How substantiating cause effect relationship for Health Claims?

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Funds, fees, cooperations:

Abbot, BASF, Bauer, BioActor, Biothera, Boehringer Ingelheim, Boehringer Mannheim, Cavis, Campina, Cognis, CRC-Kiel, Danisco, Danone, DSM/SOF, DMV, Drinkstar, Dr. Fischer Health Care, Fresenius, Chr. Hansen, HealthBoost, HSO, Humana, Infectopharm, Kühne, Medixtra, Merck, Merz, MONA, Morinaga, Müller, Nestle, NÖM, Nutrichem, Orthomol, Pegasus, Pharmatech, Schwartau, tecura, Unilever, Wakunaga, Yakult

Health Claim Regulation (EC) No 1924/2006

'health claim': "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health"

1. **Claims according to Art. 13**

- **a) on growth, development and *function of the body***
- **b) on psychological and behavioural functions**
- **c) on slimming or weight control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet**

2. **Claims according to Art. 14**

a) on reduction of *disease risk*

"any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease"

b) on development and health of children

Health Claim Regulation (EC)

„Sufficient evidence for a cause and effect relationship“

Evidence for an „*effect*“ provided by a statistically significant difference in a parameter induced by interventions in man,

whereby verum and control differ only in one item, the „*cause*“ and where bias is excluded by

- **randomised allocation of subjects to the intervention and**
- **blinding**

→ Randomised, double-blind, (placebo-)controlled intervention trial (DB-RCT) in man

Good Clinical Practice
Arzneimittel

Phase I (Sicherheit):

erste Studien mit neuartiger Substanz beim Menschen

Ziel: vorläufige Sicherheitsbewertung
erste Wirkstoffkinetik bzw. –dynamik

Phase II (Wirksamkeit):

Pilotstudien zur Wirksamkeit (DBPC)
Dosis-Wirkungskurven
Nebenwirkungen

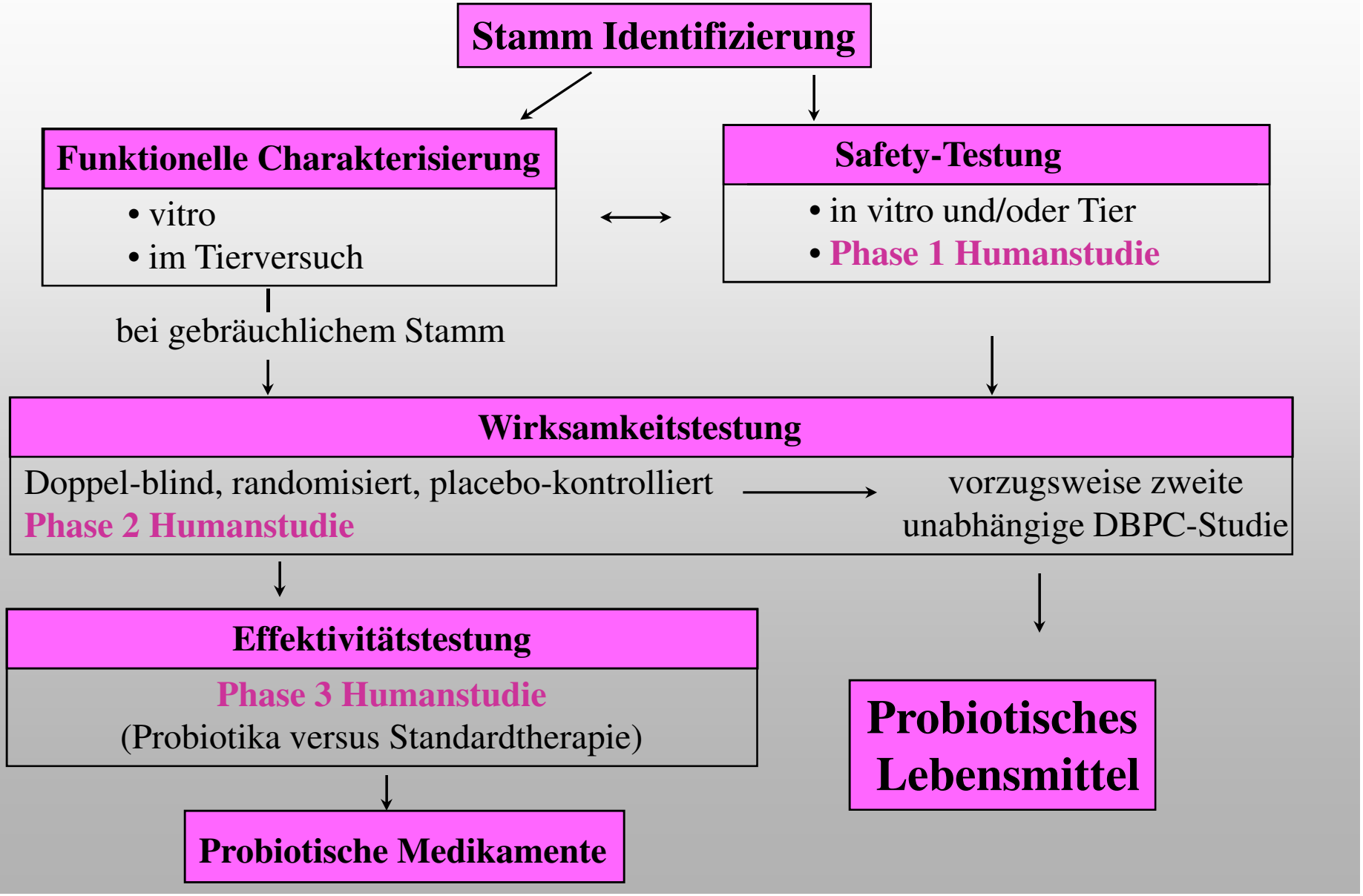
Phase III (Effektivität):

Risiko/Nutzen-Bewertung in Langzeitstudien
im Vergleich zu wirksamen Alternativen

Phase IV (Überwachung):

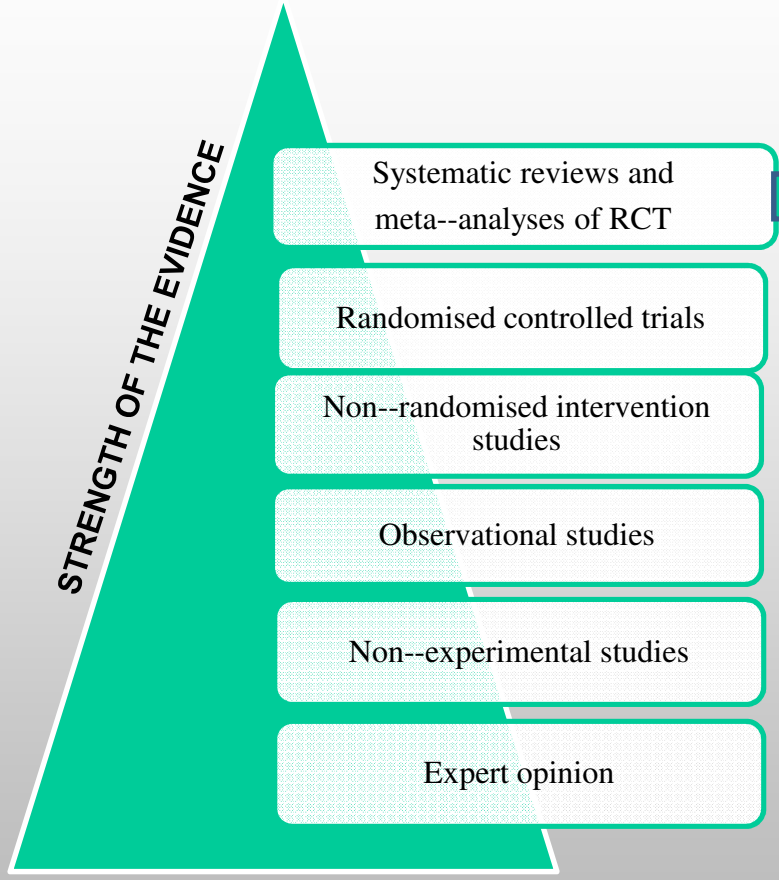
Beobachtungsstudien nach Markteinführung
Studien zu weiteren Anwendungen/Indikationen
Studien zu neuen Darreichungsformen

FAO/WHO –Richtlinien (2002) zur Bewertung von Probiotika in Lebensmitteln



LEVEL OF EVIDENCE

SIGN* System of Evidence-Based Medicine



1++ : high quality meta--analyses, systematic reviews of* RCTs *with a very low risk of bias
1+ : well conducted meta--analyses, systematic reviews* of RCTs *with a low risk of bias
1- : Meta--analyses, systematic reviews of RCTs with a high risk of bias

Adapted from Harbour R & Miller J. BMJ 2001; 323:334–6.
** : Scottish Intercollegiate Guidelines Network*

Oxford Centre for Evidence-Based Medicine Levels of Evidence (March 2009)

1A : Systematic review (SR) (with homogeneity) of RCTs
1b : Individual RCT (with narrow Confidence Interval)
1c : All or none
2a : SR (with homogeneity) of cohort studies
2b : Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c : "Outcomes" Research; Ecological studies
3a : SR (with homogeneity) of case-control studies
3b : Individual Case-Control Study
4 : Case-series (and poor quality cohort and casecontrol studies)
5 : Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles“

Quality Criteria for RCTs

Risk of bias (according to Cochrane Handbook)

- Random sequence generation
- Allocation sequence concealment
- Blinding of participants and personnel
- Attrition bias
- Exclusion bias
- Selective reporting
- Design-specific risk of bias
- Baseline imbalance

Quality Criteria for RCTs

Risk of bias (according to Cochrane Handbook)

Selection bias	biased allocation to interventions
- **Random sequence generation**	inadequate generation of a randomised sequence
- **Allocation concealment**	inadequate concealment of allocations before assignment
Performance bias	knowledge of the allocated interventions by participants and personnel during the study (unblinding)
Detection bias	knowledge of the allocated interventions by outcome assessment
Attrition bias	amount, nature, or handling of incomplete outcome data (exclusion, drop-outs, missing samples, etc.)
Reporting bias	selective outcome reporting
Other bias	Anything else, ideally prespecified
Design-specific risk of bias	*Higgins, BMJ 2011; Higgins, Cochrane Handbook for Systematic Reviews of Interventions, 2008* *See also GRADE (Oxman, 2004, BMJ); Centre for Reviews and Dissemination Guidance(CRD, 2009); EFSA Journal 2010; 8(6):1637*

EVIDENCE GRADE

← decreasing EVIDENCE increasing →

Meta-Analyses
Randomised, double-blind, controlled intervention studies in man defined primary parameter Prior sample size calculation, independent evaluation, Monitoring und Auditing* (ICH E8 (general principles), 1998; ICH E6, 1996 & 2002 (GCP); Regulation (EU) No 536/2014 ; ICH E9, 1998 (statistics); ICH E 10, 2000 (choice of control)) *(www.ich.org/cache/compo/)*
Randomised, double-blind, controlled intervention studies in man monocentric, low sample size
Non-randomised a/o open label a/o non-controlled intervention studies Limited value !

* Never demanded by EFSA in its opinions

Quality Criteria for RCTs

Quality of Reporting

EFSA Journal 2010; 8(6):1637

Simera, A catalogue of reporting guidelines for health research. Eur J Clin Invest 2010; 40 (1): 35–53

EFSA Rejections – Learning Lessons

Based on Quality Criteria for RCTs

- Inappropriate targets (e. g. not compatible with legislative frame

  not showing pathogenicity of a strain for a risk reduction claim based on a risk factor (pathogen)

  assessing C. difficile only in case of AAD applying for a risk reduction claim (risk factor C. diff.)

  → identify targets based on EFSA guidances

- Use of non-validated questionnaires assessing outcome

  → identify pertinent validated questionnaires

  → verify diagnosis/questionnaires by physicians (based on validated criteria)

- QoL questionnaires only supporting evidence (not substantiating)

  → identify other primary and secondary parameters

EFSA Rejections – Learning Lessons

Based on Quality Criteria for RCTs (continued)

- Non considering/reporting on interfering factors (medication)
  → monitor interfering medication and look for differences between verum and control

- Non considering/reporting of interfering nutritional factors
  → monitor/assess dietary intake and look for differences of relevant nutrients between verum and control

- Performance/concealment bias (double-blinding)
  → identical appearance, taste, consistency, consecutive codes

- Attrition bias (high drop out rate, missing values, post hoc exclusion of participants and centers)
  → avoid unnecessary long intervention and follow-up
  → avoid unnecessary load for the participants
  → avoid unexperienced centers

EFSA Rejections – Learning Lession

Based on Statistics

- No prior sample size calculation for the primary parameter (sufficient power?)

  → prior sample size calculation for the primary parameter ($p < 0.05$), for secondary (e.g. after adj. of p value acc. to Bonferroni-Holm)

- No adjustment for multiple testing

  → adjustment for multiple testing for the primary parameter ($p < 0.05$), for secondary (e.g. acc. to Bonferroni-Holm)

  → the fewer defined endpoints, time points and arms, the better

  all others serve exploratory purposes & imputation of missing values(LOCF)

- Selective reporting (reporting bias)

  → only base a dossier for EFSA on primary and secondary outcomes and statistical tests defined a priori in a statistical plan

- Only in post hoc analysis significance

  → may be published, but not valuable for a dossier for EFSA, unless a meta-analysis focused on this parameter provides evidence or all studies show a significant result of this parameter

  → may also be used for sample size calculation for a confirmatory trial

EFSA Rejections – Learning Lession

Based on Statistics

- No/inappropriate ITT analysis of the primary parameter
  → prior sample size calculation taking drop-outs into account
  → appropriate imputation of missing values
- Insufficient handling of missing values (No or only one method of imputation, e.g. LOCF only)
  → more than one method for imputation of single values for the primary parameter (and for secondary), e.g.:
  - LOCF (Last Observation Carried Forward)
  - BOCF (Baseline Observation Carried Forward)
  - best or worst case imputation
  - Multiple imputation methods using an appropriate stochastic model
  - mixed-effect models
  - Likelihood-based methods (MMRM and GLMM)

  + sensitivity analysis testing robustness of results

  EMA/CPMP/EWP/1776/99 Rev. 1, 2010;
  Chakraborty, 2009 doi:10.3768/rtipress.2009.mr.0009.0903
  Elobeid, 2009, PLoS ONE ;

EFSA Rejections – Learning Lession

Based on Statistics

- No consideration of multi-center design in statistics
  → consideration, e.g. analysis of covariance including study sites

- Inappropriate statistical testing in cross-over studies (paired Student t or Wilcoxon test, not taking hang-over effects into account)
  → Repeated-Measures ANOVA

Examples for Potential Targets

Defence against Pathogens (URTI)

Guidance on the scientific requirements for health claims related to gut and immune function

EFSA Journal 2011;9(4):1984

Discussion paper on the revision of the guidance on the scientific requirements for health claims related to gut and immune function

EFSA supporting publication 2014

Outcome of a public consultation on the discussion paper for the revision of the guidance on the scientific requirements for health claims related to gut and immune function

EFSA supporting publication 2015

Primary target: defence against pathogens
As assessed by Upper Respiratory Tract Infections

EFSA guidance:

"For function claims related to defence against pathogens in the [upper respiratory] tract, appropriate outcome measures are [upper respiratory tract] infections (e.g. number of episodes and severity or duration of infection) …
The infectious nature of the disease should be established,
e.g. by clinical diagnosis and/or the use of validated questionnaires"

EFSA Journal 2011;9(4):1984

EFSA opinion on Yestimun:

EFSA Journal 2013; 11(4):3159

"applicant does not establish the validity of the questionnaires and the criteria used in these studies to assess
the incidence, duration or the severity of common cold episodes"

Criteria for Diagnosis:

To be classified as having developed a common cold
the subjects have to meet 2 of the following 3 criteria:

1. A score of ≥14 points above baseline in 6 days based on the following symptoms:
   sneezing, nasal discharge, nasal obstruction, sore throat, coughing, chilliness, headache, and malaise.
2. The impression of the subject that a cold has developed.
3. An increase in nasal discharge on 3 of the 6 days.

Defined by *Jackson et al. 1958* and acknowledged by the EFSA
(see EFSA Opinion on Yestimun; *EFSA Journal 2013; 11(4):3159*.

Confirmatory Study on the Effect on URTI

Primary Parameter:

- **Incidence as expressed by**
  - **1. rate of individuals with ≥ 1 common cold episode**
  - **or**
  - **2. mean number of episodes per individual**
    - **(see criteria of diagnosis)**
  - **Sample size calculation:**
    - **N = 300 to 350 per group** (assumed effect ca. 20% reduction)

Secondary Parameters:

- **Severity as assessed by cumulative symptom score (Jackson)**
  - **per episode**
- **Mean duration of episodes**
  - **(definition of beginning and end of episodes)**

Claim options – targets

"maintaining normal defence against pathogens":

- number, severity and duration of infections (URTIs)

"maintaining immune function" :

- numbers of various lymphoid subpopulations
- proliferative responses of lymphocytes
- phagocytic activity of phagocytes
- lytic activity of NK cells and cytolytic T cells
- production of cellular mediators → secondary option (*see above*)

all have to be accompanied by beneficial clinical outcomes (see above)
(food item may not work via adaptive immunity)

- higher vaccination responses → *primary option*

by itself sufficient

EFSA Journal 2011;9(4):1984

Influenza Vaccination

Pro:

- Flu associated with URTI
- Vaccination recommended to the general population > 60 (50)y

Contra:

- 3 antigens → sample size↑ (multiple testing)
- Seasonal variation of immunity and antigens → no reproducibility
  → varying memory
- No confirmation of previous results with probiotics in recent studies with high sample size (N=1104) *Jespersen, 2015 AJCN*
  (N=737) *van Puyenbroeck, 2012*
- i.m. application → no simultaneous presentation of antigen and adjuvant



Oral Polio Vaccination

Effect of L. rhamnosus GG and L. a.CRL431 - primary target: antibody response to oral polio vacciation

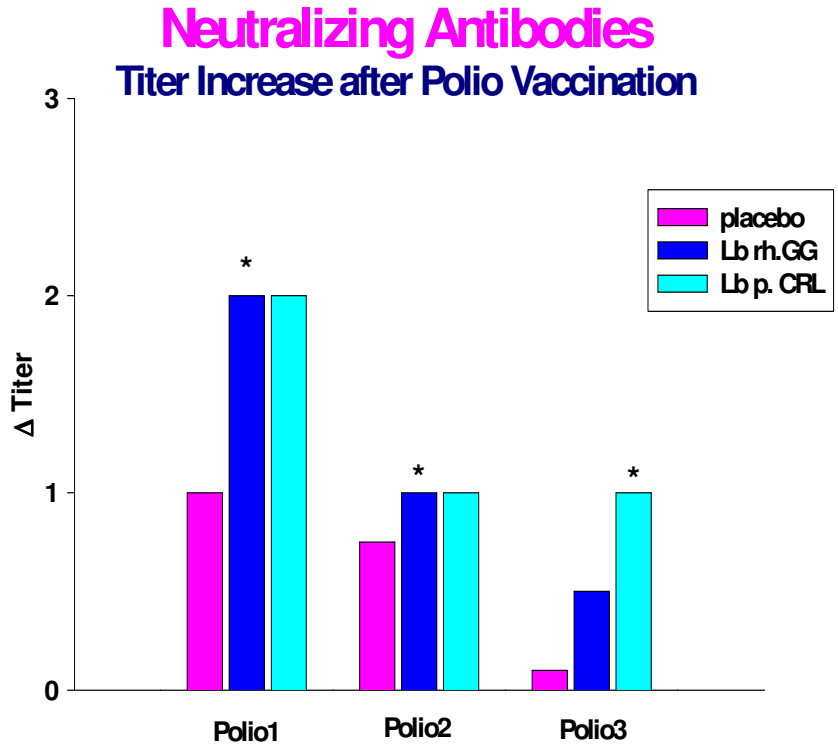
Probiotic bacteria stimulate virus–specific neutralizing antibodies following a booster polio vaccination (DRCT, n=64, antibody determination by standard neutralization test (WHO)).

Cooperation:

MRI Kiel

Inst. Med. Microbiol.Virology, Univ. Kiel

RIVM, Bilthoven, NL



De Vrese et al., EJN 2004

Oral Rotavirus Vaccination
(with attenuated virus)

Findings in favour of probiotic effect:

L. acidophilus → neutralizing antibody titers ↑ after vaccination in neonatal gnotobiotic (Gn) pigs
Zhang, Vaccine 2008

L. rhamnosus GG → *IgA seroconversion* ↑ (26/28 vs. 20/27) after v. in infants
Isolauri, Vaccine 1995

L. rhamnosus GG → *IgA seroconversion* ↑ (10/12 vs. 2/13)
vs. *LGG heat inact.* in infants with rotavirus infection
Kaila, Arch. Dis. Child 1995

Probiotics → *better clinical outcome of rotavirus infections in several studies*

Primary Target: Retention of Minerals

EFSA opinion related to fructooligosaccharides (FOS)

(*EFSA Journal 2010;9(4):2023*)

"improved nutrient absorption is only considered beneficial where absorption is a limiting factor for the maintenance of adequate status of the nutrient, and where increased absorption leads to increased retention.

…. an increase in magnesium and/or calcium absorption leading to an increase in magnesium and/or calcium retention may be a beneficial physiological effect"

Primary Target: Retention of Minerals

EFSA opinion related to fructooligosaccharides (FOS)

(*EFSA Journal 2010;9(4):2023*)

"A first study by Tahiri et al. (2001) was conducted in 11 healthy postmenopausal women not receiving hormone replacement therapy who consumed 10 g/day of FOS for five weeks, and placebo for another five weeks … Isotope-labelled ^{25}Mg retention was reported to be significantly higher with FOS … than without FOS …, however the increase in urinary excretion of magnesium was similar to the increase in magnesium absorption …. No significant increase in apparent magnesium retention was observed."

"A second study by Tahiri et al. (2003) was … conducted in 12 healthy post-menopausal women … who consumed 10 g FOS and placebo for five weeks …. Calcium absorption from the diet … was determined using oral isotope-labelled ^{44}Ca and a faecal marker. Changes in intestinal absorption of calcium were not different between groups. Calcium retention was not measured"

"… only two chronic studies in a low number of human subjects were provided, and … these studies, though suggesting an effect on magnesium (but not calcium) absorption, do not show an effect of FOS … on **mineral retention**.

… a cause and effect relationship has not been established"

Prebiotics and Mineral Absorption

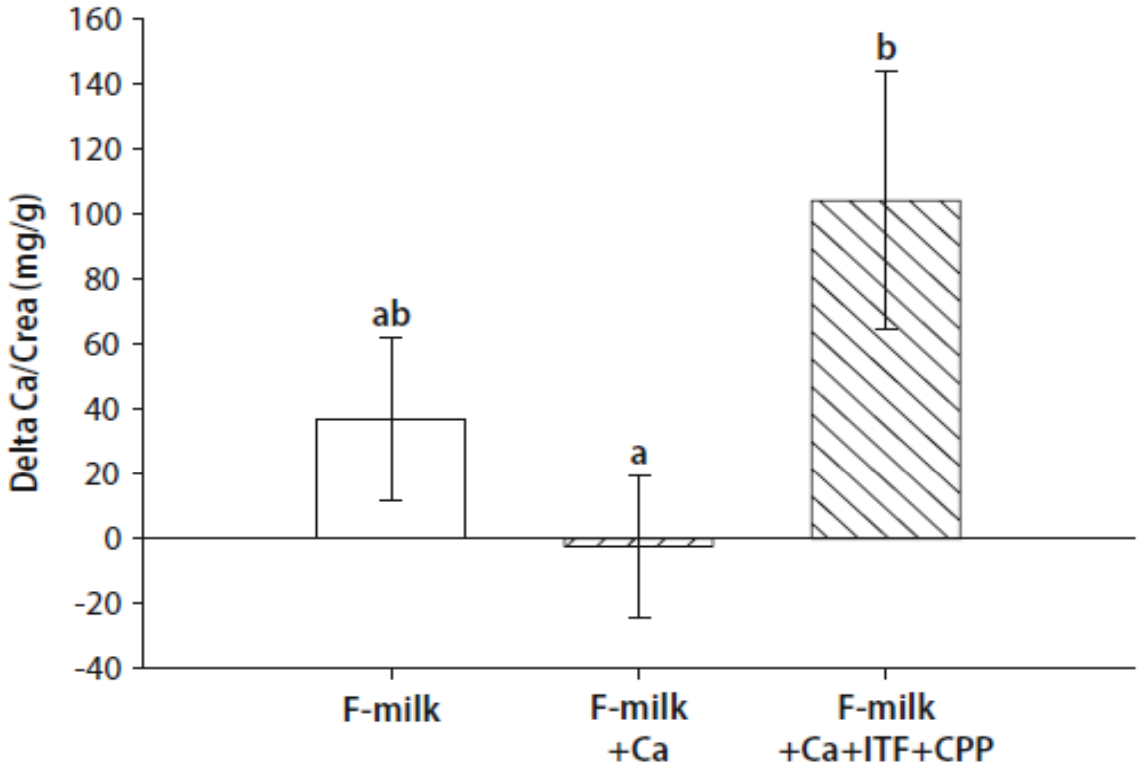


Fig. 1 Changes from baseline of calcium excretion in the night urine fraction (Delta mg/g creatinine) in postmenopausal women who consumed 175 ml of a fermented milk at bedtime for 2 weeks: Without supplement (*open bar* F-milk, $n = 28$), fermented milk supplemented with calcium from milk minerals (Lactoval®), (*striped bar* F-milk + Ca, $n = 28$), and fermented milk supplemented with calcium from milk minerals, inulin-type fructans and caseinphosphopeptides (*striped bar* F-milk + Ca + ITF + CPP, $n = 29$). Least square means ± SEM from ANOVA. Columns not sharing the same superscript letter are significantly different

Adolphi et al., EJN 2009

Prebiotics and Mineral Absorption

Table 2 Effect of intervention with supplemented fermented milk compared to a control milk on change from baseline of plasma and urine parameters of calcium and bone metabolism

	Fermented milk ($N = 28$)	Fermented milk + Ca ($N = 28$)	Fermented milk + Ca + ITF + CPP ($N = 29$)	P value[§]
Serum/plasma				
TAP (U/l)	−4.50 ± 5.90	−7.39 ± 5.98	−2.00 ± 4.88	0.79
BAP (U/l)	−4.41 ± 4.81	−11.03 ± 5.74	−2.88 ± 4.95	0.50
PTH (ng/l)	−12.56 ± 3.44	−8.21 ± 3.79	−8.67 ± 5.13	0.73
P (mg/l)	3.50 ± 0.64	0.83 ± 1.14	2.51 ± 0.71	0.16
Ca^{tot} (mg/l)	−8.24 ± 1.33	−9.54 ± 1.28	−8.81 ± 1.41	0.79
$Ca^{ion.}$ (mg/l)	−0.07 ± 0.26	−0.03 ± 0.22	0.12 ± 0.18	0.81
Day urine				
Ca/Creat. (mg/g)	10.52 ± 22.05	4.15 ± 12.04	26.75 ± 17.34	0.64
P/Creat. (mg/g)	2.92 ± 39.74	−24.10 ± 51.29	38.81 ± 36.57	0.58
DPD/Creat. (µmol/mol)	−1.05 ± 1.11	−0.23 ± 0.87	−0.66 ± 0.77	0.83
Night urine				
P/Creat. (mg/g)	−15.36 ± 53.00[a]	97.27 ± 40.46[a]	242.96 ± 53.01[b]	0.002
DPD/Creat. (µmol/mol)	−3.72 ± 1.09	−1.20 ± 0.84	−0.75 ± 0.92	0.068

[§]By one-way ANOVA. Least square means ± SEM by ANOVA; values not sharing a superscript letter are significantly different; *BAP* bone alkaline phosphatase, Ca^{tot}, Ca^{ion} total resp. ionic calcium, *+Ca* calcium from milk mineral, *CPP* caseinphosphopeptides, *ITF* inulin-type fructans (Synergy®), *P* phosphorus, *PTH* parathyroid hormone, *TAP* total alkaline phosphatase **DPD: Desoxypyridinoline**

Adolphi et al., EJN 2009

Effect of Prebiotics on Mineral Retention of Minerals

Design of studies providing evidence

- DB-RCT with cross-over design

  2 intervention periods (lasting e.g. 4 weeks, each) interposed by a washout period (4 weeks).

  Two weeks before the first intervention period a low dietary fibre diet and abstaining from fermented foods will be started and maintained during the total observation period (reduction of background noice)

  The cross-over design is expected to show the effect with lower number of subjects, e.g. N = 50.

  For a confirmative trial with cross-over or parallel design it would provide a basis for sample size calculation.

- Primary parameter: Calcium retention

  Calcium intake has to be determined, which was not done in the study published by Adolphi for budgetary reasons. This may be achieved by

  - standardized meals ingested during 3 days before and 3 days during stool and urinary sampling and
  - by determination of the calcium content of the meals, stools and urinary excretions.

Examples of Positive Opinions by EFSA

- **Fructo-oligosaccharides (FOS) from inulin reduces post-prandial blood glucose** (and insulinaemic) responses compared with the consumption of sugars on a weight-by-weight basis

  accepted based on iAUC glucose in 3 cross-over trials (N=12 to 40)

  "Consumption of foods/drinks containing non-digestible carbohydrates instead of sugars induces a lower blood glucose rise after meals compared to sugar-containing foods/drinks"

  EFSA Journal 2014;12(1):3513

- **Fructose in place of sucrose or glucose reduces post-prandial glycaemic response**

  accepted based on iAUC glucose in cross-over trials in healthy subjects, impaired glucose tolerance and diabetes (N=10 to 17, each)

  EFSA Journal 2011;9(6):2223

- **beta-glucans from oats and barley reduce post-prandial glycaemic response**

  EFSA Journal 2011; 9(6):2207

Examples of Positive Opinions by EFSA

- **"Native chicory inulin" and maintenance of normal defecation by increasing stool frequency**

  accepted based on stool frequency in 6 studies (N=4 to 44) with 12 to 40 g/d

  2 studies using 5 to 8 g/d did not affect stool frequency

  Accepted because of consistent results although studies were heterogeneous

  regarding the dose used, the administered form (powder in sachets, in bakery products, breakfast cereals, chocolate drinks), the duration of the intervention (from one to four weeks), the sample size, the type of subjects recruited (healthy volunteers, subjects with constipations), the age of participants and the study settings

  although stool frequency was only a secondary outcome in the majority of the studies, and statistics was not always clearly reported *EFSA Journal 2015;13(1):3951*

- **Water-soluble tomato concentrate and maintenance of normal platelet function**

  accepted based on reduction of **platelet aggregation** in 7 studies with consistent results

  although most of them were not double-blind, etc.

  EFSA Journal 2009; 1101: 2-15

Examples of Positive Opinions by EFSA

- **plant sterols/stanols lowering/reducing blood cholesterol and reducing risk of (coronary) heart disease by reducing LDL-C levels**

  accepted based on 19 controlled human studies, 1 uncontrolled human study, and 3 published and 2 meta-analyses provided by the applicant

  EFSA Journal (2009) 1177, 1-12

- **oat beta-glucans and lowering of blood cholesterol (LDL-C) and reducing risk of (coronary) heart disease**

  accepted based on 3 meta-analyses and 19 randomised controlled trials

  EFSA Journal 2010;8(12):1885

- **barley beta-glucans and lowering of blood cholesterol and reducing risk of (coronary) heart disease**

  accepted based on 1 meta-analysis including 11 RCTs, and 1 additional RCT

  EFSA Journal 2011;9(12):2471

CONCLUSIONS

- **Select carefully primary and 1 or 2 secondary parameters according to EFSA guidances and look for prior EFSA opinions**
- **Use only validated questionnaires and critieria for primary and sec. parameters**
- **Design, conduct and evaluation according to GCP** (except monitoring and auditing?)
  - appropriate design
  - prevent risk of bias
  - sample size calculation
  - appropriate statistical approach (e.g. adjustment for multiple testing; ITT-analysis, handling of missing values, sensitivity analysis)

- **First a pilot trial for sample size calculation of a pivotal trial**
- **Then a confirmatory pivotal trial for showing the evidence**
- **If non-significant outcome in one of 2 or more studies → meta-analysis**
- **Conduct only in centers experienced in GCP and nutrition trials**

ß GLUCANS
EFSA Acknowledged Health Claims

Scientific Opinion on the substantiation of a health claim related to oat beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14

EFSA Journal 2010;8(12):1885

" three meta-analyses and 19 randomised controlled trials, as being pertinent to the health claim. In weighing the evidence, the Panel took into account that most of the trials investigating the effects of oat beta-glucan at doses of at least 3 g/d have shown a statistically significant decrease in LDL-cholesterol concentrations, and that there was strong evidence supporting the biological plausibility of the effect. The Panel concludes that a cause and effect relationship has been established between the consumption of oat beta-glucan and lowering of blood LDL-cholesterol concentrations. The following wording reflects the scientific evidence: "Oat beta-glucan has been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of (coronary) heart disease". "

Gesundheitsbezogene Angaben

Funktionelle Aussagen

- **Generisch**

  „Vitamin C schützt Körperzellen“
  „Ballaststoffe fördern die Verdauung“

  Die EU wird eine Liste mit zugelassenen **generischen Health Claims** veröffentlichen

- **Individuell**

  „L.casei xy aktiviert die Abwehrkräfte“

  „Produkt z hilft den Cholesterinspiegel zu senken“

  Individuelle Health Claims müssen mit ausreichenden wissenschaftlichen Studien belegt werden und von der EFSA genehmigt werden

Angaben zur Risikoreduktion

Angaben zur Risikoreduzierung

„kann das Risiko von Osteoporose deutlich senken“

Jede Angabe die zum Ausdruck bringt, dass der Verzehr eines LM einen Risikofaktor für die Entwicklung einer Krankheit deutlich senkt

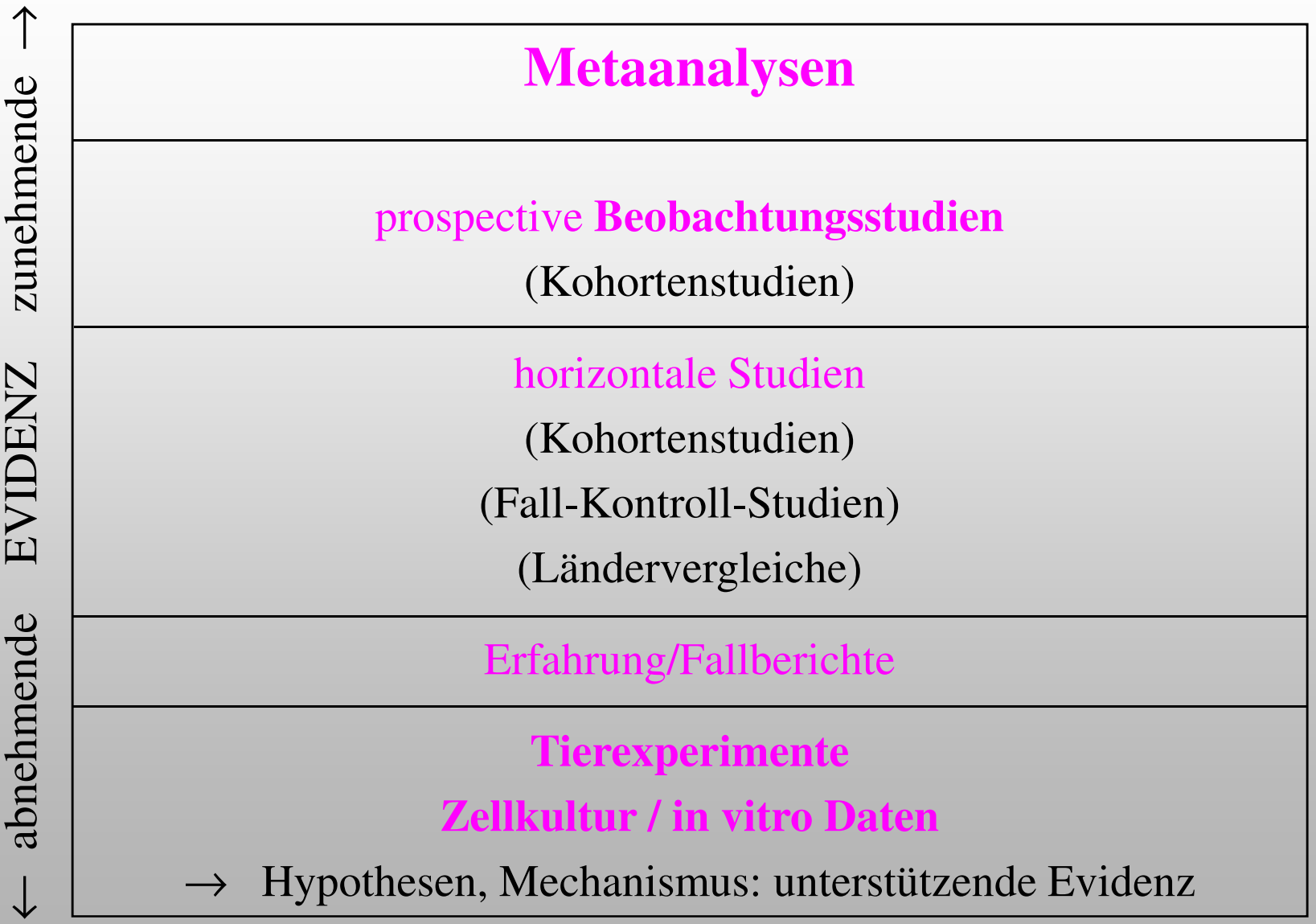
- unter strengen Voraussetzungen erlaubt, nach Zulassungsverfahren
- Nachweis wissenschaftlicher Studien, die Angaben bestätigen
- Erklärung, dass die Krankheit durch mehrere Risikofaktoren bedingt ist und die Veränderung eines Risikofaktors eine positive Wirkung haben kann – oder auch nicht (z.B. „die Senkung des Cholesterinspiegels ist nur eine von vielen Maßnahmen, die das Risiko einen Herzinfarkt zu erleiden reduzieren kann“)
- Wörter „deutlich“ und „Risiko“ sollten enthalten sein

CLAIMS APPROVAL PROCESS



POQ

EVIDENZ GRADE II



BELEG EINES HEALTH CLAIMS

(Wirksamkeitsnachweis)

- **1 pivotale/beweisende humane Interventionsstudie (DBPC)**

  nach GCP-Richtlinien

  + unterstützende klinische Studien und/oder

  + epidemiologische Studien und/oder

  + mechanistische/tierexperimentelle/in vitro Daten

  oder

- **≥ 2 DBPC Studien durch unabhängige Untersucher**

offene Studien, epidemiologische, tierexp. oder in vitro Daten reichen nicht

der Primärparameter (Endpunkt) ist kritisch