10 March 2025

Shelf Life Determination of Foods for Special Medical Purposes (FSMP)

Position Paper – Packaging Factors

Summary

- Shelf life tests should be conducted using primary packaging with barrier properties equivalent to the commercial product
- As the primary packaging used for FSMPs are impermeable to moisture and opaque, stability tests under controlled humidity conditions are not required and light is not a concern for shelf-life tests.
- Since humidity is not relevant for FSMP stability tests, ISDI considers that the four ICH climatic zones can be simplified to three with stability tests evaluated using the following temperature zones:
  - Zone I: "Temperate" 21° +/- 2°C
  - Zone II: "Subtropical" 25° +/- 2°C
  - Zone III: "Hot" 30° +/- 2°C
- Statistical analysis of shelf-life data in paste and liquid FSMPs collected by industry indicates that Vitamin C was the only nutrient the degradation of which was accelerated when inert gas was not used to flush the oxygen out of the headspace of packaging. When necessary, in relation to Vitamin C and as determined by the manufacturer, similar flushing conditions may be used in the stability test and the commercially available products.
- No difference in nutrient degradation was observed between different packaging types in FSMP shelf-life tests. There is therefore no need to repeat shelf-life tests for a same recipe in different types of packaging
- As supported by the shelf-life data of FSMP collected by industry, when a product is stored in different sizes of a same primary packaging, shelf-life tests conducted on a single pack size are sufficient to justify the shelf-life of the product in all the different pack sizes

Introduction

In 2019, following a literature review that emphasized the lack of relevant references and studies, the International Special Dietary Industry (ISDI) launched a multiyear project to develop guidance on shelf-life tests for Food for Special Medical Purpose (FSMP).

The major global manufacturers of FSMPs (Abbott, Fresenius, Nestlé Health Science, Nutricia, Reckitt) set up a Stability Guidelines Task Force. Available stability data on FSMPs were

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gathered to be analysed and used to provide recommendations on which nutrients should be included in stability tests to determine the shelf-life of foods for special medical purposes[1].

The data collected comprised 32,798 data points and 1,471 datasets (or recipes) covering more than 70 nutrients. The datasets were categorized into 9 categories (physical state, temperature, humidity, pH of the product, level of protein hydrolysis, presence/absence of fat, adult vs infant FSMP, type of packaging and protective atmosphere) with 29 subcategories. For each nutrient, statistical analyses were performed to identify which factors among these 29 subcategories were responsible for losses and to which extent.

The recommendations applicable to FSMP would be the same for other Foods for Special Dietary Uses (FSDU) that are manufactured in a similar way, such as for example, infant formula or follow-up formula.

Results

The ISDI project has identified several aspects directly related to the packaging of FSMP.

Type of Primary packaging

Primary packaging used for FSMPs can be classified under the following categories:

- Metal cans;
- Opaque plastic bottles;
- Composite cans (cans made of multilayered materials, such as LDPE, PE, aluminum and paper);
- Flexible packaging (i.e. collapsible tubes, flexible plastic bags, sachets, pouches and stick packs); and,
- Cartons

Shelf-life tests should be conducted using primary packaging with barrier properties equivalent to the commercial product. The materials that compose the packaging protect the product from extrinsic factors such as oxygen, light, moisture, temperature through several barrier properties that vary from one type of packaging to another (i.e. different abilities to prevent external light, ultra-violet light, oxygen and humidity). The type of packaging used can impact the quality and shelf life of an FSMP product. However, no difference in nutrient degradation was observed between different packaging types in FSMP shelf-life tests. There is therefore no need to repeat shelf-life tests for a same recipe in different types of packaging.

Packaging & Humidity

As the primary packaging of FSMPs are impermeable to moisture, stability tests under controlled humidity conditions are not required for FSMPs. This is confirmed by the analysis of FSMP shelf-life tests in which no nutrient was affected by the humidity conditions of the tests.

ISDI notes the International Council for Harmonisation of Technical Requirements for

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Pharmaceuticals for Human Use (ICH)[1,2] which divides the world into four climatic zones[3]. Although the ICH is relevant to pharmaceuticals, **it is not applicable per se** to FSMPs.

Since humidity is not relevant for FSMP stability tests, **ISDI considers that the four ICH climatic zones can be simplified to three with stability tests evaluated using the following temperature zones:**

- **Zone I:** **"Temperate" 21° +/- 2°C**
- **Zone II:** **"Subtropical" 25° +/- 2°C**
- **Zone III:** **"Hot" 30° +/- 2°C**

Packaging & Light

Light, especially ultra-violet light (wavelengths < 460nm), can lead to degradative loss of vitamins. Product exposure to visible light can also compromise the product's organoleptic quality (e.g. accelerating free radical reactions that lead to fat degradation). Most FSMP primary or secondary packagings have good light barrier properties. Light is therefore not a parameter of concern for shelf-life tests.

Influence of Oxygen, Packaging Headspace and Size

Oxygen content within the primary packaging is a critical factor in determining the stability of functional ingredients and nutrients found in FSMPs. Degradation is typically first-order and dependent on the amount of oxygen present[4]. Fats and oils are also susceptible to oxidation, which can cause rancidity via the generation of hydroperoxides, leading to smaller, volatile aldehydes and ketones and associated "off" flavours/odours.

Headspace is the portion above the FSMP product level (brim volume minus fill volume). This headspace is filled with air or with an inert gas (e.g. nitrogen) that is used to replace air and the oxygen that it contains. If the headspace is filled with an inert gas (e.g. nitrogen), oxidation reactions in the product can be prevented or decelerated. When the headspace is filled with air, the oxygen it contains may impact the stability of some nutrient and/or the sensory properties of the product. From a nutritional point of view, vitamin C in our analyses of FSMP shelf-life tests was the only nutrient the degradation of which was accelerated when inert gas was not used to flush the oxygen out of the headspace (see Appendix I). This was observed in paste and liquid FSMPs but not in powder FSMPs.

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[1] International Conference of Harmonisation Q1A(R2) and Q1F: (link; accessed on 10 March 2025)

[2] World Health Organisation, Technical Report Series, No. 953, 2009 (link; accessed on 10 March 2025)

[3] For reference

- Zone I: "Temperate" 21°C +/- 2°C / 45% +/- 5% RH
- Zone II: "Subtropical" 25°C+/- 2°C / 60% +/- 5% RH
- Zone III: "Hot/dry" 30°C+/- 2°C /35 +/- 5% RH
- Zone IVa: "Hot/humid" 30°C +/- 2°C / 65% +/- 5% RH
- Zone IVb: "Hot/very humid" 30°C +/- 2°C / 75% +/- 5% RH

[4] Factors influencing the stability of ascorbic acid in total parenteral nutrition infusions; J Clin Hosp Pharm. 1984 Jun;9(2):75-85.

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Packaging size may impact the shelf-life of the product. When oxygen drives nutrient losses, the higher the headspace/product ratio is, the higher the risk the shelf-life duration of the product may be reduced[5].

Also, when the barrier properties of the primary packaging materials do not fully protect the product from the external environmental factors, the higher the packaging surface/product volume ratio will be, the higher the risk that the shelf-life duration of the product may be reduced5.

Shelf-life test results indicate that the packaging size does not affect the stability of any nutrient except marginally for Vitamin C. In this case, the smallest the packaging is, the highest the vitamin C degradation is. However, the impact of the packaging size on the amplitude of vitamin C losses is small compared to other factors such as temperature and pH (see Appendix II).

Since small packaging size presents the highest headspace/product ratio and packaging surface/product volume ratios and the worst-case scenario, it is not surprising that higher losses of vitamin C are observed in smaller packaging size[5].

When a product is stored in different sizes of a same primary packaging, shelf-life tests conducted on a single pack size are sufficient to justify the shelf-life of the product in all the different pack sizes.

[5] Commission Regulation (EU) 2017/752 of 28 April 2017 Article (12)

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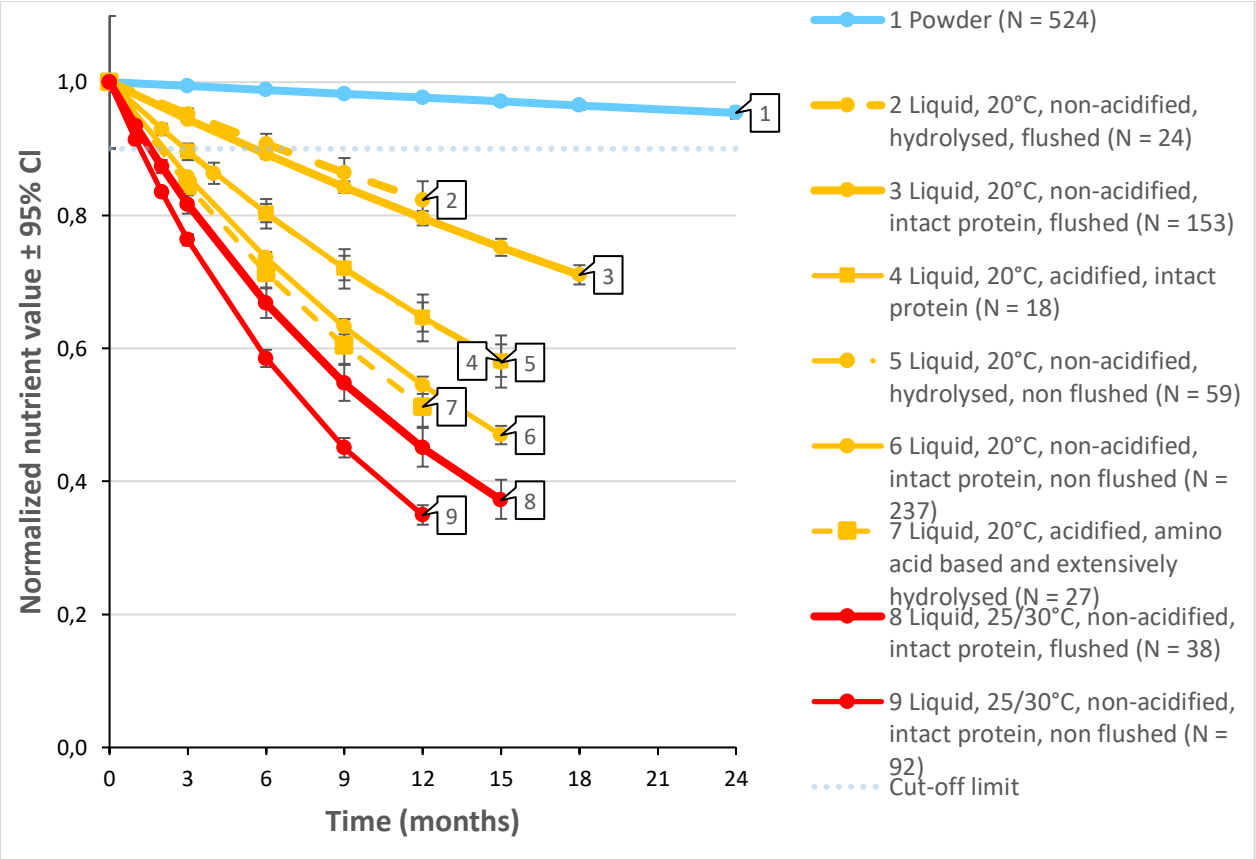
Appendixes

Appendix I – Impact of flushing the headspace of FSMP packaging with inert gases such as nitrogen

As can be seen in the Figure 1 below, flushing the headspace of FSMP packaging with inert gases such as nitrogen reduces the degradation over time of vitamin C under otherwise similar conditions: compare for example the curve N°2 that depicts the degradation of vitamin C in non-acidified liquid FSMPs with hydrolyzed protein at 20°C under flushed conditions with the curve N°5 that depicts the degradation of vitamin C in similar non flushed products or the curve N°3 that depicts the degradation of vitamin C in non-acidified liquid FSMP with intact protein at 20°C under flushed conditions with the curve N°6 that depicts the degradation of vitamin C in similar non flushed products

Figure 1: Degradation over time of Vitamin C in different FSMP products under different conditions



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Appendix II – Effect of Packaging size on nutrient stability in FSMPs.

For all vitamins*, except for Vitamin C, the 95% confidence interval of a packaging change of 500 mL are within the ISDI defined stability limits** in liquid FSMPs (see Figures 1, 2 and 3 below). Hence, the degradation rate of all studied nutrients except vitamin C can be considered as 'equivalent' in all different packaging sizes.

Even for vitamin C, the differences in losses between different sizes of a same packaging remain small compared to losses induced by temperature and a low pH: -10% for liquid FSMPs in packaging sizes differing by 500 ml (see Figure 1 below and Appendix I). Therefore, for a product commercialized in different sizes of a same primary packaging, shelf-life tests conducted on a single pack size are sufficient to justify the shelf-life of the product in all the different pack sizes.

*Nutrients for which sufficient data per physical state was available -i.e. at least 10 affiliated recipes.
**Vitamins were qualified by ISDI as stable based on conservative limits. They were qualified as stable if the losses after one year were lower than 10%.

Examples We show here as examples the results obtained on Vitamin C(the most unstable nutrient in liquid FSMPs), Vitamin A and E.

Figure 1: Effect of packaging size on the degradation rate of Vitamin C at 1 year in liquid FSMP ($P < 0.0001$).

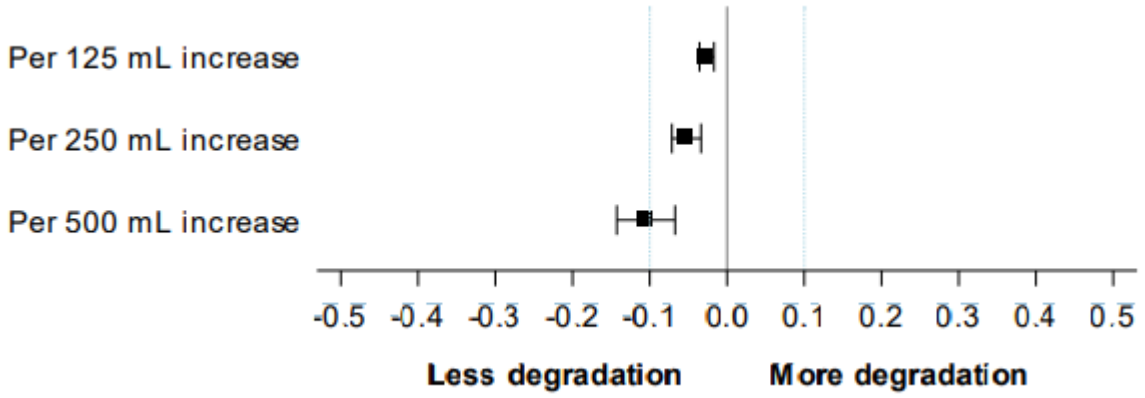

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Figure 2: Effect of packaging size on the degradation rate of Vitamin A at 1 year in liquid FSMP (P = 0.2985)

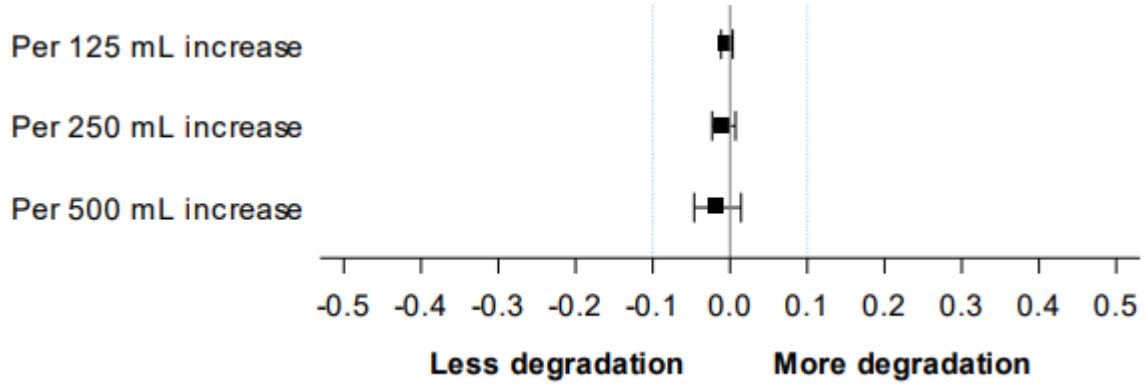
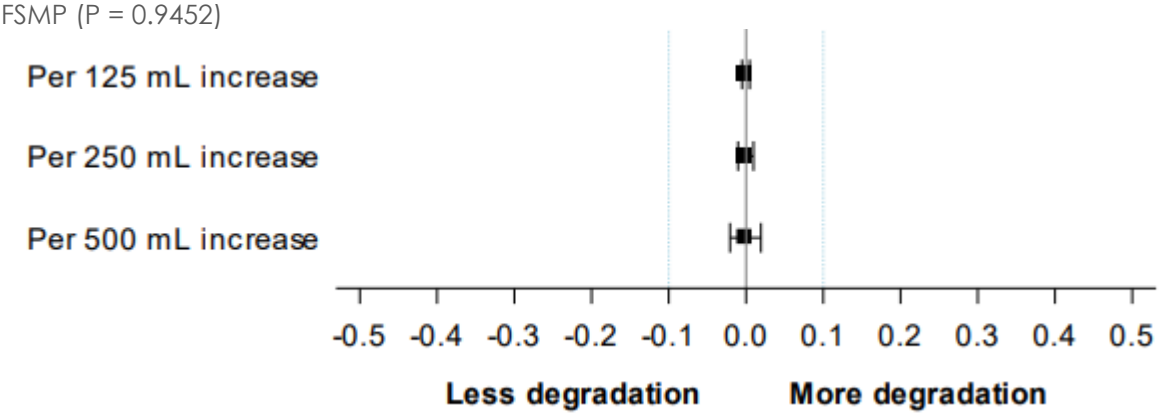


Figure 3: Effect of packaging size on the degradation rate of Vitamin E at 1 year in liquid FSMP (P = 0.9452)



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Annex – Statistical Analysis

The full statistical analyses of the shared stability data were outsourced to SOCAR Research (SOCAR) a third party statistical provider.
FSMPs were classified in categories defined according to the 9 below characteristics with the following 28 indicators thought to have the potential to affect nutrient stability:

- Physical state (liquid, paste, powder),
- Intended age (infant, non-infant),
- Packaging type (metal can, carton, composite, flexible packaging, plastic opaque bottle),
- Nitrogen flushing (No, Yes),
- Level of protein hydrolysis (intact protein, extensively hydrolysed protein, partially hydrolysed protein, amino acid based),
- Fat content (with, without),
- pH (acidified i.e. with a pH below 4.6 in agreement with CXC 23-1979, non-acidified, Not applicable),
- Storage temperature (20°C [18°C-23°C], 25-30°C [23°C-33°C], 35-40°C [33°C-44°C]),
- Storage humidity (less than 60%, 60%-75%, 70%-75%, Not applicable).

In total, data for 150 combinations of these 28 indicators were available in the database for the analysis.
All nutrients quantified at Time 0 (T0 – straight after manufacturing) and at least one time point after T0 were included in the final database, resulting in a total of 31'262 stability curves from 1'463 recipes on 67 different nutrients of interest. These nutrients included the 3 macronutrients (protein, fat, total available carbohydrate, excluding dietary fibre in line with the Codex Alimentarius guideline on nutrition labelling CAC/GL 2-1985 revised in 2011 and amended in 2021), total sugars, glucose and lactose, minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium, iron, zinc, copper, manganese, chromium, molybdenum, selenium, iodine, fluoride), fatty acids (linoleic acid, alpha-linolenic acid, arachidonic acid, docosahexanoic acid, eicosapentanoic acid, erucic acid, saturated fatty acid, monosaturated fatty acids, polyunsaturated fatty acids), amino acids, vitamins (A, C, B6, B12, D, E, K, beta carotene, biotin, niacin, pantothenic acid, riboflavin, thiamin, folic acid), total nucleotides and some other nutrients (choline, inositol, carnitine, taurine). All stability curves have been normalized by dividing the data by the value at Time 0, such that all normalized stability curved started from 1 and decreased towards 0 in case of nutrient loss.

Estimation of the degradation rate for each nutrient

The adaptive Least Absolute Shrinkage and Selection Operator (LASSO) method (Zou 2006) was used to identify the indicators driving degradation for each nutrient. The slope of each nutrient stability curve was correlated with the possible 28 indicators, in addition to the double interaction and triple interaction indicators (i.e. 1757 potential effects) to identify the statistically significant effects on the degradation rate.
Following the LASSO selection for statistically significant effects, the following post selection process was used:

- Selected effects with less than 5% of the total degradation were removed from the model.
- Selected effects present in less than 5 stability curves were removed as potentially not reliable.

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- The three physical state indicators (liquid, powder, paste) were always maintained as separate subgroups by default as it was visible that they were the main driver of the difference in nutrient stability.
- If an interaction of indicators was selected, the single indicators were added, e.g. if "Flushed * Acidified" was selected, "Flushed" and "Acidified" were added.
- If a middle indicator was selected (e.g. 23-33°C, extensively or partially hydrolysed protein,…), the other indicators of the same category were also selected.

Degradation rate model by nutrient

The adaptive LASSO method identified the indicators driving degradation for each nutrient. For each nutrient, data was then split into several subsets of stability curves which share the same combination of indicators responsible for driving degradation. For each subset, a repeated measure model was used with the degradation percentage as the dependent variable; time (in months) as the covariate/fixed effect and the identifier of the stability curve as the random effect.

Both the linear degradation rate, i.e 1-normalised value and log-transformation of the normalised value, i.e log (normalised value) were investigated. In both cases, the value at time 0 was 0 (due to the normalisation) so no intercept was added. For each transformation, linear or log-transformation, the LASSO effect selection, the post selection process and the repeated model was used for each nutrient. For each nutrient, the most appropriate model (linear or log-transformed) was identified using the smallest mean square error (MSE), converted in the linear normalised scale. For each nutrient, the best model was then used to estimate the degradation at 12 months for liquids and at 24 months for powders for each subset.

Nutrient Stability categorization

Through the above-mentioned models, the losses were estimated 12 months after manufacturing for liquid products and after 24 months for powder products, the most common shelf-life durations for these categories of food products. For the purpose of this study, nutrients were considered stable if their estimated degradation was less than the following thresholds established for this study: 5% for macronutrients; 7.5% for fatty acids and 10% for vitamins and minerals, amino acids and nucleotides. These thresholds are much tighter than most of the global tolerances for the nutritional declaration defined in relevant food guidances and regulations. Tolerances are the accepted difference between the value declared in the nutrient declaration on the label of the product and the value obtained by analysis from the time of manufacture through the end of the product shelf life. Tolerances consider shelf-life losses, analytical and manufacturing variabilities and variabilities in nutrient content of raw materials.

Complementary statistical analysis:

As part of this work, a specific statistical analysis was performed on the stability data of affiliated recipes. Affiliated recipes are recipes that only differ by a single parameter such as for example the size of the packaging.

The impact of these specific single differences on the degradation rate of nutrients in the affiliated recipes was analysed using a three-level organizational model with a random slope

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nested by record ID (level 2) and Affiliated ID (level 3). The three-level organizational model enabled the grouping of the data available not only by record ID as the random effect but also by an upper affiliation ID nest.

The affiliation ID identified a group of records from the same recipe code and with the same characteristics related to physical state, age, fat content, type of protein hydrolysis, nitrogen flushing, pH, storage humidity, packaging type and packaging size and storage temperature. This analysis was performed for each nutrient and physical state (i.e. liquid, powder, paste) for which sufficient data was available (i.e. at least 10 affiliation IDs). Only data for liquid recipes was used in the analysis of affiliated recipes due to the limited number of available data. This is not seen as an issue, since the main analysis had shown that powder products were generally stable and the only nutrient which was unstable was Vitamin A.

The goal of the analysis of the affiliated recipes was to show the equivalence of degradation rate for different values of the variable of interest. For example, to show equivalence in degradation rate across the different packaging sizes. In order to show no effect of the variable of interest, the 95% confidence interval of the difference was compared with the stability limit (used as the equivalence margin). Nutrients were qualified as stable based on conservative limits (see above). In order to show equivalence, the 95% confidence interval must have been within the limit of the equivalence margin. In order to show a significantly relevant effect beyond the stability limits, the effect P value must be below 0,05 and the 95% confidence interval must exceed the limit of the equivalence margin.

Reference

H. Zou, 2006. The Adaptive Lasso and Its Oracle Properties. J. Am. Stat. Assoc. 101: 1418– 1429. doi:10.1198/016214506000000735

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