Effect of E171 (titanium dioxide) in the colon

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20868

Source
Nationaal Trial Register

Health condition

E171, Titanium dioxide, Gut inflammation, Biomarker

E171, Titanium dioxide, Darm inflammatie, Biomarker

Sponsors and support

Primary sponsor: Maastricht University
Source(s) of monetary or material Support: Maastricht University

Intervention

Outcome measures

Primary outcome

The primary outcome parameters are differences in transcriptomic markers after consumption of food additive E171. These outcomes in humans will shed light on the relevance of markers identified in preclinical studies, and how the animal data on the risk of facilitation of tumour growth can be extrapolated to humans

Secondary outcome

Secondary outcome parameters include inflammatory markers such as ROS in the rectal epithelium. These outcomes will help to understand the inflammatory mechanisms that may be indicative of the risk to developing colorectal cancer.

Study description

Background summary

Rationale:

The food additive E171 (titanium dioxide) is present at significant levels mainly in sweets, cookies, icing and chewing gum. Consumers are exposed between 1 and 2 mg/kg bw/day depending on the age, it is important to evaluate the potential risk of this compound on human health. E171 comprised titanium dioxide (TiO2) particles of various sizes, among others in the nanoparticle size range. TiO2 is not considered genotoxic, but in an animal model in which colon cancer is induced by the genotoxicant AOM (Azoxymethane), E171 was able to dramatically enhance the tumour formation induced by AOM.

The intervention study that is described in this METC protocol is done in the context of a project that aims to establish the potential risk of stimulation of the development of colorectal cancer in humans due to ingestion of the food additive E171. The hypothesis for the mechanism that may explain the effect is that E171 induces inflammation in the colon, and that the inflammatory condition would facilitate the development of colorectal cancer. The intervention study aims at measuring inflammatory and genomic markers that may be early indicators of the development of colorectal cancer. The information yielded by this study will allow to extrapolate the findings in animals concerning the facilitation of the development of colorectal cancer to humans, and perform a risk assessment. The selection of markers, that will include gene expression changes, to be used in the intervention study will be based on preclinical research using in vivo animal models and cell systems of human origin in vitro exposed to E171.

Objective:

In this intervention study, the primary aim is to evaluate the influence of E171 exposure on the gene expression profile in rectal biopsies. In addition, inflammatory markers such as ROS in the rectal epithelium will be measured as secondary outcome.

Study design:

This human volunteer study has a cross-over design with only healthy volunteers divided in 2 groups, one that will start with the control period and the other one that will start with the intervention period. Each participant will undergo proctoscopy after each study period, rectal biopsies and rectal swap will be taken. In addition, subjects will be asked to donate blood. Data analysis to examine effects of E171 in food will be done after the end of the study and

the wash-out period serves as a control.

Study population:

All subjects will be recruited by the University of Maastricht (UM), the Netherlands, using advertisements in local newspapers as well as other media. Healthy subjects of both sexes will be selected based on predefined inclusion criteria (BMI: 18-27; > 18 years) and randomly assigned to one of the different experimental groups.

Intervention (if applicable):

During the study, the subjects will follow two different periods: a two weeks control period and a two weeks intervention period.

The aim of the control period is to reduce to a minimum the exposure to E171. Therefore, the subjects will be given a list of products to avoid during these two weeks.

The aim of the intervention period is to observe the effect of E171 in the colon, by making a gene expression profile and measuring biomarkers of exposure to E171. For this, the subjects will be given yoghurt to eat 3 times a day in which a normal daily amount of E171 will be added.

After each period of two weeks, colonic biopsies will be taken at the hospital of Sittard during a proctoscopic examination made by a specialised nurse. In addition, blood and rectal swaps will be sampled and stored appropriately at UM for later analysis.

Main study parameters/endpoints:

- The primary outcome parameters are differences in transcriptomic markers after consumption of food additive E171. These outcomes in humans will shed light on the relevance of markers identified in preclinical studies, and how the animal data on the risk of facilitation of tumour growth can be extrapolated to humans.

- Secondary outcome parameters include inflammatory markers such as ROS in the rectal epithelium. These outcomes will help to understand the inflammatory mechanisms that may be indicative of the risk to developing colorectal cancer.

Study objective

The hypothesis is that E171 induces inflammation in the colon, and that the inflammatory condition would facilitate the development of colorectal cancer

Study design

At the end of each period of 2 weeks (2 periods in total), colon biopsies will be obtained during a proctoscopic examination of the rectum/sigmoid colon region and 10 mL of blood

will be collected.

Intervention

This study is a cross-over design, including only healthy volunteers. A cross-over design was chosen because it is the most appropriate design for this study: it will reduce the individual differences by allowing every subject to be his own control.

This study will be done in 4 weeks and include 2 periods. The volunteers will be randomized in two groups: one group will start with the intervention period and the other one will start with the control period. After, these 2 weeks of intervention or control periods, the volunteers will start the control period and intervention period respectively for another 2 weeks.
The time of exposure is 2 weeks. Indeed, it takes 5 to 7 days for the turnover of the epithelial cells in the gut. This will ensure the exposure of all the cells of the luminal surface of the colon.

The control period, is meant to reduce to a minimum the ingestion of E171 in order to have all the volunteers to start the same level of E171. During this period the volunteers will receive a list of products to avoid like cookies, chewing gum, certain toothpaste that are known to contain a significant amount of E171.

The intervention period, is meant to control the amount of E171 that the volunteers will ingest. A concentration, 0.82 mg/kg bw/day, corresponding to a normal daily consumption will be given to the volunteers. The quantity will be adjusted to the body weight and dispersed in yoghurt that will be eaten at breakfast, lunch and dinner.

In order to verify the compliance of the subjects, once in every period the subjects will prepare a package that include exactly what they ate and drank all day. This food package will be mixed and tested for TiO2 content.

Contacts

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Eligibility criteria

Inclusion criteria

- Healthy with a Body Mass Index (BMI) between 18-27, male or female

- Between 18-70 years old

Exclusion criteria

- Alcohol abuse up to 6 months before participation in this research, i.e. more than 4 drinks on any single day and more than 14 drinks per week for men and more than 3 drinks on any single day and more than 7 drinks per week for women
- Current presence of any diseases related to the gastrointestinal tract, kidney, liver, heart or lungs

- Current presence of symptoms related to diseases of the gastrointestinal tract, i.e. vomiting, diarrhoea or constipation, and altered stool, such as blood in stool

- Current presence of diseases related to the endocrine or metabolic system

- Current presence of anaemia

- HIV infection or hepatitis

- Use of antibiotics and other prescribed medication and painkillers over the last 3 months (exception: paracetamol and anti-contraceptive)

- Current smokers

- Vegetarians

- Pregnant women

- Participants of other intervention studies during this intervention period.

- Participants who use anticoagulant medicine

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2016
Enrollment:	80
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

Study registrations

Followed up by the following (possibly more current) registration

ID: 54542
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL5735
NTR-old	NTR5880

Register	ID
CCMO	NL52433.068.16
OMON	NL-OMON54542

Study results

Summary results

Urrutia-Ortega, I.M., Garduño-Balderas L.G. , Freyre-Fonseca V., Delgado-Buenrostro N.L. , González-Robles A., Pedraza-Chaverri J., Hernandez-Pando R., Terrazas-Balderas L.I., van Loveren H., Chirino Y.I. (2016) E171 exposure exacerbates tumor formation in azoxymethane-induced colorectal cancer. Food and Chemical Toxicology.