

## **Splenda Alters Gut Microflora and Increases Intestinal P-Glycoprotein and Cytochrome P-450 in Male Rats**

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Mohamed B. Abou-Donia, Eman M. El-Masry, Ali A. Abdel-Rahman, Roger E. McLendon, and Susan S. Schiffman

Authors are from the Departments of Pharmacology and Cancer Biology, Pathology, and Psychiatry, Duke University Medical Center

### FROM ABSTRACT:

Splenda is comprised of the high-potency artificial sweetener sucralose and the fillers maltodextrin and glucose.

Splenda was administered by orally at 100, 300, 500, or 1000 mg/kg to male Sprague-Dawley rats for 12-wk, during which fecal samples were collected weekly for bacterial analysis and measurement of fecal pH.

After 12-wks, half of the animals from each treatment group were sacrificed to determine the intestinal expression of the membrane efflux transporter P-glycoprotein (P-gp) and the cytochrome P-450 (CYP) metabolism system by Western blot.

The remaining animals were allowed to recover for an additional 12-wks, and further assessments of fecal microflora, fecal pH, and expression of P-gp and CYP were determined.

At the end of the 12-wks treatment period, the numbers of total anaerobes, bifidobacteria, lactobacilli, Bacteroides, clostridia, and total aerobic bacteria were significantly decreased.

Splenda also increased fecal pH and enhanced the expression of P-gp by 2.43-fold [143%], CYP3A4 by 2.51-fold [151%], and CYP2D1 by 3.49-fold [249%].

Following the 12-wk recovery period, the total anaerobes and bifidobacteria remained significantly depressed, and the pH values, P-gp, and CYP 450 isozymes remained elevated.

These changes occurred at Splenda dosages that contained sucralose at 1.1–11 mg/kg (the US FDA Acceptable Daily Intake for sucralose is 5 mg/kg).

Evidence indicates that a 12-wk administration of Splenda exerted numerous adverse effects, including:

- 1) Reduction in beneficial fecal microflora
- 2) Increased fecal pH
- 3) Enhanced expression levels of proteins which are known to limit the bioavailability of orally administered drugs and nutrients.

THESE AUTHORS ALSO NOTE:

The artificial high-potency sweetening compound sucralose is a chlorinated disaccharide.

"Sucralose is ubiquitous in the world food supply as an ingredient in over 4000 products, including tabletop sweeteners and sugar substitutes (e.g., Splenda), baked goods, beverages such as soft drinks, coffee and tea, breakfast cereals, chewing gum, desserts, and pharmaceutical products."

"Because sucralose is approximately 600 times sweeter than sucrose by weight sucralose formulations such as Splenda utilize fillers including maltodextrin and glucose for volume."

Sucralose is a chlorinated hydrocarbon, an organochlorine molecule with appreciable lipid solubility. **[Very Important]**

Adverse consequences from the elevated presence of sucralose have been reported in animal models, which included gastrointestinal tract DNA damage.

Unabsorbed sucralose in the gut may affect the intestinal microbial milieu. Gut microflora carry out many important functions, including:

- 1) Fermentation of dietary carbohydrates,
- 2) Salvage of energy as short-chain fatty acids
- 3) Production of vitamins
- 4) Maintenance of normal immune system functioning
- 5) Gastrointestinal tract mobility
- 6) Inhibition of pathogens
- 7) Metabolism of drugs

The Splenda used in this study was purchased from the supermarket.

The dosage levels of sucralose given "were selected because they span the range of values below and above the accepted daily intake for sucralose of 5 mg/kg/d established by the U.S. Food and Drug Administration (FDA)."

The following results were documented:

- 1) The lowest Splenda dose showed a significant increase in body weight gain during and after Splenda supplementation.

- 2) "The number of total anaerobes and aerobic bacteria began to decrease immediately after the beginning of oral administration of Splenda. By the end of the 12-wk dosing period, at the lowest dose (100 mg/kg/d) of Splenda, the number of total anaerobes was reduced by 49.8% relative to control."
- 3) "Higher doses of Splenda (300, 500, and 1000 mg/kg/d) produced significant reduction in the number of total anaerobes and other anaerobic bacteria, ranging from 47.4 to 79.7% of control."
- 4) "Higher doses of Splenda (300, 500, or 1000 mg/kg/d) resulted in significant reduction of the numbers of total aerobes, which ranged from 51.2 to 67.8% compared to control groups."
- 5) "Relative to control, at the end of 12-wks of Splenda treatment at dosages of 100, 300, 500, or 1000 mg/kg/d, there were significant increases in pH values."
- 6) "At the end of the 12-wk treatment with Splenda, numerous alterations were observed that did not occur in control animals, including lymphocytic infiltrates into epithelium, epithelial scarring, mild depletion of goblet cells, glandular disorganization, and focally dilated vessels stuffed with intravascular lymphocytes."

## DISCUSSION

This study showed that intake of Splenda for 12-wks exerted several adverse effects on the intestines of rats, including a significant decrease in beneficial intestinal bacteria, elevated fecal pH, histopathological changes in the colon, increased body weight, and enhanced intestinal expression of proteins that inhibit absorption of drugs and nutrients.

"The intake of Splenda by rats significantly reduced the number of indigenous intestinal bacteria resident in the gut, with the greatest suppression for the generally beneficial anaerobes (e.g., bifidobacteria, lactobacilli, and Bacteroides)."

"Disruption in the number and state of balance of intestinal microflora may potentially interfere with many essential gut functions, including nutrient metabolism, normal immune system functioning, gastrointestinal mobility, inhibition of pathogens, vitamin synthesis (B group and K), and metabolism of drugs."

"The reduction in intestinal bacteria in this study was accompanied by an increase in fecal pH that typically occurs when there is a decrease in the production of short-chain fatty acids (SCFA) by colonic bacteria. SCFA decrease luminal pH and hence provide antagonistic properties against intestinal pathogens and invading organisms. Suppression of bacteria, alterations in microbial composition, and reduction in SCFA in the gut might have clinical significance for humans in the management of many medical conditions such as irritable bowel syndrome, inflammatory bowel disease, cardiovascular disease, obesity, and cancer, in which gut flora play an important role."

Splenda increased the expression of the intestinal proteins “at levels that have been associated with reduced bioavailability of drugs and chemicals.” The magnitudes of these increases “are greater than or comparable to those shown to reduce the bioavailability of many drugs.”

“The present finding of increased expression of [intestinal] proteins by Splenda at the low dosages used in this experiment is clinically important with regard to potential drug interactions.”

Splenda suppresses beneficial bacteria and directly interferes with the bioavailability of drugs and nutrients at doses that are approved by the FDA for use in the food supply.

#### KEY POINTS FROM DAN MURPHY

- 1) “Splenda is comprised of the high-potency artificial sweetener sucralose and the fillers maltodextrin and glucose.”
- 2) The US FDA Acceptable Daily Intake for sucralose is 5 mg/kg body weight.
- 3) In this study, a 12-wk administration of Splenda to mice in human dose equivalents exerted numerous adverse effects, including:
  - A)) Reduction in beneficial fecal microflora
  - B)) Increased fecal pH
  - C)) Enhanced expression genes which reduce the absorption of orally administered drugs.
- 4) The artificial high-potency sweetening compound sucralose is a chlorinated disaccharide.
- 5) “Sucralose is ubiquitous in the world food supply as an ingredient in over 4000 products, including tabletop sweeteners and sugar substitutes (e.g., Splenda), baked goods, beverages such as soft drinks, coffee and tea, breakfast cereals, chewing gum, desserts, and pharmaceutical products.”
- 6) Sucralose is a chlorinated hydrocarbon, an organochlorine molecule.
- 7) Adverse consequences from the elevated presence of sucralose have been reported in animal models, which included gastrointestinal tract DNA damage.
- 8) Unabsorbed sucralose in the gut affects the intestinal microbial milieu. Gut microflora carry out many important functions, including:
  - A)) Fermentation of dietary carbohydrates,
  - B)) Salvage of energy as short-chain fatty acids
  - C)) Production of vitamins
  - D)) Maintenance of normal immune system functioning
  - E)) Gastrointestinal tract mobility

- F)) Inhibition of pathogens
- G)) Metabolism of drugs

9) The lowest Splenda dose showed a significant increase in body weight gain during and after Splenda supplementation. **[Very Ironic]**

10) "At the end of the 12-wk treatment with Splenda, numerous alterations were observed that did not occur in control animals, including lymphocytic infiltrates into epithelium, epithelial scarring, mild depletion of goblet cells, glandular disorganization, and focally dilated vessels stuffed with intravascular lymphocytes."

11) The intake of Splenda for 12-wks exerted several adverse effects on the intestines of these rats, including a significant decrease in beneficial intestinal bacteria, elevated fecal pH, histopathological changes in the colon, and increased body weight.

12) "Disruption in the number and state of balance of intestinal microflora may potentially interfere with many essential gut functions, including nutrient metabolism, normal immune system functioning, gastrointestinal mobility, inhibition of pathogens, vitamin synthesis (B group and K), and metabolism of drugs."

13) Sucralose ingestion "might have clinical significance for humans in the management of many medical conditions such as irritable bowel syndrome, inflammatory bowel disease, cardiovascular disease, obesity, and cancer, in which gut flora play an important role."

14) Splenda suppresses beneficial bacteria and directly interferes with the bioavailability of drugs and nutrients at doses that are approved by the FDA for use in the food supply.