ABSTRACT
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Different types of claims – equal or different standards of evidence

The composition of nutrition has an important impact on human health and wellbeing. Depending on the quantity and quality, nutrition prevents and promotes diseases such as cancer, coronary heart disease, metabolic syndrome, osteoporosis etc. To document the prevention of any nutrition pattern or a special nutraceutical present within the pattern, a disease endpoint, either intermediate or terminal, needs to be influenced by the nutraceutical. The compound in question related to the proposed health claim should be directly linked to the endpoint and the endpoint needs to be clearly related to the "preventable" disease. However, nutrition related diseases do not acutely appear like a common cold. They have a long latency and show many interactions with other factors such as genes, lifestyle, environment and epigenetic influences. For example, vitamin C might be of great importance for endothelial function and the immune system. In the long term, endothelial function or dysfunction contributes to CHD. Sufficient vitamin C (and E) intake may help prevent endothelial dysfunction and, in the long term, CHD. However, the impact of vitamin C on endothelial dysfunction is more or less transient and might appear and disappear, depending on other factors during a treatment study. The impact of vitamin C on endothelial dysfunction might be taken as an "evidence of benefit" similar to the effect of compounds lowering cholesterol or blood pressure.

In contrast, vitamin C might show beneficial effects against the common cold as a more or less acute effect. This might be explained by an effect on the immune system. Depending on the focus, disease risk, duration or immune reaction might be addressed as biomarkers to substantiate the health claim. With respect to regulation, a proper vitamin C supply has a long standing effect on the immune system. If the supply is inadequate, either due to low intake or higher demand, a negative effect appears which can be compensated by supplementation. This makes vitamin C an **essential** nutrient with clearly defined evidence of benefit.

To create an approach for **non-essential** bioactive compounds, it is necessary to define endpoints for chronic and/or acute delivery of the compound. Because we do not know whether any "non-essential" bioactive compound might be yet essential, it is indeed not simple to document a harmful effect if the compound is not present in the diet of healthy people and vice versa to document a benefit if the compound is supplied. The major problem is the fact that with non-essential compounds there is no daily value which is accepted to have a positive impact on health, or vice versa has harmful effects if the daily value is not covered. If a reference value does not exist defining the border between long term risk or benefit, it is at present not possible to define a health claim for that substance. An alternative approach might be to find a biomarker or endpoint which is defined for an essential nutrient which might be substituted by the non-essential compound. Consequently, in cases of a low intake of the essential compound the non-essential would be an alternative.

In cases of structure function claims, it has to be documented that a compound contributes to a process ensuring the regular structure and/or function of a metabolic pathway or tissue. The function of insulin is to lower glucose. A substance lowering glucose independent from insulin might be beneficial in cases of insulin resistance, if the population is healthy. Lowering blood pressure in a “healthy” population with a bioactive compound within a food may be an approach in cases of genetic salt sensitivity. Impact of selenium on prostate cancer may be related to a “healthy” population with benign prostate hyperplasia and MnSOD polymorphism. At least it depends on the clear definition of the population and the relationship between function, biomarker and disease prevention.

Finally, the main aspect of understanding and elucidating the effect of either essential or non-essential nutrients is the fact that nutrients, in contrast to drugs, are not xenobiotics. Very rare bioactive compounds which are present in the diet of a small ethnic group might exert xenobiotic affects in another group due to different epigenetic influences and genetic adaptations. However, the approach recommended for studies with nutrients is a clear pharmacological approach, designed for drugs. This overlooks the fact that nutrients are part of a wide network of metabolic and functional interactions. In contrast, drugs have a specific target which can be defined and at least measured. Based on the guidelines for an RCT, it is easy to define a placebo group in drug research but not for nutrients, in most cases. (See also daily value). Whereas co-medication can be an exclusion criterion in drug research, nutrient “co-medication” (synergism, antagonism of different bioactive compounds) always appears and cannot be excluded.

To substantiate the evidence related to the type of claim on the basis of either nutrient content or structure-function statements, interacting biomarkers or biomarker endpoint interaction is needed. Maintenance of a function as a result of a nutrient interaction in the short term may be related to a dynamic answer of a biomarker in the long term.