KOEMELKEIWITALLERGIE IN THEORIE EN PRAKTIJK

Dr. Bruno Hauser en Mevr. Karen De Brul
Universitair Kinderziekenhuis Brussel - GASTROKIDS

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Diagnostic approach and management of CMPA in infants and children: ESPGHAN GI Committee practical guidelines.

Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, Mearin ML, Papadopoulou A, Ruemmele FM, Staiano A, Schäppi MG, Vandenplas Y;
J Pediatr Gastroenterol Nutr. 2012;55:221-9

Koemelkeiwitallergie : theorie

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- **Introduction**
- Symptoms
- Diagnosis
- Treatment
- Prevention
- Conclusion

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Definition

Reproducible clinically abnormal reaction
to cow's milk protein due to
the interaction between one or more milk proteins
and one or more immune mechanisms

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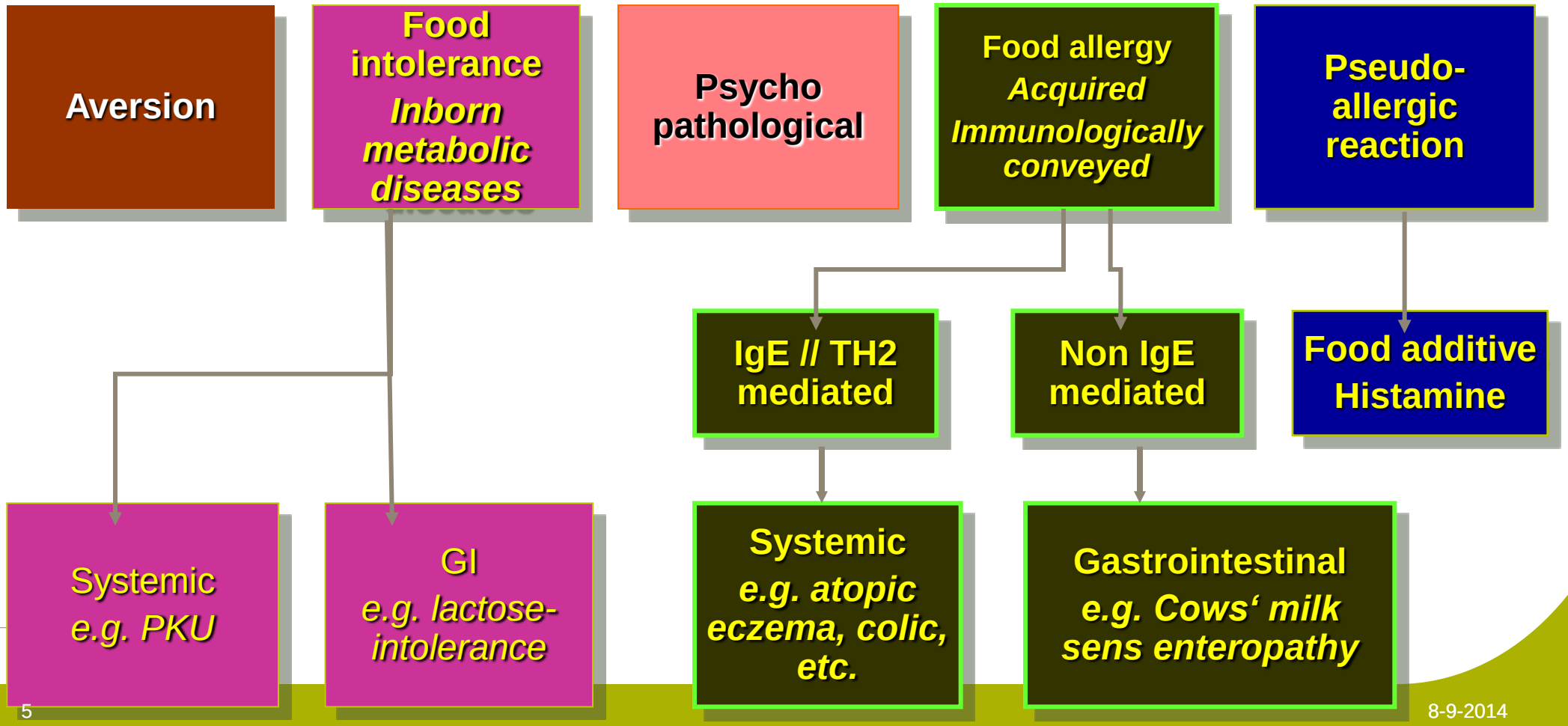
Adverse Reactions to Food



Incidence

- Most frequent etiology of atopic disease in infants:

  - 0.5 % in breast-fed
  - 2.0 to 3.0 % in cow's milk formula fed

- CMPA perception parents > CMPA proven oral challenge test

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Evolution

- Tolerance: 50% at 1years / >75% at 3years / >90% at 6years
- IgE mediated CMPA has an increased risk of persistant CMPA
- IgE mediated CMPA has an increased risk of developing allergy to other foods <3y
- Asthma, allergic rhinitis and eczema are more common in children with a history of CMPA than would be expected in the general population

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Symptoms

	Infants & toddler	Older children	Immediate reaction (within minutes until 2 h after ingesting CMP)
Digestive tract	• Dysphagia • Frequent regurgitation • Colic, abdominal pain • Vomiting • Anorexia, refusal to feed, • Diarrhea +/- enteral protein or blood loss • Constipation +/- perianal rash • Failure to thrive • Occult blood loss • Iron defic. anemia	• Dysphagia • Food impaction • Regurgitation • Dyspepsia, • Nausea, vomiting • Anorexia, early satiety • Diarrhea +/- enteral protein or blood loss • Constipation? • Abdominal pain • Occult blood loss • Iron defic. anemia	• Vomiting
Respiratory tract	• Runny nose • Wheezing • Chronic coughing (all unrelated to infections)	• Runny nose • Wheezing • Chronic coughing (all unrelated to infections)	• Wheezing with laryngospasm • Difficulties breathing
Skin	• Urticaria (unrelated to infections, drug intake or other causes) • Atopic dermatitis • Angioedema (swelling or lips or eye lids	• Urticaria (unrelated to infections, drug intake or other causes) • Atopic dermatitis • Angioedema (swelling or lips or eye lids	• Angioedema • Urticaria
General	• Anaphylaxis • Shock like symptoms with severe metatobolic acidosis, vomiting & diarrhea (FPIES) Wheezing	• Anaphylaxis	• Anaphylaxis • PFIES

Atopic dermatitis

With milk

15 days without milk

Symptoms

- There are no pathognomonic symptoms for CMPA !!!

- The diversity of symptoms associated with CMPA, their non-specific nature and the variable temporal relationship with milk ingestion may complicate diagnosis especially for non-specialists

- <u>When is suspicion of CMPA stronger:</u>
  . symptoms develop within 2 months after introduction of cow's milk
  . symptoms develop within 2 hours after ingestion of cow's milk
  . more than one organ system involved
  . family history of atopy

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Skin Prick Test
IgE and Specific RAST

There is not one single laboratory test that can give you the answer

- A negative test result does not exclude CMPA what is the case in most infants

- The higher the antibody titer or the larger the diameter of the SPT reaction, the greater the probability for CMPA and for a longer persistance of allergy

- Children with gastrointestinal manifestations of CMPA are more likely to have negative specific IgE results compared to patients with skin manifestations

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Food challenge: Golden Standard

Oral food challenge: open single (double blind) challenge under medical supervision with treatment of anaphylaxis available

Oral Food Challenge:

- Increasing amounts of cow's milk every 30 minutes:

1-3-10-30-100 ml if delayed reaction

0,1-0,3-1-3-10-30-100 if ml severe reactions

- Observation 2 hours after challenge

- Further 200 ml at home every day

If no symptoms within 2 weeks of regular cow's milk feeding: CMPA is excluded

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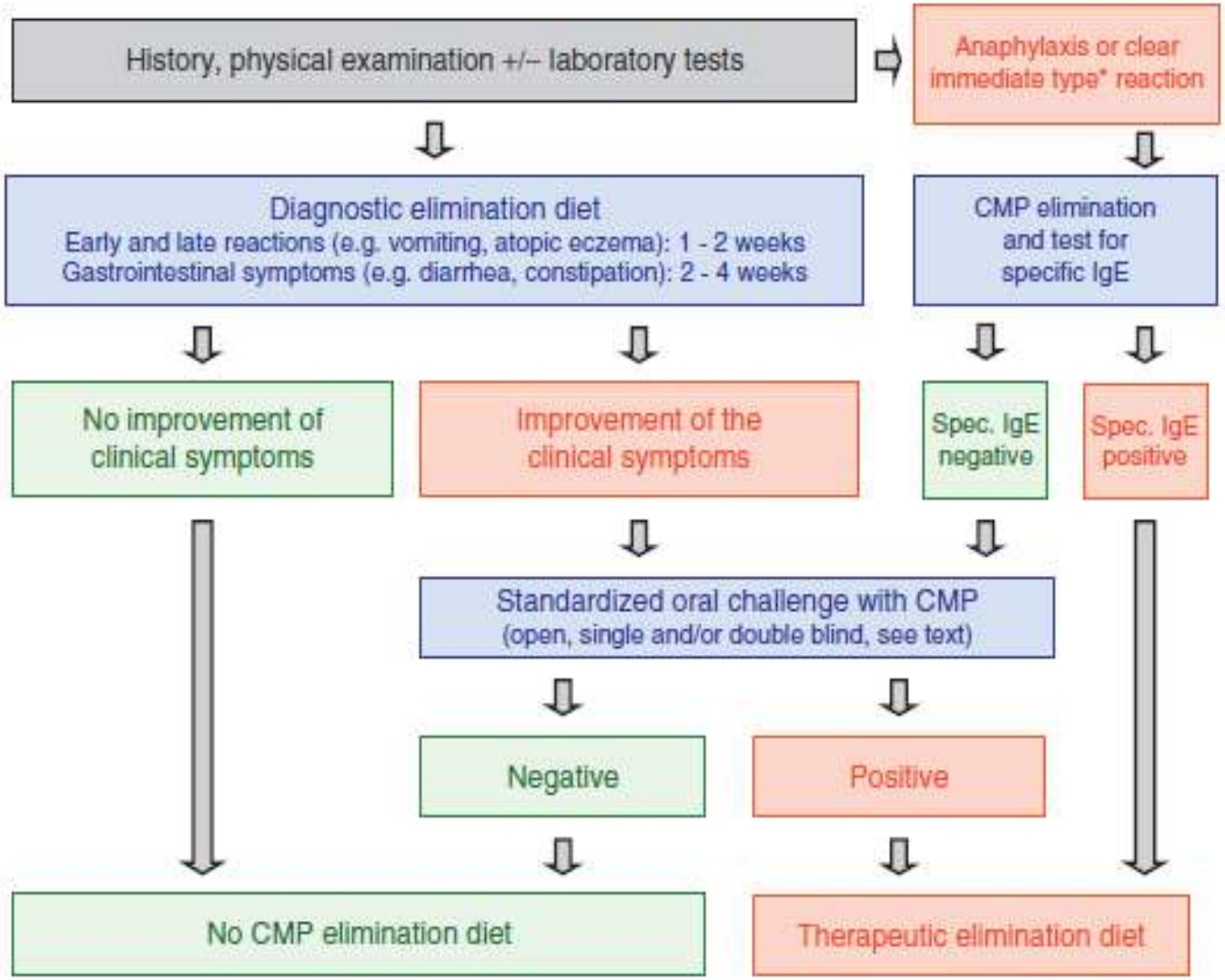

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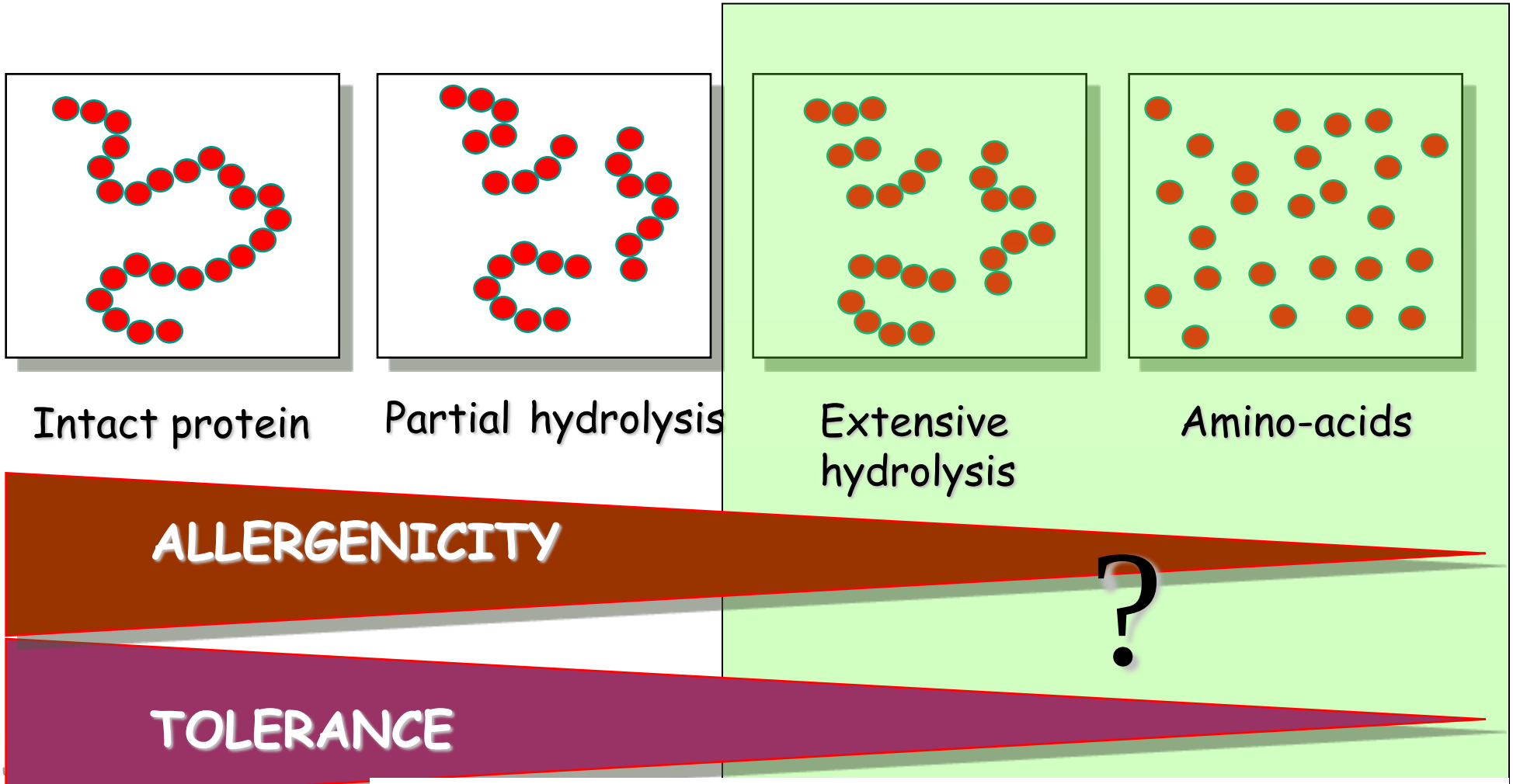
Hydrolysed formulas



Influence protein source, hydrolysis method and degree of hydrolysis

Hypoallergenicity of an extensively hydrolyzed whey formula.

Giampietro PG. Pediatr Allergy Immunol. 2001;12:83-6.

No allergic reactions in at least 90% of children
with a proven CMPA

Table 1. Results of skin prick and challenge tests for the different formulas

Type of formula	SPT*	DBPCFC*
Cow's milk	32/32 (100%)	31/31 (100%)
Nutrilon Pepti (e)	6/31 (19%)	1/31 (3%)
Profylac (e)	4/26 (15%)	2/26 (8%)
Nan HA (p)	10/31 (32%)	9/25 (36%)

*Data are expressed as: number of positive reactions/total number tested (%).
e, extensive hydrolysate; p, partial hydrolysate.
DBPCFC, double-blind, placebo-controlled food challenge; SPT, skin-prick test.

Treatment

First choice = Extensive Hydrolysate cow's milk based proven efficacy

expensive
poor palatability (bitter)

Amino Acid Formula =

- Second choice if reaction to extensive hydrolysate (<10 %)
- First choice if severe anaphylactic reactions and severe enteropathy

<u>< 12 months:</u> for 6 months or until 9-12 months of age
until 12-18 months of age if severe IgE-mediated reactions

<u>>12 months:</u> for 6-12 months

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Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition.
ESPGHAN Committee on Nutrition JPGN 2006;42:352-61

ESPGHAN CMPA 2012

- Before 6 months:
  - Soy not recommended
  - 10% to 14% of infants with CMPA will also have a soy protein allergy (mainly infants < 6 months)
  - high concentrations of phytooestrogens (isoflavones), aluminium and phytates

- After 6 months:
  - Soy can be used if tolerance first established
  - benefit : acceptability, cost, veganism…

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Sensitization and Allergy to Soy-Based Products. Is it a problem that should concern us? Systematic Review of the Evidence. *Katz Y. Clin Rev in All & Immunol 2014*

Since 1943, cases of sensitization or allergy to soy-based formulas (SBFs) have been described without any consensus on their real prevalence. We identified the adjusted prevalence of IgE-mediated soy allergies in children, and performed a secondary analysis of the impact of age (less than and more than six months). We performed a systematic review with meta-analysis of studies published from 1909 to 2013 in PubMed, Embase, LILACS, ARTEMISA, Cochrane, Bandolier, DARE and the GRADE system for grading quality. Results are presented in tables and graphs using a forest plot. The 40 studies identified established weighted prevalence of soy allergies of 0.1% to 0.7% for the general population, 1.9% to 12.7% for the referred population and 2.7% to 27.1% for atopic children. Prevalence of sensitization after the use of SBFs is 8.7% and 8.8%, depending on the method used.

The prevalence of allergies to soy and IgE sensitization to the use of SBF are less than reported. Not enough evidence exists to show a higher risk of allergy in infants younger than six months. The concern about soy allergy is no reason to postpone the use of SBFs in IgE-mediated cows-milk allergy infants until the age of six months.

Safety of Soy-Based Infant Formulas (SBIFs) in Children: A Systematic Review With Meta-Analysis. *Vandenplas Y. Br J Nutr* 2014 Apr;111(8):1340-60

Children fed SBIFs have similar anthropometric patterns when compared to cow's milk formula (CMFs) or human milk (HM).

Despite the high levels of phytates and aluminum in SBIFs, the haemoglobin, serum protein, zinc and calcium and BMC were similar to those with CMFs or HM.

Levels of genistein and daidzein are higher in children fed SBIFs; however, we did not find strong evidence of a negative effect on reproductive and endocrine functions.

Immune measurements, and neurocognitive parameters were similar in all feeding groups.

<u>Modern SBIFs are evidence-based safety options to feed children who require them. Patterns of growth, bone health and metabolic, reproductive, endocrine, immune and neurologic functions are similar to those observed in children on CMBFs or HM.</u>

Is rice an option?

- DRACMA guidelines 2010:
  - → No recommendations in several international societies: ESPGHAN, Australian Consensus Panel, AAP
  - → Care should be taken for the nutritional requirements while replacing a protein source by another one
  - → Like any other extensive hydrolysate formula, 90% efficacy has to be demonstrated

- ESPGHAN CMPA 2012: may be considered in selected infants which are refusing or not toleranting a cow's milk based extensive hydrolysate formula or in vegan families

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An extensive rice protein hydrolysate in the treatment of CMPA: preliminary results after 1 month. *Vandenplas Y. Arch Dis Childh 2014* Jun 9. [Epub ahead of print].

39 infants (mean age 3.4 months, range 0.5–6 months) diagnosed with CMPA were enrolled.
All infants tolerated the extensive-rice-hydrolysate-formula *(Novarice*) and experienced a normal growth.
In accordance with current guidelines, this extensive-rice-hydrolysate-formula is tolerated by more than 90% of children with CMPA and therefore could provide an adequate and safe alternative to cow milk based extensive hydrolysate formula.

- Cheaper than CM based eHF
- Better palability than CM based eHF
- No safety issue as for soy

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Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Osborn DA, Sinn J. Cochrane Database Syst Rev. 2006:CD003664*

No evidence to support feeding with a hydrolysed formula for the prevention of allergy compared to exclusive breast feeding.

In high risk infants who are unable to be completely breast fed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces:

- infant and childhood allergy
- infant CMPA.

Reviewed in 2007; no change

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Hydrolysed formulas for allergy prevention.

Vandenplas Y. JPGN 2014 Feb 25. [Epub ahead of print]

In high risk infants,
when breastfeeding is not possible,
hydrolysates of documented safety and efficacy
have an indication in infant feeding up to the age
of 4 to 6 months

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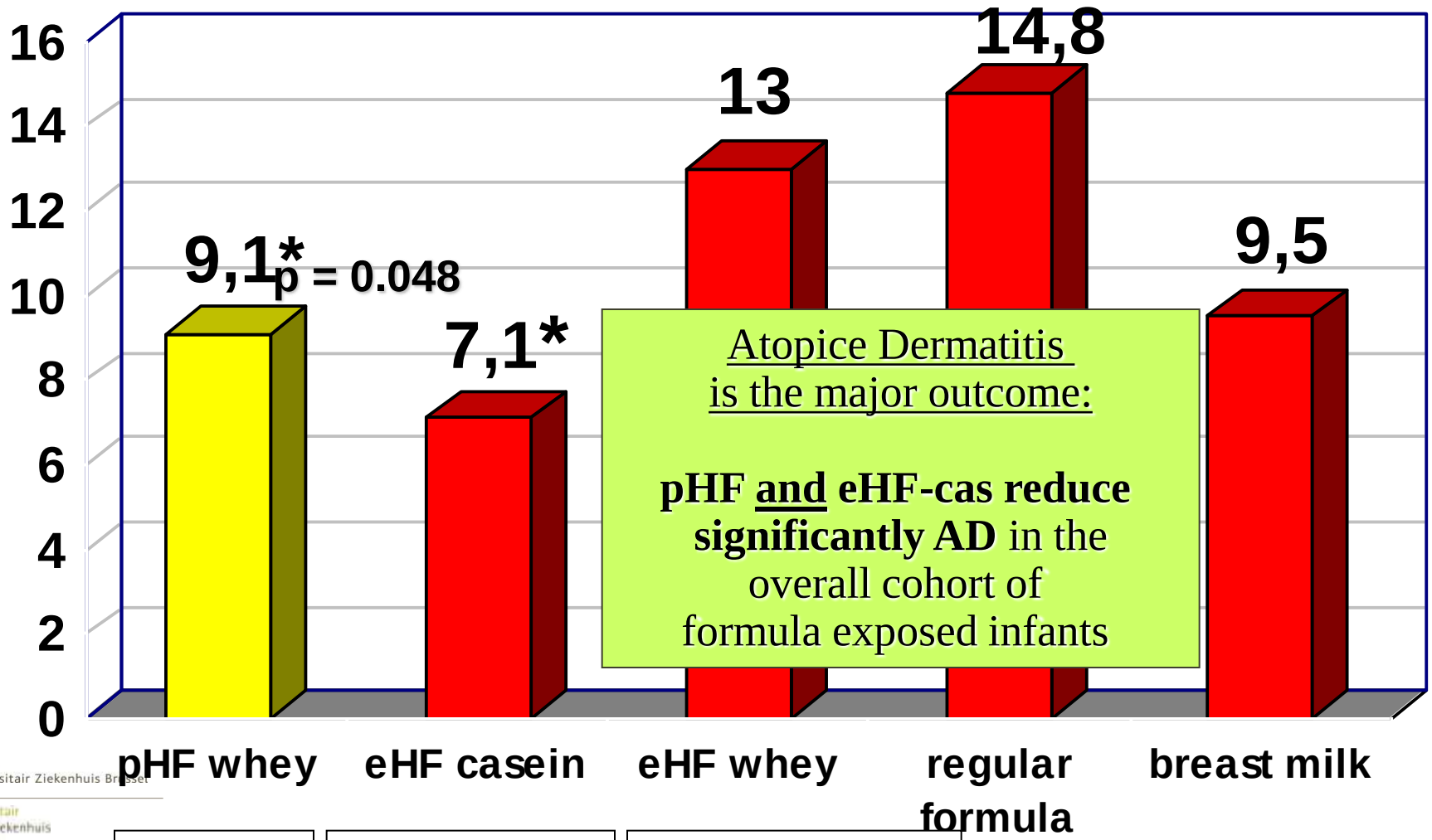
The effect of hydrolysed cow's milk formula for allergy prevention in the 1st year of life: the GINI-study? *A. Von Berg. J Allergy Clin Immunol 2003;111:533-40*

Results of the 945 infants, mixed fed: breastmilk and formula exposed



Atopice Dermatitis is the major outcome:

pHF and eHF-cas reduce significantly AD in the overall cohort of formula exposed infants

NanHA | *Nutramigen* | *Nutrilon pepti*

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Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the GINI study.

von Berg A. Allergy Clin Immunol 2013;1311565-73

TABLE I. ITT analyses: cumulative incidence from 10-year follow-up and period prevalence at 7 to 10 years

	CMF	pHF-W	eHF-W	eHF-C
No. of followed children (n = 2252)	556	557	559	580
AM* cumulative incidence, birth to 10 y	63.1%	58.6%	59.9%	54.2%
RR (95% CI)	1	0.87 (0.77-0.99)	0.94 (0.83-1.07)	0.83 (0.72-0.95)
AM prevalence in 7th to 10th years (n = 1377)	34.3%	34.1%	35.0%	27.7%
RR (95% CI)	1	1.0 (0.81-1.23)	1.02 (0.83-1.26)	0.81 (0.64-1.01)
AD cumulative incidence, birth to 10 y	40.5%	35.3%	34.8%	29.3%
RR (95% CI)	1	0.82 (0.68-1.00)	0.91 (0.76-1.10)	0.72 (0.58-0.88)
AD prevalence in 7th to 10th years (n = 1389)	11.2%	13.2%	9.6%	8.2%
RR (95% CI)	1	1.18 (0.79-1.77)	0.86 (0.55-1.34)	0.74 (0.47-1.16)
Asthma cumulative incidence, 3-10 y	8.05%	11.4%	11.4%	8.9%
RR (95% CI)	1	1.56 (0.97-2.49)	1.58 (0.99-2.52)	1.08 (0.66-1.79)
Asthma prevalence in 7th to 10th years (n = 1407)	7.4%	9.3%	11.3%	6.3%
RR (95% CI)	1	1.26 (0.76-2.07)	1.53 (0.95-2.48)	0.85 (0.49-1.47)
Rhinitis cumulative incidence, 4-10 y	20.4%	18.9%	21.0%	18.7%
RR (95% CI)	1	0.95 (0.69-1.30)	0.93 (0.69-1.26)	0.92 (0.67-1.25)
Rhinitis prevalence in 7th to 10th years (n = 1393)	17.2%	14.7%	19.4%	14.0%
RR (95% CI)	1	0.85 (0.60-1.21)	1.13 (0.82-1.55)	0.82 (0.58-1.15)

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CONCLUSIONS

- Symptoms of CMPA are aspecific
- Family history and good clinical examination are mandatory
- CMPA is *suspected* in 5-15% of infants
- CMPA is *confirmed* in 2-5% of infants
- In >90% of infants, CMPA is temporary
- Adequate diagnosis is necessary to avoid unnecessary and expensive diets ⇒⇒ Food Challenge !

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CONCLUSIONS

- Early diagnosis limits growth impairment

- Prevention = partial hydrolysate formula versus extensive hydrolysate formula (bad taste - more expensive)

- Treatment = eliminate allergen:
  - breastfeeding: cow's milk free diet for mother
  - mild to moderate symptoms: extensive hydrolysate formula is sufficient in > 90% of patients
  - severe symptoms: amino acid formula
  - soy-based and extensive rice hydrolysate formula ?

Cow Milk Protein Allergy (CMPA)

? CMPA based on symptoms ?

Breastfed baby

Continue BF, mother on CM-free diet

Symptoms improve or disappear

No → Reconsider compliance
Consult dietician & medical specialist
Not CMPA? ?

Yes → Consider Cow's milk challenge

Formula fed baby
Anaphylaxis
(spec IgE positive or pos SPT)

2- 4 weeks AAF

Symptoms improve or disappear

No → Not CMPA

Yes → Consider Cow's milk challenge

Formula fed baby
No anaphylaxis

eHF 2-4 weeks
(soy or eRHF if eHF not accepted)

Symptoms improve or disappear

No → Not CMPA

Yes → Consider Cow's milk challenge

?

Consider Cow's milk challenge
May not be undertaken if clinical diagnosis is obvious or symptoms are life threatening

Long-term management
- Elimination of cow milk sources
- Consider: Breast milk as the first option
  Extensively hydrolyzed formula (CM/Rice) / Soy formula / AAF
- Monitor for tolerance

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SPT: skin prick test
BF: breastfeeding
AAF: amino acid based formula
E(R)HF: extensive (rice) hydrolysate formula

Koemelkeiwitallergie : praktijk

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Theoretische voedingsrichtlijnen

Dé enige behandeling bij koemelkeiwit-allergie is

eliminatie van ALLE koemelkeiwitten in voeding

(≠ lactose-arme voeding)

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Praktische voedingsrichtlijnen

- Voedingsrichtlijnen bij borstvoeding
- Voedingsrichtlijnen bij flesvoeding
- Voedingsrichtlijnen bij diversificatie
- Voedingsrichtlijnen bij oudere kind en volwassene
- Knelpunten in behandeling
- Praktische tools

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Voedingsrichtlijnen bij borstvoeding

Stoppen van borstvoeding NIET aangewezen !

Aanbeveling weglaten van ALLE zuivelproducten en voedingsmiddelen die melk of melkbestanddelen bevatten

Aanbeveling van dagelijkse inname van 450ml melk en 30g kaas (Kind en gezin)

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Voedingsrichtlijnen bij borstvoeding

Eiwitten? Calcium? Vit B2?

(HGR Belgische voedingsaanbevelingen 2009 :
0.9g/kg LG – 1200mg Ca – 1.8mg Vit B2)

- Dekking calcium- en vitaminebehoefte
  - → OF ¾ liter sojamelk, verrijkt met Ca en vitaminen
  - → OF supplement van Ca (1000mg)
    en Vit B2 (1.5mg)
- Dekking eiwitvoorziening
  - → Gebruik voldoende vlees (200g per dag)

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Voedingsrichtlijnen bij flesvoeding

ESGHAN Practical Guidelines
Diagnostic approach and management of CMPA in infants and children 2012

Niet geschikt voor dieetbehandeling bij KMEW-allergie

- Intact koemelkeiwit

NAN PRO, Nutrilon , Novalac premium, Enfamil premium

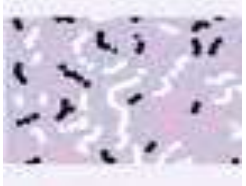
- Partieel hydrolysaat

NAN HA, Nutrilon HA, Novalac HA, Enfamil HA digest

Dieetbehandeling bij KMEW-allergie

- Intensief hydrolysaat

Alfare, Nutrilon pepti (lactosevrij), Novalac Allernova AR, Nutramigen



- Vrije aminozuren

Neocate (advance), Nutramigen AA

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Voedingsrichtlijn bij flesvoeding

- Naast intensief hydrolysaten obv koemelk ook intensief hydrolysaat obv rijst

  Novalac Novarice

- Belangrijk verschil in kostprijs/ smaak

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Voedingsrichtlijn bij flesvoeding

- Zuigelingenmelk obv soja pas vanaf leeftijd 6 maanden (smaak/kostprijs)

  Nutrilon soja Nutricia
- Geiten-, schapen-, ezelinnen- en paardenmelk af te raden

  → Hoog risico kruisreactie
- Granen-, rijst- en notenmelk af te raden

  → Geen volwaardige nutritionele vervanging

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Voedingsrichtlijnen bij diversificatie

- Introductie groentenpap/fruitpap
  - → Zelfbereid of kant- en klaar
  - → Obv kindermelen of pletkoekjes zonder melk
  - → Noodzaak correcte en up-to-date productinformatie!

- Europese richtlijn (nov 2005) verplichte vermelding op verpakking al of niet bevatten van melk
  - → Duidelijke vermelding in ingrediëntenlijst
  - → Op verpakking " bevat melk"
  - → Benaming van voedingsmiddel verwijst naar melk

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? Betterfood start ?

Ingrediënten:

Erwtenzetmeel 38.1%, aardappelzetmeel 22.7%, glucosestroop, suiker; ongehard en gehard plantaardig vet, erwteneiwit, rijstzetmeel, rijsmiddel, calciumcarbonaat, emulgator (sojalecithine), magnesiumcarbonaat, aroma, vit B1

MET ZEER LAAG GLUTENGEHALTE, BEVAT SOJA.

KAN GLUTEN, TARWE, EI, MELK EN SESAM BEVATTEN

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? Nestlé baby cereals rijst-vanille?

Ingrediënten:

Rijstmeel en gehydrolyseerd rijstmeel, calciumcarbonaat, vitamines (C, E, PP, B1, A, B6, foliumzuur, D), vanilline, ijzerfumaraat, Bifidus cultuur, zinksulfaat.

Mogelijke sporen van melk.

Glutenvrij.

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Voedingsrichtlijnen oudere kind en volwassene

- Gebruik verrijkte sojamelk met Ca en vit
- Nieuwe soorten plantaardige “melken” geen volwaardig alternatief ter vervanging koemelk

/100ml	Kcal	E(g)	V(g)	Kh (g)	Ca (mg)	Vit B2 (mg)
Alpro soya original®	39	3	1.8	2.5	120	0.21
Rice dream original®	47	0.1	1.0	8.1	120	-
Alpro almond original®	24	0.5	1.1	3	120	0.21
Halfvolle koemelk	*46*	*3.3*	*1.6*	*4.8*	*119*	*0.18*

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Knelpunten in behandeling

- Etikettering
  → Vermelding “melk” als verplicht allergeen
  → Vermelding sporen van melk

- Opmars gamma plantaardige “melken”

- Uitbreiding gamma weaning food

(kindermelen, maaltijden, desserts …)

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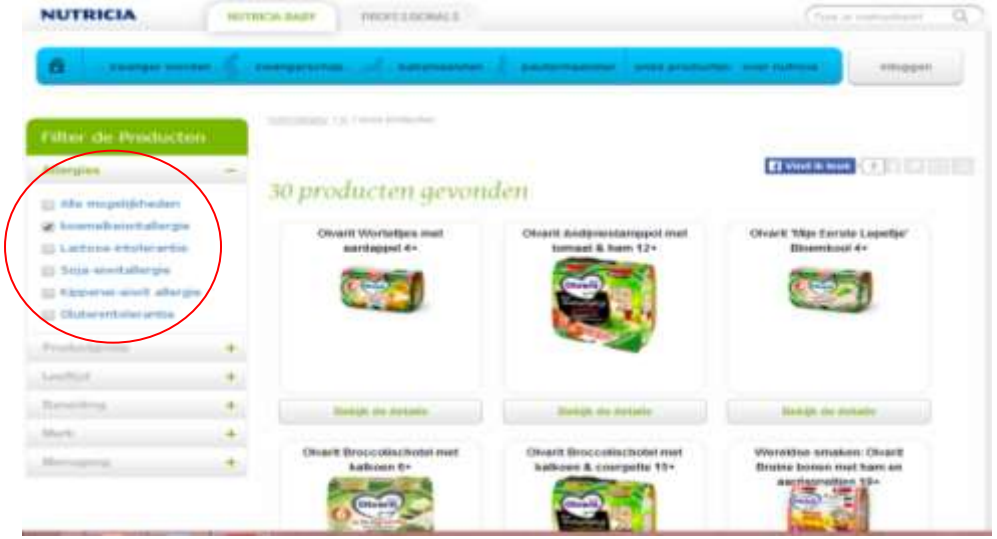
Praktische tools : productinformatie



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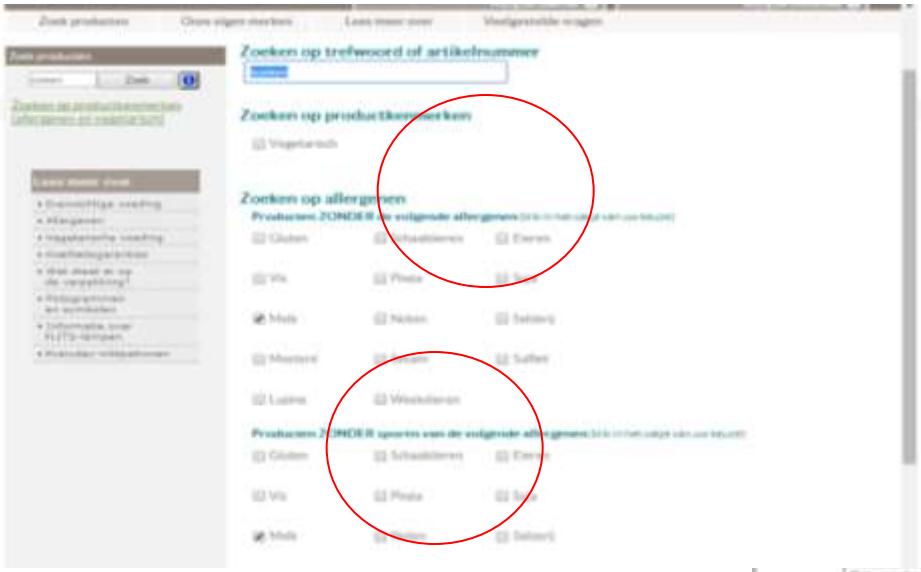
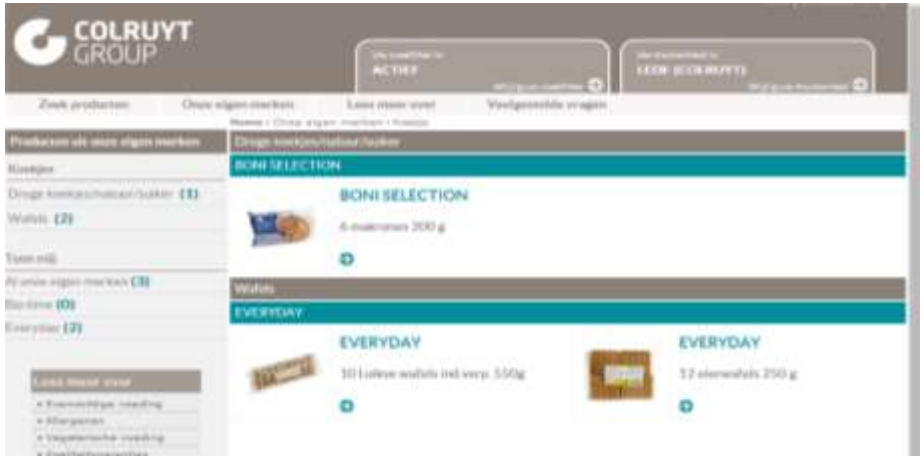
Praktische tools: productinformatie





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Praktische tools: receptuur

- via websites firma's, kookboeken

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Vragen?

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