exposure. The study of types and concentration of antioxidants may be appropriate to support the QTTP. Adequate in-process controls during development studies should be challenged to alleviate the risk of oxidative degradation.

- **Stability studies**

  Where possible (and depending on formula components) stability studies should be carried out to predict and confirm the oxidative stability of individual dosage forms in the final packaging. The specific stability studies that have to be carried out for encapsulated EPA/DHA (PV, Anisidine Value, TOTOX, and EPA/DHA content) depend on the target market and the storage condition. The stability of intermediate products should also be evaluated if a longer than normal time before the next process step is expected.

  Encapsulated products should not be sold in markets that have conditions outside the range of stability conditions validated in stability tests.

- **Mixing**

  Mixing tanks should be blanketed with nitrogen throughout the manufacturing process. This includes instances where the oil is stored in mixing tanks overnight. Ideally tanks
can be blanketed and sealed, but if this is not possible a constant nitrogen purge must be done.

Mixing/blending should be done at room temperature or colder. For more complicated products that require a paste-type formulation, working at cold temperature may not be possible, and protection under inert gas is necessary to achieve a high-quality product.

- Quality control for product release:

  The Peroxide Value should be monitored on the final product. Product release should not be based on PV values of the input oils. Once a trend is collected on a particular product where process parameters are constant each time, PV value testing could be reduced to rotational (for example every 10th batch, or time-based).

  The para-Anisidine Value (p-AV) should be measured on the final product if it is unflavoured. Although a suitable method is not available currently to reliably measure p-AV for many flavoured products, the p-AV of the input oil can be used to estimate the p-AV of the released product, taking into account the concentration of flavour/antioxidant in the formulation.

  TOTOX should be calculated using the testing results of the final product.

  The fatty acid profile, EPA and DHA content, and total omega-3 content should be measured on the final product, and not calculated based on the input oils.

Control of oxidation in the production of encapsulated finished products

Due to its peculiarity (single dose, shell as barrier, no headspace, low water activity (typically 0.3)), softgel technology is an ideal dosage form to contain oils in both triglycerides and ethyl ester forms and to protect from oxidation of EPA/DHA when the previous “General Indications” are followed. However, oxidation is a serious risk when encapsulation is not properly carried out. Under the strictest controlled conditions, the increase in PV can be limited to below 1 point (given a bulk oil ingredient that has a PV as close to zero as possible, but recommended to be below 3).

NOTE: as aforementioned, the combined factors of LCPUFA concentration in the bulk oil along with the degree of initiated oxidation impacts the said rate of oxidation progression in manufacture. EPA/DHA softgel product preservation requires strict control through the entire supply chain process from the source species and bulk oil production all the way through to consumer packaging, storage, and handling of the end product. Softgel encapsulation control starts from partnering with a quality bulk oil manufacturer in understanding and establishing the opportunities for oxidative control, from bulk oil container closure systems to order fulfillment management. Many of the softgel manufacturers do not use controlled conditions to limit oxidation, and the below suggestions for control are suggested to be implemented. Good communication between the manufacturer of the omega-3 raw material and the softgel manufacturer is necessary to consistently produce high quality products.

- Bulk oil storage and sampling:

  Critical control measures start from the above-mentioned controls of bulk oil receipt, storage, and sampling. To reiterate the points above, bulk oil storage should be in securely sealed containers with minimal headspace (flushed with inert gas) and in temperature controlled facilities. The sampling of the oil for inbound evaluation for use in manufacture should be timed as close to point of use as possible, by an experienced staff member familiar with oxidation sensitive materials, and with reflushing of the bulk oil containers with inert gas and secured resealing.

- Ingredients and materials for the encapsulation products

  The softgel product formula should be uniquely evaluated for respective oxidation preservation opportunities with antioxidant(s) or systems designed for the specific formula within the product brand’s desired claims. Antioxidant(s) and/or antioxidant systems could be designed for the softgel fill formula and the softgel shell may also be an opportunity to further protect the fill content.

- The encapsulation process

  The controls mentioned above for bulk oil handling remain equally critical in the entire encapsulation process. All transfer vessels should be pre-flushed with inert gas and enclosed wherever possible. Hoses and hoppers can be pre-flushed as well, but this is not as critical given the presence of nitrogen in the fill vessel. The storage of oils
during work-in-progress should be minimized, and the operation schedule well managed for as close as possible to “just-in-time.” Oil receptacles should have temperature control, and protect from oxygen and light exposure, especially if other substances are present in the oils that act as photo-sensitizers.

- **Storage of capsules**

  During the encapsulation process of the softgel, from tumbler through to bulk softgel inspection and packaging, absorb and wipe off any excess oil that may remain on the exterior of the capsule to minimize such oil oxidizing on the exterior of the capsule. Softgel capsules should be stored/maintained in temperature- and humidity-controlled environments, with minimal storage in bulk form.

  Bulk softgel capsules are typically packed in a suitable number/configuration in plastic bags (polyethylene, for example) inside hard cartons. Based on capsule size, different configurations are possible. Plastic bags that can be tightly sealed should be used, to avoid humidity from entering bags. Bags should not be left open, or only closed with tie wraps. Ideally, bulk capsules should be packaged in thick (100-micron at least) plastic bags with no water permeability, such as polyethylene, that can be weld sealed. Store the bagged capsules in boxes at room temperature or colder, away from direct sunlight. The storage condition recommendation for soft gelatin capsules is 15-25°C (controlled conditions). Bulk capsules must be labeled with recommended storage conditions for temperature, humidity and maximum holding time.

  If stability data do not support a defined holding time for bulk capsules, double-bag packaging can be evaluated to further protect the capsules. In tropical zones, it is recommended to include silica sachets in polyethylene bags (with sufficient amount) determined by the holding time study of the storage location.

  Usually consumer packaging serves as a better storage system for soft gels than bulk storage.

- **Sampling of content of encapsulated oils**

  The following indications are recommended for the isolation of oil from capsules for the analytical measurement of oxidation, fatty acid content, or other determinations:

  For each analysis, it is critical to as quickly as possible analyze the oil once taken out from the required number of capsules. A good way to take the material out of the capsules is to puncture the capsules with a syringe and squeeze the material out of the capsules in a glass recipient. Do not collect more oil then needed for the specific analysis you intend to do. Transferring the oil sample with a syringe directly into the solvent reduces
exposure time. Cutting capsules with a scissor gives too much spilling and exposure to air, and the oil can more easily oxidize. Each capsule should be used completely for one test - if you partially squeeze out some of the oil, the gelatin expands like rubber and sucks in an air bubble, which comes in contact with the remaining oil. Any remaining oil will likely be partially oxidized after a few minutes. Since the capsules contain very small amounts of oil it is not a big waste to use each capsule once only.

Prepare the material for each analysis separately. It is very important that the material for the PV and p-AV analyses is analyzed immediately after the oil has been taken out of the capsules. Work under a nitrogen atmosphere if possible.

For near-infrared spectroscopy, if it is not possible to fill the sampling vials under a nitrogen atmosphere, it is best to reduce the headspace as much as possible and seal the cap with Parafilm or similar (see Figure 1, below).

![Figure 1. Left; a glass vial with oil sample having too much headspace and no proper sealing. Right; a vial with no headspace and sealed with parafilm.](image)

**General notes on finished products**

It is critical to understand that softgel products that are properly designed and formulated for the targeted market support good stability at room temperature. Shelf life at the point of sale is an important aspect of product quality with respect to oxidation. A significant risk exists that products may oxidize in a warehouse or on the shelf, even if they were properly manufactured and encapsulated. Distributors should show that their distribution does not cause TOTOX to pass maximum applicable limits.

A sensible recommendation is the implementation of refrigeration at the point of sale. Polyunsaturated fatty acids are at a similar, if not higher, risk for spoilage as milk, vegetables and meat products, which are kept refrigerated in stores. Alternatively, humidity absorbers and oxygen-free packaging may be suitable, and these options must be studied for each EPA/DHA product. In areas with high humidity and/or tropical zones, barriers against excessive transmission of moisture to the capsules are decisive for confirming the shelf life of the finished product allied to high ambient humidity (for example, zone IVb (ICH classification), is defined as 30 °C and 75% RH), but also against condensation occurring as a result from storage at low temperatures in these conditions.

Considerations to reduce the risk for oxidation at the consumer level can be made as well, for example by using a smaller bottle packaging of 30 or 60 capsules/bottle that is consumed in a shorter time than a 200 or 300 capsules/packing unit.

**References**


