ACTISTAR and gut health system:
Physiological and metabolic properties of a digestion-resistant retrograded maltodextrin, classified as type 3-Resistant Starch

Emphasis on the colon health related properties of resistant starch in the framework of the new EU regulation

Dr. Karl-Heinz Zirzow

59. Starch Convention
April 17, 2008
Besides ageing our modern lifestyle has a major impact on our health.... but the role of nutrition is still unclear.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>Obesity</td>
</tr>
<tr>
<td>Prediabetic condition: insulin resistance, elevated insulin levels</td>
<td>Diabetes Type 2</td>
</tr>
<tr>
<td>Elevated blood lipid and LDL levels</td>
<td>Atherosclerosis, cardiovascular diseases</td>
</tr>
<tr>
<td>Joint problems</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Intestinal disorders: gut irregularity, weak state of immune defense</td>
<td>Low immune defense can lead to various diseases</td>
</tr>
</tbody>
</table>

....there is no easy and simple fix with (functional) food to provide solutions for health disorders.
Cargill’s Portfolio of Ingredients and Systems

- Acidulants
- Chocolate
- Fibers
- Flavor
- Flour
- Functional Health
- Juice
- Malt
- Natural/Organic
- Oils
- Protein
- Salt
- Sweeteners
- Texturizers/Emulsifiers
- Whole Grains
- Cargill Capabilities

Flavors - Sweeteners - Texturizers
What Cargill can offer in the “health food” segment?

**Solutions for better and more balanced nutrition**

- reduced sodium chloride intake (SaltWise)
- reduced sugar intake: slowly digestible sweetener with low glycemic response (Isomaltulose (Xtend))
- reduced calory intake with sweetener Erythritol (Zerose)
- less trans fatty acids and replacement by healthier oils
- reduced fat intake (TexDesign)

>>>>>”Less evil food”

- phytosterol (CoroWise)
- barley beta glucan (Barliv)
- phosphatidylcholine (Epikuron, Leci-Choline)
- pectin (Unipectine)
- fish oil (omega-3)

>>>>> Solutions for heart health

- glucosamin (Regenasure)
- hydrolysed collagen (Arthred)
- fish oil (omega-3)

>>>>> Solutions for joint health

- probiotic cultures (Biogarde)
- inulin (OligoFiber)
- dietary fibers, prebiotics:
- Resistant starch (Actistar)
- inulin/resistant starch co-extrusion (FiberKrunch)

>>>>> Solutions for colon health

- resistant starch (Actistar)
Agenda

1. Health claims – new EU regulation
2. Health claims proposed in the Article 13 list by the food industry for Resistant Starch (RS)
3. C*Actistar (Retrograded Maltodextrin, classified as type 3-Resistant Starch)
Health claims will become part of a new EU regulation

- The regulation of the EP and of the council on Nutrition & Health claims on foods has been published in January 2007 and entered into application as from July 1st of 2007.
- **Main objectives of regulation:**
  - To achieve a high level of **consumer protection**
  - To ensure **fair competition** in the area of foods
- **Scope of regulation**
  - Voluntary claims about foods, ingredients, nutrients and other substances with a nutritional or physiological effect
  - Labelling, presentation and advertising
  - Foods to be delivered as such to the final consumer
  - Trademarks and brand names (15 years transition period for existing ones)
General principles for claims in the EU

• **Claims must be supported by generally-accepted scientific evidence**
  – SCIENTIFIC SUBSTANTIATION
    • Human intervention studies (randomized controlled studies)
    • Human observational studies
    • Animal data (studies related to absorption, bioavailability, mechanisms,..)
    • In vitro data

• **Food must contain a “significant” quantity of the beneficial substance to be able to deliver the claimed effect:**
  – In a quantity of food “reasonably expected to be consumed”
  – Substance must be biologically available

• **Claims must be understood by the “average consumer”**
  – Should NOT mislead the consumer
Classification of claims

- Nutrition Claim
  - Children Development & Health (Article 14)
  - Reduction of disease Risk claim (Article 14)
  - Other Health Claims

Nutrient Profiles (Article 14)

List of approved Nutrition Claims (Annex)

Authorization procedure through EFSA (Article 15, 16, 17, 19)

Authorization procedure through EFSA (Article 18)

List of approved Health Claims (Article 13)

Based on generally accepted scientific evidence

Other (e.g. based on new scientific data or proprietary data)

Adopted in Jan 2010
1. Health claims – new EU regulation

2. Health claims proposed in the Article 13 list by the food industry for Resistant Starch (RS)

3. C*Actistar (Retrograded Maltodextrin, classified as type 3-Resistant Starch)
Proposal of health claims for Resistant Starch (RS) in the Article 13 list

• “Contributes to a normal colon metabolism” / “Resistant starch is a butyrogenic fiber, butyrate participates to a normal colonic function and metabolism” / “Resistant starch supports a normal stool pattern”

• These claims depend on the condition of use and should be mentioned in the context of a healthy, balanced diet (low in fat, saturated fat and cholesterol, and rich in Dietary Fiber)

• RS is known to positively impact several biomarkers of colonic function when at least 17g/d is consumed → Foodstuffs that would contain around 4g per food serving could bear this claim
What is Resistant Starch (RS) ?

- RS is defined as the sum of starches and starch degradation products that are not digested nor absorbed in the small intestine in a healthy individual (Euresta, 1993).

- Different types of RS:
  - **Type 1 RS**: physically inaccessible (e.g.: grains, lentils, beans, ...)
  - **Type 2 RS**: amylose-rich starch granules, that are naturally resistant to the amylolitic digestion (e.g.: potato starch, banana starch ...)
  - **Type 3 RS**: Retrograded starches (e.g.: cooled cooked potatoes, ...)
  - **Type 4 RS**: Chemically-modified starches
Scientific substantiation for the potential health claims on RS

- Intervention studies looking at markers of colonic function
  
  
  
  
  
  
  - decreases fecal water cytotoxicity (Van Munster et al, 1994; Heijnen et al, 1998)
  
  - reduces the incidence of diarrhea and improves intestinal barrier function in children suffering of chronic diarrhea (Rabbani et al, 2004; Raghupathy et al, 2006)
  
  - RS induces DNA damages (Wacker et al, 2002)
Scientific substantiation for potential health claims on RS

- **Animal studies on markers of colonic function**
  
  - increases faecal output (Sakamoto et al., 1996; Young et al., 1996; Mazière et al., 1998; Cassand et al., 1997; Ferguson et al., 2003; Dongowski et al., 2005)
  
  - stimulates metabolic activity of microbiota and enhances SCFA production, notably **butyrate** (Sakamoto et al., 1996; Cassand et al., 1997; Silvi et al., 1999; Perrin et al., 2001; Toden et al., 2005; Toden et al., 2007; Le Leu et al., 2005; Le Leu et al., 2007; Jacobasch et al., 2006; Dongowski et al., 2005; Moreau et al., 2003; Morita et al., 2004; Lopez et al., 2002)
  
  - decrease caecal pH (Le Leu et al., 2005; Dongowski et al., 2005; Lopez et al., 2002; Cassand et al., 1997)
  
  - decrease faecal protein fermentation products (**ammonia**, **phenols**) (Toden et al., 2005; Silvi et al., 1999; Toden et al., 2007; Toden et al., 2007; Le Leu et al., 2007)
  
  - **prebiotic** (Le Leu et al., 2005; Jacobasch et al., 2006;)
  
  - improves histological markers of inflammation and restores colonic permeability in chemically-induced colitis suffering rats (Moreau et al., 2003; Morita et al., 2004)
  
  - reduces colonic DNA damages caused by protein-rich diets and thickens the mucus layer (Todden et al., 2005; Toden et al., 2007; Toden et al., 2007)
  
  - induces apoptosis (Jacobash et al., 2006; Toden et al., 2007; Le Leu et al., 2005; Bauer-Marinovic et al., 2006)
Scientific substantiation for potential health claims on RS

**Fuel for colonic cells**

**Anti-inflammatory actions**
- Inhibits production IL12, TNF-\(\alpha\) and interferon \(\gamma\)

**Inhibits cell proliferation**
- Inhibits histone deacetylase
- Transcription of p21/Cip1 and p16 (Inhibitors of cdk 4- cdk6- cyclin D complex)
- Up-regulates cyclin D3
  => Block in the G1 phase of the cell cycle
  => Differentiation of cancerous cells

**Induces apoptosis**
- Upregulates expression of BCL-2 antagonist/killer (Bak)
- Induces Caspase-3-mediate cleavage

**Curative effects:** Down-regulates angioneogenesis
Up-regulates immunosurveillance

\[ \text{BUT} \rightarrow \text{Histone acetylation} \]
Scientific substantiation for potential health claims on RS

- Studies looking at effect of RS on colorectal cancer biomarkers show conflicting results:
  - Cell proliferation
    - Studies in adenoma patients: no effect (Grubben et al, 2001; Van Gorkom et al, 1999), decreased (Caderni et al, 1999)
    - Animal studies:
  - ACF
    - Carcinogenic compounds: no effect (Mazière et al, 1998), increased (Young et al, 1996), decreased (Thorup et al, 1995; Cassand et al, 1997; Perrin et al, 2001)
  - Tumor incidence
    - Min mouse: no effect (Pierre et al, 1996; Williamson et al, 1999)
    - Carcinogenic compounds: no effect (Sakamoto et al, 1996), increased (Young et al, 1996), decreased (Bauer-Marinovic et al, 2006)
Scientific substantiation for potential health claims on RS

• Epidemiological studies
    • International correlative study across 12 population
    • Strong inverse associations between starch intake and both colon and rectal cancers.
    • Effect remained significant after adjusting for fat and protein
    • The Health Professional follow-up study
    • The highest levels of starch intake were associated with lower risk of colorectal adenomas (RR=0.47)

• Case-control studies
    • Positive correlation between starch intake and CRC
1. Health claims – new EU regulation

2. Health claims proposed in the Article 13 list by the food industry for Resistant Starch (RS)

3. **C*Actistar (Retrograded Maltodextrin, classified as type 3-Resistant Starch)**
## Resistant starch content in Actistar

<table>
<thead>
<tr>
<th>Actistar(%)</th>
<th>In vivo</th>
<th>In vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actistar(%)</td>
<td>59 a</td>
<td>63 b</td>
</tr>
</tbody>
</table>

a: Lankilde et al., 2001

b: Analysis run in the laboratory of the inventor

c: Analysis performed in the Cargill R&D Center Europe
Impact on the glycemic response

- Helps to reduce the glycemic response to foods (Cargill data)
  - Healthy volunteers, 50g Actistar (=25g RS), blood samples over 120min (15, 30, 45, 60, 90, 120min)
  - Relative glycemic response was 58.5% compared to glucose set at 100%
Impact on colon health biomarkers (Arrigoni et al., 2002)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Acetate</th>
<th>Propionate</th>
<th>Butyrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructo-OS</td>
<td>65</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Xylo-OS</td>
<td>67</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Gluco-OS</td>
<td>72</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>RS3</td>
<td>59</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Polydextrose</td>
<td>67</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>
Actistar: butyrogenic properties (Arrigoni et al., 2002)

Actistar is fermented more slowly than the other Oligosaccharides. Actistar could reach more distal parts of the large intestine and provide butyrate to the colon’s cell.
Actistar: butyrogenic properties (Arrigoni et al., 2004)

- Intercomparison between different fermentation profiles using different inoculum

Controls are highly reproducible

High variability for butyrate production
Actistar: butyrogenic properties (Arrigoni et al., 2004)

RS fermentation is flora-dependent

High butyrate yield:
- presence butyrogenic bacteria using RS3 as an energetic source and/or absence of bacteria using butyrate as an energetic source
Actistar: butyrogenic properties (Arrigoni et al., 2004)

- ActiStar is not used by gut flora of babies
- Actistar is used by gut flora of babies after weaning, once changes in microflora profile occurred
- Actistar is then used by microflora of adults and elderly people

RS is not an interesting ingredient in baby foods, but is of interest for the adults and elderly to maintain good colonic health. Elderly is clearly a target as we know that DF consumption is extremely low.
Effect of RS fermentation supernatants on colon cells (Fässler et al., 2007)

Effect of batch *in vitro* fermentation of RS on genotoxicity:
Effect of RS fermentation supernatants on colon cells (Fässler et al., 2007)

Effect of batch *in vitro* fermentation supernatants on TER:

![Graph showing changes in TER over time for different supernatants.](image)
**Actistar: prebiotic effect (Bounhik et al., 2004)**

- **Double blind, parallel, randomized, controlled study in 64 volunteers (8 groups of 8 subjects)**
  - 8 NDC, 2 x 5 g/d NDC, 1 week treatment
  - Bifidogenic effect of RS3:
    - Initial bifidobacteria count: $7.41 \pm 0.37 \log \text{CFU/g}$ vs $9.43 \pm 0.49 \log \text{CFU/g}$ after RS intake ($p<0.05$)

- **Dose-response study in 136 volunteers (4 groups of 32 subjects, 8 subjects per dose)**
  - 2.5 g/d, 5 g/d, 7.5 g/d and 10 g/d of bifidogenic NDC (4 were tested)
  - No dose-response effect observed (effect observed at 5 g/d and 7.5 g/d but not at 2.5 g/d and 10 g/d)
  - BUT the initial number of bifidobacteria before treatment was not taken into consideration !!
Conclusions

- The effect of RS 2 and RS 3 on colorectal cancer biomarkers is not clear
  - Conflicting data on ACF, tumor occurrence and cell proliferation: no real validated biomarkers
  - Outcome depends a lot on the animal model used, the time of exposure to the carcinogenic compound (CC), the nature of the CC, the dose of CC
  - How close does these studies relate what would happen in humans?
- A disease risk reduction claim is far to be substantiated BUT
- RS 2 and 3 have been shown to alter positively several biomarkers of colon health
  - Reduction of the toxic compounds in the colon lumen: reduction of fecal water toxicity
  - Butyrate production: trophic effects
    - Contributes to a normal intestinal barrier function
    - Reduces inflammation
    - Reduces DNA damages
  - Potential prebiotic effects that still needs to be demonstrated in humans
- Based on the current evidence, the contribution of RS to a normal colon metabolism when part of a low fat and DF-rich diet is well established