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Human Exposure Assessment of Engineered Inorganic Nanoparticles in Food

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Declaration

I declare that this Master Thesis is written independently and in accordance with "Reglement for sivilarkitekt- og sivilingenøreksamen" at the Norwegian University of Science and Technology.

Trondheim, July 10th 2011

Lars Fabricius

Preface

Dear reader

I started thinking about combining Nanotechnology with Industrial Ecology in my first year at the university. 5 years later at the end of my master studies, my specialisation is to combine these two worlds. Part of this study has been to learn about risk. Risk is something special. In one end of the scale it is a yes/no question, while at the other it is incredibly complicated, including such a difficult question as what is acceptable. For new drugs, the acceptable risk of death varies from relatively high to nothing depending on the use of the drug. What should be the acceptable risk for the different parts of a new technology, nanotechnology?

I have listened to many ethicists lecture these last few years. In biotechnology, ethic considerations have been very important, and I believe it will be so in nanotechnology as well. However, with nanotechnology being something new, the ethicists have all struggled to explain why we should consider ethic aspects, simply because defining nano, separating it from everything else, is very difficult.

Recently I listened to a brilliant ethicist at a conference discussing everything concerning nano. To many listeners shock, she raised a most interesting question. Is nano risk really that important? Shouldn't we focus on other areas (chemicals, pharmaceuticals, water etc.)? Nanotechnology is the future; it can solve problems thought unsolvable, and create solutions thought impossible. Should the worry of risk affect the advancement? Should we be precautious?

The precautionary principle does affect technological advancements, but hopefully the benefits are greater than the disadvantage. If we through human exposure research can create a filter, somehow separating the bad from those with potential, then I would say we are precautious. Technology will always run ahead, risk assessors can only try to keep up.

This master thesis is the second part of a one year research project. My specialisation project written Autumn 2010 is the foundation for half of my thesis. This research was presented at the NanoImpactNet conference in Lausanne, February 2011. Results from this are included in the introduction, but unless otherwise stated all experimental results in this thesis are from new experiments completed after handing in the project report in December 2010.

In this master thesis I have worked with additives used in the food industry. None of which are naturally there, none of which have any nutritional value. Their only purpose is to add some properties such as colour, prolonged shelf life or being anti-caking. The special with nanoparticles is that we cannot feel that they are there, they might change texture or the visual effect, but you will never say; "I wish there was more "nano" in this chocolate bar."

My aim with this thesis is to evaluate the exposure and risk to two inorganic nanoparticles.

I hope you will enjoy reading this report.

Lars Fabricius

Trondheim 10.07.2011

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This master thesis represents the end of a long education and there are few people close to me that deserve a special remark. I will like to thank them in my mother tongue.

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Abstract

An increasingly important part of food technology is nanotechnology. Inorganic nanoparticles are added directly or indirectly to food in order to create new tastes, appetizing looks or to preserve it longer. Exposure to these nanoparticles is fairly unknown, and there is a need to evaluate the dose that humans are exposed to.

In this master thesis, two inorganic substances have been chosen. The first one is silver nanoparticles, commonly known as an antimicrobial agent and added to plastic food containers to preserve food. The second is the food colour E171, titanium dioxide. This is not defined as a nanoparticle because of an average particle size of 200-300 nm, but it is assumed that the size distribution may include nanoparticles. In both cases the intention has been to create an exposure model.

For silver, experiments were performed to evaluate the leaching from the food containers to food simulant. The experiments show that first time use of the plastic container will give a concentration in the food simulant of up to a total of 30 ng Ag/g. However, after some use the concentration will be lower than 1 ng Ag/g. The silver experiments show that usage of silver doped food containers will not result in an increase in silver exposure and in general the food containers will not have the claimed antimicrobial effect. However, disposable packaging containing silver may be of concern as the dose of silver leaching from this may be larger.

Titanium dioxide data is based on a literature review. Analysis of an E171 sample, showed that up to 50 % of the particles were nanoparticles with a size smaller than 100 nm. Modeling of the exposure to titanium dioxide (TiO_2) shows that exposure is diet dependent with an average of 1-3 mg/day/kg_{bw}. The modeling shows that children consume a larger dose than adults, and are more exposed to dietary products containing TiO_2. For TiO_2 the average dose is larger than the background of 5 mg/day, but lack of an effect threshold makes it difficult to conclude whether this is a unsafe or safe dose.

Exposure to inorganic nanoparticles through food will be very dependent on the way of distribution. If added to consumer products the exposure is likely to be less than nanoparticles added directly to the food. Some of the results in this project have been unexpected, like the lack of silver leaching from the plastic containers and a large fraction of nanoparticles in E171. The project only includes two substances and further research into human exposure to other inorganic materials is recommended.

Nomenclature

ICP-MS	Inductively Coupled Plasma Mass Spectrometry
MOS	Margin of Safety
NDNS	National Diet and Nutrition Survey
NEL_{man}	No Effect Limit for humans
PDI	Predicted Daily Intake
TEM	Transmission Electron Microscopy
TiO_2	Titanium Dioxide

Contents

1 Introduction

Humans are exposed to natural occurring materials every day. With the introduction of nanotechnology, engineered inorganic nanoparticles have now entered our system and daily life. One important field of nanotechnology is food technology, where many nanoparticles are added to improve the quality and experience of food. The aim of this thesis is to evaluate the human exposure to engineered inorganic nanoparticles from food, focusing on two specific substances.

Silver is/was one of the most advertised nano additives to consumer products and is present in many products today [1].

Titanium dioxide is one of the most abundant additives to food, used in a vast amount of consumer products [2].

In order to estimate the exposure to silver nanoparticles, laboratory experiments have been performed with the aim to build an exposure model based on these results. For titanium dioxide the data is derived from literature and the model is constructed based on that.

1.1 Nano - Definition and terminology

Nano is a prefix, indicating size, just as Mega or Kilo. Nano specifically means the measure of 10^{-9} units. For the metric scale, this means 1-999nm i.e. less than 1μm. The International Organization for Standardization (ISO) defines the nanoscale in the ISO/TS 27687 as:

"Nanoscale: Size range from approximately 1 nm to 100 nm." [3]

Nano is used in everyday language, also as a label describing something small or with state of the art technology. For example, The Tata Nano car refers to a small car rather than something revolutionizing. A Nano-Trip is another example of a reference to something small , here a weekend trip, while a Nano tennis racquet is referring to a lighter and stronger high end product, potentially made with novel nanotechnology [4] [5] [6].

Regulating "nanoproducts" and "nanotechnology"

Regulating "nano" in its widest sense is a challenge beyond imagination. Simple challenges such as defining "nanotechnology", "nanomaterials" and "nanoparticles" has proven very difficult and there is still no unanimous agreement on this subject. Is "nano" everything between 1 and 100 nano-something or is it up to 500 or even 1000? What do we do if "nano" is used for a car; is this still nanotechnology? Before evaluation the exposure to nanoparticles, it is therefore very important to set some boundaries and the following definitions will provide a background for the exposure assessment.

Nanotechnology

Defining nanotechnology in a few sentences is quite difficult. The UK Royal Society and Royal Academy of Engineering defines nanotechnology as:

"Nanotechnology is defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometer scale. The nanometer scale ranges from the atomic level at around 0.2 nm (2 Å) up to around 100 nm." [7]

While the International Risk Governance Council [IRGC] uses the following:

"Nanotechnology uses techniques, processes and materials at the supramolecular level, approximately in the range between 1-100 nanometers (nm), in order to create new properties and to stimulate particular desired functionalities." [3]

Even though these definitions are very similar, slight differences will have an effect when regulations are concerned. The word "application" used in the first definition is so widespread that it covers much more in terms of law than what is probably intended in the definition.

Nanomaterials

Health Canada considers any manufactured product, material, substance, ingredient, device, system or structure to be nanomaterial if [7]:
a. It is at or within the nanoscale in at least one spatial dimension, or;
b. It is smaller or larger than the nanoscale in all spatial dimensions and exhibits one or more nanoscale phenomena.
"For the purposes of this definition: The term "nanoscale" means 1 to 100 nanometers, inclusive; The term "nanoscale phenomena" means properties of the product, material, substance, ingredient, device, system or structure which are attributable to its size and distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and, The term "manufactured" includes engineering processes and control of matter and processes at the nanoscale."

In many definitions, size in one or more dimensions is within a specific size range. A lower limit of 1 nm is commonly used, while the upper limit is limited to 100 nm. However, the appropriateness of this size range is not scientifically proven. In some cases nano-specific properties might also be included.

Nanoparticles

The ISO/TS 27687 defines a nano-object as an object with one or more dimensions in the nano-scale. A nanoparticle is an object with three dimensions in the nano-scale. However, in relation to consumer products, many different labels are used for nano particles and ions. As an example, silver is labeled as Ag-NP (Silver nanoparticles), Ag-ENP (Silver Engineered Nanoparticles), NanoSilver (Particles and/or ions) and Ag-Ion (Silver Ions).

Nanotechnology in food

Nanomaterials are in general a very natural part of food manufacturing and traditional foods. Emulsions and foams have characteristic properties that many foods rely on and include nanometer sized components. Technological developments have made way for engineered nanoparticles as food additives. These may be in the form of novel structures or finely dispersed forms of existing ingredients.

Nanotechnology in food can be used in four major sectors: Agriculture, Food Processing, Food Packaging and Food supplements. For agriculture, nanocapsules can be used for targeted delivery of pesticides, fertilizers, vaccines and other agrochemicals as well as nanosensors for monitoring growth conditions etc. In food processing, nanotechnology can be found in nanotubes and nanospheres from milk as gelation and viscosifying agents, nanocapules with flavor enhancers or to control the quality of emulsions and foams. For food packaging biodegradable nanosensors can be used to measure temperature and moisture, surfaces can be coated with antimicrobial agents, UV protection with nanoparticles and lighter and stronger packaging. Nanosupplements include nanosized powders that increases the absorption of nutrients and encapsulations that increase the stability or target delivery. [3][8]

Inorganic nanoparticles in food

Inorganic particles are primarily used for two tasks. They are used as additives in food processing, like the food colours E171 Titanium dioxide and E174 Silver, or as anti-caking and anti-foaming agents, like E551 Silicon Dioxide, E552-559 Silicates, E529 Calcium Oxide and E530 Magnesium oxide. These substances are not necessarily defined as nanoparticles, but it is expected that the size distribution of each substance will when used, include nanoparticles. In addition, nanoparticles are used in food packaging, where nanoform TiO_2 is a transparent, but UV protecting additive and nanoform silver is an antimicrobial agent.

1.2 Exposure and risk analysis

Exposure assessment related to food safety is defined by WHO as:

"Qualitative and/or quantitative evaluation of the likely intake of biological, chemical or physical agents via food as well as exposure from other sources if relevant." [9]

In this definition, quantitative exposure refers to an absorbed dose where the concentration can cause a reaction in the related organism, thus referring to the vulnerability of the organism.

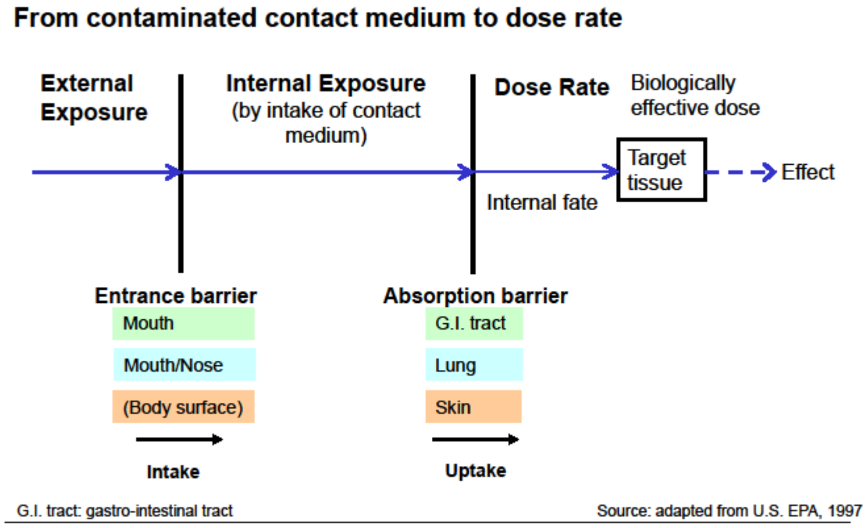

Figure 1: *Pathway of a chemical from external to internal exposure (Copied from a lecture by Prof. Konrad Hungerbühler, ETH, Zurich).*

Figure 1 shows the pathways related to chemical exposure with green representing the oral pathway, blue inhalation and brown dermal. External exposure is when the source or product that the organism is exposed to is outside the organism, while internal exposure is the exposure of an organ to a chemical. The dose rate refers to an internal dose, which is based on the sum of concentrations of various substances and exposure routes that the organism is subject to multiplied with a chemical absorption fraction. A toxicological effect is normally a result of the uptake of the medium.

Aggregated external human exposure can be calculated according to equation 1, predicting the daily intake of a substance. In equation 1 the Predicted Daily Intake (PDI) for all pathways j and all sources i is calculated.

$$PDI_{total} = \frac{1}{m_{bw}} \sum_{j=1}^{m} \sum_{i=1}^{n} (C_{ij} * q_{ij}) \tag{1}$$

PDI_{total}: Predicted daily intake [μg/kg$_{bw}$/day]
C_{ij}: Concentration in medium i [μg/kg]
q_{ij}: Consumer contact with medium i [kg/day]
m_{bw}: Body weight [kg$_{bw}$]

Equation 1 can be modified to predict the PDI for food. The exposure to food is generally oral and equation 1 can therefore be reduced to equation 2 with j representing the oral pathway:

$$PDI_j = \frac{1}{m_{bw}} \sum_{i=1}^{n} (C_{ij} * q_{ij}) \tag{2}$$

PDI_j: Predicted daily intake orally [μg/kg$_{bw}$/day]
C_{ij}: Concentration in foods i [μg/kg]
q_{ij}: The amount of foods i consumed [kg/day]
m_{bw}: Body weight [kg$_{bw}$]

In the research described in this report, C will be based on laboratory experiments, while q will be based on consumer habits surveys and available dietary data.

For food, with only one pathway, internal exposure can be calculated with equation 3:

$$D_j = \frac{1}{m_{bw}} \sum_{i=1}^{n} (C_{ij} * q_{ij} * r_{ij}) \tag{3}$$

D: Dose [μg/kg$_{bw}$/day]
C_i: Concentration in foods i [μg/kg]
q_i: The amount of foods i consumed [kg/day]
r_i: Chemical specific absorption rate of foods i ($\leq$1)
m_{bw}: Body weight [kg$_{bw}$]

It is important to differentiate between intake and uptake when coupling exposure to effect, as the effect might be dependent on whether or not the substance is absorbed.

Risk assessment for humans

The assessment of risk from exposure to a substance is based on the degree and the effect of exposure. Quantification of the risk is essential in order for political bodies to determine the acceptability of the identified risk. For food, risk is defined as:

"a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food."[9]

In humans, risk is defined as the Margin of Safety (MOS). MOS is a function of the Predicted Daily Intake (PDI, exposure) and the No Effect Limit for humans (NEL$_{man}$, toxicological effect):

$$MOS = \frac{NEL_{man}}{PDI} \tag{4}$$

The PDI is obtained from an exposure analysis, while NEL$_{man}$ is a toxicological (effect) analysis. A MOS value above 10 is considered acceptable and below 0.1 unacceptable risk. External exposure, PDI, is used, as this is the most conservative approach. For nanoparticles, the adsorption is expected to be much less than the intake. This means that the Dose will be much smaller than the PDI. If the toxicological effect is linked to the dose and no effect is seen in the gastro-intestinal tract the approach using external exposure may be far too conservative. Thus, resulting in an incorrect margin of safety.

NanoRisk - is it real?

The MOS is a result that can be used by the regulatory bodies which in the end is the final aim of an exposure analysis. As nanotechnology is a fairly young research field, making an exposure analysis is a way of following the precautionary principle. By assessing exposure and risk it may be possible to create a filter, stopping the worst at their cradle. Not all nanomaterials will be dangerous because of their size. In many cases it is dependent on the material, the surface and the product itself. For all cases the problem is that nanotechnology necessitates a case by case approach. It is therefore very difficult to say if there is a risk or not [3].

2 Silver

2.1 Introduction

Silver

Silver (Ag) is a metallic chemical element which in the natural state consists of two stable isotopes, ^{107}Ag (≈52%) and ^{109}Ag (≈48%). It is commonly known as a precious metal used in different kinds of silverware. However, silver and its compounds are because of their properties also used in medicinal science and in electric utilities, such as batteries. Silver has long been known for its antimicrobial properties and has been used because of this in fields such as surgery [10]. Resently, silver has been added to many consumer products, such as bandaids, textiles, paints and cooking utilities, and in most cases in the form of nanosilver.

Although silver is ubiquitous in the human environment, it has no physiological function in the human body and is not a trace metal. The human body is exposed to silver through oral and dermal routes as well as inhalation. Absorption is dependent on the origin and the state of the silverproduct, as well as its capability to release silver ions [10].

Nanosilver

Nanosilver is a common description for silver nanoparticles used in commercial products. Nanoparticular silver is a broad spectrum antibiotic and is also believed to be antifungal, antiviral and cytotoxic. A major part of the bactericidal effect is attributed to the release of silver ions from the nanoparticles. Foldbjerg et al. have shown that silver ions have an antimicrobial effect at concentrations from 0.6 mg/kg, while silver nanoparticles need a concentration of 2 mg/kg [11]. Nanosilver can disturb the function of the cell membrane, reducing transportation and respiration, or can diffuse into the cell nucleus and react with sulfur and phosphor in the DNA [12][13][14].

Silver in food

Nanosilver is introduced to food through food packaging and cooking utilities, including food containers, disposable packaging and cutting boards. The nanosilver added to these utilities are normally in the form of elemental silver or added through carrier materials such as zeolites. Silver nanoparticles are used to add an antimicrobial layer on the surface of the utility ("self-cleaning") and/or to transfer to the food in order to preserve it. Through oral intake, humans may therefore be exposed to silver with a potential antimicrobial effect in the gastro-intestinal tract. The average daily consumption of silver according to WHO is 20-80 μg [15]. However, up to 90% of the ingested silver is believed to leave the body directly through feces. Naturally occurring sulphur in the food may also bind to the silver creating an insoluble compound, Ag_2S (K_{sp} 10^{-49}), changing the properties of silver. Absorbed silver has an estimated half-life of 5 days in most tissues, but up to 30 days in specific organs such as bone. A general concern is that silver will accumulate in the body and specifically in the brain. However, silver is metabolised and will eventually be eliminated through the liver and kidney. This does not rule out that a large exposure can affect the brain by accumulation of a potentially cytotoxic agent. There is no scientific evidence that silver is life-threatening to man, and the most common effect related to silver ingestion is argyria, which is a change in skin colour to gray or blue [10].

Other silver sources

Other types of human exposure are mostly related to dermal exposure from silver-coated medical utilities and textiles [16].

Previous experiments

Food packaging are either disposable or reusable. The disposables are intended for a single time usage, and are used by producers to prolong the shelf life of the product and as general protection during transportation and storage. Reusable products, such as food containers, have a long lifetime and are used by the consumer directly to store food. Release of silver nanoparticles from both types of packaging has been studied.

Fabricius et al. showed the release of silver nanoparticles from the polypropylene material of reusable food containers to food simulants [17]. They described the leaching of silver based on experiments using small pieces of the box stored in little tubes filled with the food simulants. Their results showed that the leaching was significantly larger in acidic solutions, with a maximum of 5-10 ng/cm^2 after 10 days of storage and are shown in figure 2. The concentration represents the leaching from 1 cm^2 surface to 1 ml food simulant.

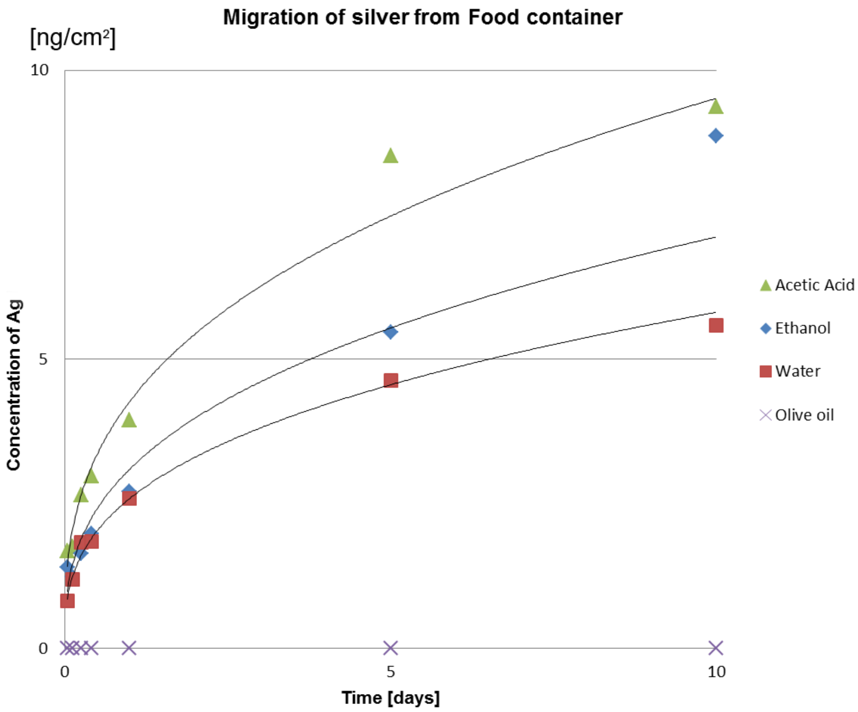

Figure 2: *Average leaching of silver from food container plastic to different food simulant. The graph represents the concentration leaching from a 1 cm^2 surface. The 10 day measurement for ethanol had a very large standard deviation. Copied from Fabricius et al. [17]*

Research by Huang et al. has also shown that nanosilver will leach from commercially available food containers to food simulants. Their experiments used polyethylene plastic bags with up to 10 ng/cm^2 released after 10 days at 25°C [18]. Their polymers contained about 5 times as much silver as in the experiments by Fabricius et al.

Disposable packaging

Fernandez et al. has added silver nanoparticles to desposable meat pads in order to see if this would have a positive effect on the bacterial growth in the meat extrudates and prolong shelf life [19]. Meat pads are used as an absorbent layer between a product and the packaging. No leaching from the pads has been measured, but as silver is a biocide it has a specific migration limit of 0.05 mg/kg [20]. However, the concentration of silver in the meat extrudes was measured as 60 ppm (mg/kg). These results will be used for evaluation the potential exposure from disposable packaging.

Leaching experiment

As the research by Fabricius et al. was done with cut pieces of the plastic containers it is important to transfer this to the real case, full scale. Using the data and extrapolating this to a real case, a worst case leaching scenario can be constructed. An open box containing 1 liter ($1000cm^3$) will have a surface area of 500 cm^2 under the following conditions:

When $a = 10$cm, $b = 10$ cm and $c = 10$ cm with $V = a{*}b{*}c$ and $S = a{*}b{*}2{+}a{*}c{*}2{+}b{*}c$ gives $V = 1000\text{cm}^3$ and $S = 500$ cm^2

$a/b/c$ = sides
V = Volume
S = Surface

Derived from the maximum amount found in the leaching experiments, the food simulant in a one liter box can after 10 days contain approximately 10 μg (10ng/ml*1000ml) of silver. Given that the polymer in such a box has a silver concentration of 20μg/g, one would need 0.5g of polymer to get the 10 μg of silver [17].

The silver will be released from the surface and down into the polymer, giving a layer that is drained of silver.
In this case $A * w * rho = 0.5g$; $rho(polypropylene) = 0.9g/cm^3$
$w = 0.5g/(A * rho) = 0.5g/(500cm^2 * 0.9g/cm^3) = 0.5/(450)cm = 1/90mm = 11\mu$m.

w = surface layer [μm]
rho = plastic density

Based on the experimental data, a particle would then have to be able to travel 1.1 μm/day (11 μm/10 days). However, the theoretical data described in the report by Fabricius et al. based on diffusion coefficients by Simon et al. indicated a diffusion rate of 9 nm/day (54 days pr μm) [21].

As the amount of silver leaching into the food simulant and the theoretical diffusion (9 nm/day) [21] does not match, two possible explanations were investigated.

1: That the cut edge of the plastic pieces in the research by Fabricius et al. would have a positive effect on the leaching.

2: That the macro surface was significantly smaller than the nano-scale surface and that more silver was actually available on the surface.

These two hypotheses will be the foundation of the experiments conducted. In order to rule out any possible effects of the cutting, a new experiment was conducted using complete (full scale) boxes. The effect of use over time was also investigated in a separate experiment. Table 1 gives an overview of the different experiments.

Table 1: Overview of the different experiments for silver leaching from the Kinetic Go Green Nano Silver Basic food container

Experiment	Aim	Set-up	Storage length
Original	Silver migration	4 simulants, 3 parallels	1h, 3h, 6h, 10h, 24h, 5d, 10d
1	Full scale experiments	1 simulant, 2 parallels	6h, 24h, 4d, 10d
2	Repeated use	1 simulant, 2 parallels	4d/10d, 10d, 10d

2.2 Materials and Methods

A full scale experiment similar to the experiment made by Fabricius et al, was performed to measure the silver leaching from food containers. Unlike in the previous experiments, only one food simulant was used, 3% acetic acid, as only worst case would be needed to compare to the old results. The experiments followed the regulations for migration analysis set by The Commission of the European Communities [22] and the method is equivalent to the experiment by Fabricius et al.[17]. In addition, a new experiment was made with the intention of measuring the effect of use over time. The containers were stored at 22°C in a dark location. All results refer to experiments using the "Kinetic Go Green^{TM}Nano Silver Basic" food container.

Four boxes of two sizes, 970 ml and 750 ml, with the same bottom surface area were investigated. Two parallels with different total sizes were used due to limited amount of same size boxes in each shipment of containers. The boxes were filled with 100 ml of acetic acid, which created a 1 cm layer in each box (100 cm^2 bottom surface). The storage time was 6 hours, 24 hours, 4 days and 10 days, see table 2.
The solutions were then analysed using a quadrupole Agilent 7500cs Inductively Coupled Plasma Mass Spectrometer (ICP-MS) with ^{89}Y as internal standard [17] [23]. Each box is only used as one sample, representing one measurement, resulting in eight absolute measurements. Experimental parameters are presented in table 3.

Table 2: Experimental set up for leaching analysis.

	Parallels	Simulant	6h	24h	4d	10d
Food container	750 ml	3% acetic acid	x	x	x	x
Food container	975 ml	3% acetic acid	x	x	x	x

Table 3: Experimental parameters used for the leaching experiments.

Experimental parameters	Amount	Description
3% acetic acid	100 ml	Food simulant
Total sample size	5 ml	Sample made for ICP-MS measurements
Acidity: sample	Eqv. 2 % HNO_3	Acidic condition of sample used in ICP-MS experiments
Yttrium concentration	1 ppb	Internal standard added due to variations in the plasma
Calibration curve	1, 10, 20 ppb	Silver concentration added to calculate silver content
Storage temperature	22 °C	Average temperature during storage of the containers

The polymer of the 975 ml and 750 ml containers were analysed using Laser Ablation ICP-MS in order to check for variations in the silver concentrations. The ablations were done by rastering the surface (one puls per spot, about 50x10spots). The first rastering of an area can be seen as kind of surface cleaning, and the data of the first ablations is therefore not taken into account. From the second rastering, the data are more stable.

The boxes that had already been stored for 4 or 10 days were kept clean for 10 days. The containers were then exposed to food simulant for 10 days on two following occasions. The concentration of silver was measured both in between and after the exposure. This made it possible to see if there was any difference if the box was allowed to "recover" after use. Table 4 shows the experimental set up for the reuse of the boxes. The conditions and analysis were the same as for the leaching experiments and are explained in table 3.

Table 4: Experimental set up for reuse analysis.

			Original Storage time		Additional storage time		
			With simulant		Dry	With simulant	
	Parallels	Simulant	4d	10d	10 d	10d	10d
Food container	750 ml	3% acetic acid	x		x	x	x
Food container	750 ml	3% acetic acid		x	x	x	x
Food container	975 ml	3% acetic acid	x		x	x	x
Food container	975 ml	3% acetic acid		x	x	x	x

AFM and surface

The surface of the plastic container was scanned using AFM imaging. The images were taken by Dr. Rao at the Laboratory of Surface Science and Technology at ETHZ. The results were analysed using the WSxM software created by Horcas et al. [24].

Modeling Silver exposure

One of the intentions of the leaching experiments was to model silver exposure to humans. Consumer data on consumption of food usually stored in plastic containers were evaluated. The model was built on equation 2, where C was the results from the experiments.

2.3 Results

The exposure assessment for the silver nanoparticles in silver-doped products are primarily based on experimental work. Using Solution Nebulisation ICP-MS, food simulants stored in food containers were analysed. The amount of silver leaching from a food container to food simulant is shown and the surface of the container is analysed.

Experiment 1

The leaching of silver from full scale boxes to food simulant acetic acid are shown in table 5 and figure 3.

Table 5: Leaching results [ng/cm^2] from full scale experiments with and without sonification for 30 seconds. The values are absolute as there is only one measurement for each timepoint and represent the amount of silver leaching from a 1 cm^2 surface to 1 ml of food simulant.

	Parallels	Sonicated	6h	24h	4d	10d
Food container	750 ml	No	3.0	6.5	10.9	19.9
Food container	750 ml	Yes	3.4	6.9	11.5	24.9
Food container	975 ml	No	7.7	14.8	24.3	30.8
Food container	975 ml	Yes	7.8	15.9	26.4	39.3

The results in table 5 show an increase in concentration in the food simulant with time. Sonication was performed to release any particles that might have either attached to the wall or precipitated at the bottom. Significant differences between sonicated and non-sonicated samples are only visible in samples stored for 10 days, although there is a systematic change increase throughout the experiment when the box is exposed to sonication for 30 seconds. It shows a significant difference between the large and small container. This difference is consistent for all parallels and since the bottom surface area is the same, this indicates a difference in surface silver concentration between the two box types.

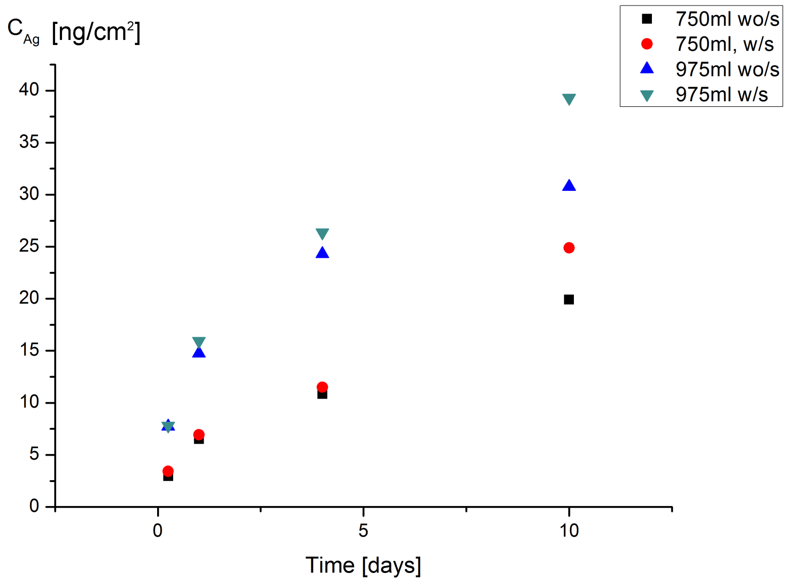

Figure 3: *Average leaching of silver from two different food containers to acetic acid over a time period of 10 days. For each container samples were taken with (w/s) and without (wo/s) 30 second sonication of the container. The concentration represents the leaching from 1 cm^2 surface to 1 ml food simulant.*

The laser ablation analysis, shown in table 6, showed that the difference in silver content between the two containers was a factor of 3.

Table 6: Table showing a comparison of the silver content in the polymer of the 750 and 975 ml food container. Values are relative compared to the carbon level.

750 ml	0.45	0.28	0.23	0.25
975 ml	0.72	0.94	0.97	1.08

Experiment 2

Results from the follow-up experiment aimed to measure concentration after some use is shown in table 7 and figure 4.

Table 7: Leaching results after 1 and 2 times reuse. One time of reuse represents 10 days storage with food simulant. Food simulant was changed after each measurement.

	Parallels	4d	10d	Extra 10	Extra 10+10	Total Silver
Food container	750 ml	10.7		2.9	1.4	15
Food container	750 ml		19.9	1.4	0.7	22
Food container	975 ml	24.3		5.7	2.1	32.1
Food container	975 ml		30.7	2.1	1.4	34.2

The experiment shows that the concentration in the food simulant will drop to almost nothing when the container is reused. The containers only stored for 4 days show a higher concentration in the simulant after the first and second reuse, partially covering the difference in concentration between 4 and 10 days initial storage time. There were no differences between sonicated and non-sonicated samples in this experiment.

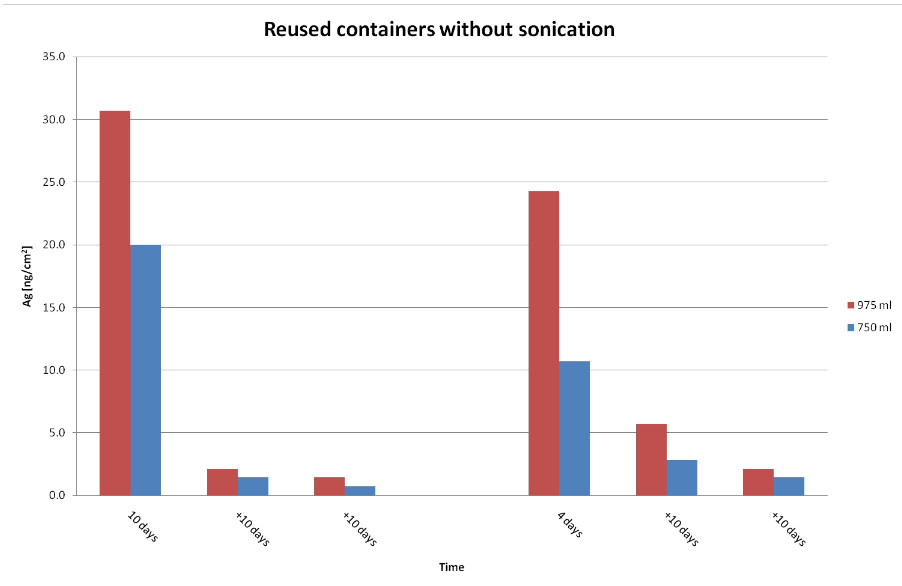

Figure 4: *Leaching of silver after reuse of a container. After 10 days the concentration is measured and the simulant is replaced.*

Figure 4 shows that after 10 days of reuse the silver concentration in the food simulant dropped dramatically, i.e. by a factor of more than ten, comparing the first 10 days of leaching with the second.

AFM

In order to explain the results in figure 4 the surface of the plastic containers were scanned using AFM. This was done to analyse the curvature of the plastic surface. Figure 5 shows a 2D (x,y) and 3D picture of the surface.

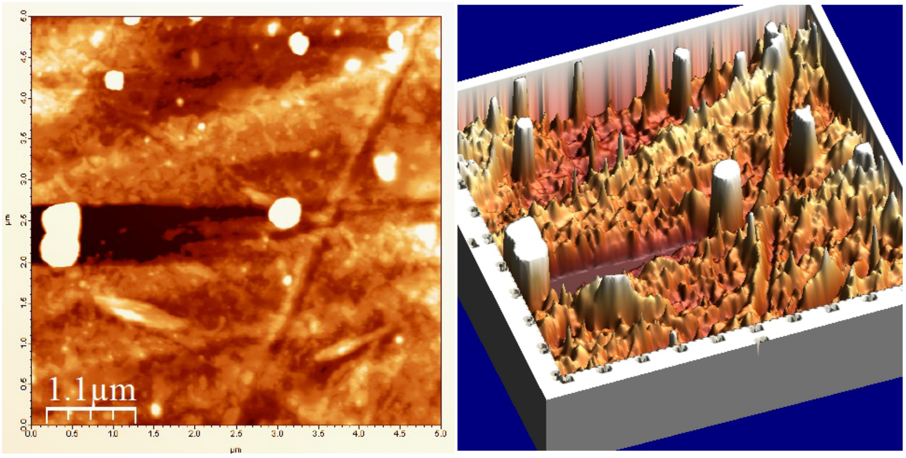

Figure 5: *Left: 2D AFM image of the surface of the food container. Right: 3D image of the surface of the food container.*

Figure 6 shows the height profile of the entire figure 5 and the profile of the diagonal from the upper left corner to the lower right.

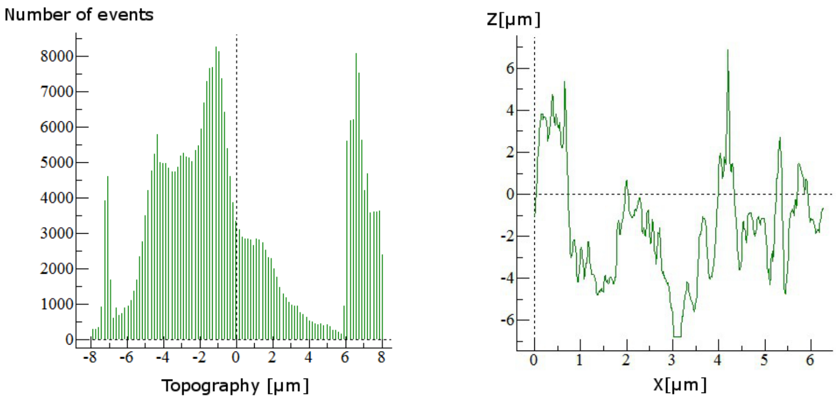

Figure 6: *Left: Histogram of the differences in height for the entire surface in figure 5. Right: Cross section from upper left corner to the lower right, showing the height profile of the sample.*

Figure 6 shows that the surface variation is of several μm. When coupling the results in figure 4 with the surface profile, the results indicate that the surface effect the leaching as liquid will penetrate deeper into the material.

2.4 Discussion

Leaching experiments for food containers

Using the same method as Fabricius et al. it was possible to show that the cut side of their experiments did not affect the overall leaching results. The silver concentration increases in the full scale experiments (figure 3) following the same trend as shown in figure 2. The difference in concentration observed is a result of different container shapes/sizes belonging to different batches and that the concentration in each batch may vary (Table 6). The maximum concentrations observed (without sonication) is 20 and 30 ng/cm^2 for the smallest and largest box, respectively. There is a significant change in concentration when the same box is used several times. The third time the box was used, the concentration was close to 1 ng/g as shown in figure 4. The difference between the container originally stored for 4 days and 10 days is as expected, as there should be some silver left at the surface in the 4 days case. This because the difference between storing for 4 and 10 days is significant. Although normal use will differ from the experimental set-up, it is safe to say that the concentration will be less after some use. Normal use will probably have shorter storage time with a lower food contact surface, but food containers will be washed with detergents which again will have a positive effect, increasing the leaching. There is still a lot of silver physically in the container, but since diffusion within the polymer is very slow, the recovery time for the surface of the container will be very long.

The AFM pictures (figure 5-6) showed that the surface is far from smooth with cracks in μm size. This explains why the initial leaching is fairly large. As liquid can penetrate deep into the cracks, diffusion rate will increase since a large surface will be exposed [25]. As a consequence of this there will not be any silver available on the surface after some use. This greatly affects the antimicrobial effect. First of all, next to no silver in the solution will lead to a none antimicrobial effect. Second of all, when there is no silver present on the surface, it removes the argument that the container might be self cleaning. If the surface profile is important for the leaching of silver, it is possible that surfaces of the plastic bags in the original study by Fabricius et al. are smooth, thereby reducing the possibility of particles leaching because of a smaller total surface [17].

Absorbent Pads with Silver Nanotechnology

Using the data from Fernandez et al., silver concentration in the meat extrudes was measured as 60 ppm (mg/kg). Under the assumption that some (here estimated to 10 ml in a 200g portion) of this will stay with the meat when removing it from the pad, the amount of silver ingested with the meat will be significant. 10 ml with 60 mg/kg silver will give a dose of 0.6 mg [19]. Despite limited data regarding disposable packaging it is important to include it. Disposable products will give a single dose to the consumers and when reviewing the results of the food containers a single use is the only case where there is a noticable dose. There are currently no studies showing the leaching potential from disposable packaging, and it is therefore difficult to evaluate the pads made by Fernandez et al. However, using the concentrations they measured, it is reasonable to assume that some silver will be on the meat. The amount estimated to 0.6 mg for a portion of meat is significantly larger than the specific migration limit (SML) for biocides of 0.05 mg/kg. However, the SML refers to particles leaching into the food and meat extrudes is technically still outside. The concentration is however large enough to have an antimicrobial effect, both the 60 mg/kg in the extrudes and the 0.6 mg/portion, compared to the 2 mg/kg requirement measured by Foldbjerg et al. [11].

Exposure model

The original intention when designing the project was to make an exposure model for nanosilver based on the achieved results. As the results indicate that reuse of food containers will lead to only a very small exposure over a long lifetime, it is not possible to make a valid model aimed to model exposure. The results from disposable food packaging represent products created for research and not commercially available products. There are also no results indication leaching from the products to the food and the results presented here are estimations based on the published data.

3 Titanium Dioxide

3.1 Introduction

Titanium Dioxide

Titanium dioxide, also known as titania, is a naturally occurring oxide of titanium . In nature it is found in minerals such as rutile, anatase and brookite. Titanium dioxide is used as a pigment, known as titanium white, which can be found as a UV filter in creams, a whitener in toothpaste, colour in cosmetics and additive to food. Titanium white accounts for 70% of the world production of pigments and is known as one of the whitest materials on Earth.

Titanium dioxide is considered to be a strong irritant. It is linked to asthma in inhalation studies [26][27], Crohn's disease in gastro-intestinal studies [28] and it has been marked as a potential carcinogen [29]. However, effects cannot always be attributed to its use, as it is one of many additives.

TiO_2 in food

In food, titanium dioxide is used as a colouring agent and for creating a specific consistency or smoothness. It is marked with E-number E171. It is added purely to make food appear more attractive and is not known to have any nutritional value. Because of this, titanium is considered as a manufacturing aid and not an ingredient, and thus in many cases exempt from the requirement for declaration of ingredients. As a food colour, the titanium dioxide particles are ideally 200-300 nm [2] in diameter. Under current legislation this is not defined as nanoparticles ($<$100nm), but it is believed that the size distribution will include particles in the nanoscale. The daily consumption of titanium, where 99% is titanium dioxide, is estimated to be about 5 mg/day [30].

Nanoform TiO_2 is not licensed as a food additive [8].

Other sources

For oral exposure the most dominant other source is toothpaste, which in many cases consist of a significant amount of titanium dioxide($>$1%). In addition, humans are exposed to titanium dioxide through cosmetics and sunscreens, both through dermal and inhalation pathways. In many cases these will be products that contain nanoform TiO_2 [16].

3.2 Materials and Methods

The exposure to TiO_2 was modeled using the best available data. Point estimates that are presented, are based on a worst case approach with and without refinements. Also, a more realistic approach based on Monte Carlo simulations has been followed. A Monte Carlo simulation is a simulation using algorithms that rely on repeated random sampling. This can create a fictitious representation of reality. For this simulation, specific UK consumption data are coupled with data on products purchased in the UK [31].

Size distribution

To determine whether or not E171 consist of nanoparticles, one commercially available sample of E171 was purchased in order to evaluate the size distribution of TiO_2. Using transmission electron microscopy (TEM) images were taken by the Laboratory of Inorganic Chemistry, ETHZ. The TEM sample was made by solving the E171 in water and adding 1-2 droplets onto the grid.

Using the program ImageJ [32], the sizes of the different particles were measured from the images. The requirements were that at least 10 single particles should be visible and that they should be representable. The program is similar to using a ruler measuring the particles manually and was chosen because of the uncertainty of the orientation of the particles on the grid that an automatic program might not take into account.

Data gathering

In order to create a model for consumer exposure, data regarding consumer behaviour is necessary. For this model UK consumer data for food has been evaluated and used. The data originates from the National Diet and Nutrition Survey (NDNS) undertaken in 2002 [31]. This survey assessed the mean consumption of specific products both for the consumers and the whole population (consumers and non-consumers). The model has an age range from 1.5 to 64 years old with children divided into groups of 1-3 years difference and adults from 10-15 years difference. In order to create worst case scenarios the consumption of consumers has been used. The model is based on the exposure equation 2 and gives PDI as the output.

Product concentration [C]

The different products in the NDNS have been evaluated for potentially containing TiO_2. This evaluation was based on data from the study by Lomer et al. [30] shown in table 8.

Table 8: TiO_2 concentration in different products. Data from Lomer et al. [30]

Product	TiO2 Amount - mg	portion size - g	Percent	Producer
Coffeemate	0.045	4.5	0.001	Nestle
Non-dairy creamer	1.935	4.5	0.043	Dixie
Non-dairy creamer	13	4.5	0.289	Farmer
Teamate	35.19	4.5	0.782	Nestle
Skittles	3	60	0.005	M&M Mars
Softmints	4.95	45	0.011	Trebor Bassett
Liquorice comfits	4.5	10	0.045	Haribo
White chocolate mini eggs	6.75	15	0.045	Nestle
Smarties	28.12	37	0.076	Nestle
Icing	54.9	30	0.183	Supercook
Marshmallows	9.95	5	0.199	Kidd's
Low fat caesar dressing	27.9	30	0.093	Cardini's
Tartare sauce	34.2	30	0.114	Waitrose
Caesar dressing	30.3	30	0.101	Hellmann's
Creamed horseradish	56.8	20	0.284	Rayner Burgess
Italian dressing	224.7	30	0.749	Hellmann's

From the NDNS the products shown i table 9 were chosen. The concentration is fixed (worst case) or based on Lomer et al. (refined case, table 9).

Table 9: TiO_2 concentrations in different types of food used in the model. Note: concentrations in dairy represents the maximum concentration found potentially used in milk.

Products		Amount of TiO_2 in the product		
Consumer data	Product with TiO_2	Worst case	Refined	Ref.refinement
Coffee	Coffee mate/Non-dairy creamer [1 tsp]	1 %	0.20 %	Lomer et al. [30]
Herbal Tea	Tea mate/Non-dairy creamer [1tsp]	1 %	0.75 %	Lomer et al.
Tea	Tea mate/Non-dairy creamer [1tsp]	1 %	0.75 %	Lomer et al.
Cottage Cheese	Cottage Cheese	1 %	0.10 %	Lomer et al.
Ice Cream	White Ice cream	1 %	0.10 %	max in milk [33]
Other dairy	Dairy dessert	1 %	0.10 %	max in milk
Yogurt	White low-fat yogurt	1 %	0.10 %	max in milk
White Chocolate	White Chocolate	1 %	0.20 %	Lomer et al.
Sweets	Sweets, coating	1 %	0.20 %	Lomer et al.
Icing	Coatings etc.	1 %	0.20 %	Lomer et al.
Salad	Salad dressing [Portion size 30g]	1 %	0.50 %	Lomer et al.

Several products in the NDNS may contain TiO_2 although not included here. In most cases these are not included due to low consumption or large uncertainty of TiO_2 content. A few of the most relevant can be found in table 10.

Table 10: Food types that may contain TiO_2

Product	Why removed
Skimmed milk	Additive not allowed used in milk in the EU
Biscuit	Concentration uncertainty large
Chocolate	Concentration uncertainty large
Baby food	Additive not allowed used in baby food in the EU
Energy bars	Consumption uncertainty large

Consumer behaviour [q]

Three scenarios have been created, the worst case scenario where all products contain 1% TiO_2, the refined case scenario where TiO_2 values were adjusted to expected maximum values, and a scenario that incorporates data on non-use and operates based on a Monte Carlo simulation. The consumption data can be found in the appendix A.

Consumers [bodyweight]

The consumers' bodyweight was taken from the NDNS. For adults the weight is provided in age sections similar to the food, while for the children it had to be modified. For age groups up to 14 years the weight is the average of the different weights linked to an age within a section. For the section 15-18 years the weight is the average between a 15 year old and the average weight of the age group 19-24 years. No data was available for the weight of the 16-18 age group. Table 11 shows the data used in this model.

Table 11: Average bodyweight of the British population for different age groups

Age [y]	Sex	Weight [kg]	Sex	Weight [kg]
1.5-2.5	mf	12		
2.5-3.5	mf	15		
3.5-4.5	m	17	f	16
4-6	m	21	f	21
7-10	m	31	f	31
11-14	m	48	f	50
15-18	m	71	f	63
19-24	m	79	f	66
25-34	m	83	f	67
35-49	m	85	f	70
50-64	m	87	f	71

Worst case base

The following assumptions are used as the base for the worst case scenario:

Consumption of Coffee, Herbal Tea and Tea are used as base for the consumption of Coffee mate/Tea mate/non-dairy creamer. It is assumed as a worst case that every coffee portion of a consumer is supplied with a mate. Furthermore, one portion is assumed as one teaspoon (tsp) as used in Lomer et al. [30]. Herbal tea is included in those cases where it is available.
The consumption of all dairy desserts is adjusted to 20% of the original value, this is due to that TiO_2 is more likely to be added to low/no fat products. There are no data for the consumption of low-fat products, and the value is therefore an estimation. Consumption of chocolate is adjusted to 5% to account for white chocolate ([34] only, as this is believed to contain more TiO_2. The consumption of salad accounts for the consumption of salad dressings as well as other premade sauces and garnish. Since all these products can be consumed with salad, this is assumed as the worst case, although some might be used with other food as well. The portion is set to 30g as used in Lomer et al. [30]. These adjustments are made based on that the consumption of other similar products within each food category is lower than the product used here.

Refinements of the worst case assumptions

The following assumptions are used as a refinement of the base worst case:

Above 0.1% TiO_2 will give sediments [33] in milk products which will lower the visual quality of the product. Dairy products were therefore set to have a maximum concentration of 0.1% because of this. Concentration in coffee is set to 0.2% as this is the maximum observed concentration in a non-dairy creamer. For tea the concentration is set to 0.75% as this is the concentration in Tea Mate. As salad consumption is a mix of the consumption of different raw products (lettuce, tomato, carrots etc.) the consumer fraction for salad is difficult to set. As the model is based on worst case, the product with the highest percent consumers in the mix is set as the percent consumers for the whole mix (generally lettuce).

Further details is in table 9.

Monte Carlo simulation

In order to evaluate the consumption of a population, a Monte Carlo simulation was used. Using Matlab, a population of 100.000 for each age group has chosen whether they consume a product or not based on statistical data from the NSDS. The data refers to q in the equation and can be found in appendix A.

The Matlab code can be found in appendix B.

Special case modification

Since consumption of coffee/tea/salad is not equivalent to consumption of non-dairy creamer/premade dressing the consumer percent was adjusted to 10% of the original for coffee/tea and 50% of the original for salad. These values are maximums based on observations in two cafeterias and represent the final refinements of the model presented in this thesis.

3.3 Results

A sample of E171 has been analysed to find the size distribution of the particles. The exposure to titanium dioxide has been modeled and the sensitivity of the model is analysed.

Size distribution, TEM analysis

In order to evaluate the size distribution of the particles in a sample of E171, TEM images were taken and analysed using ImageJ.

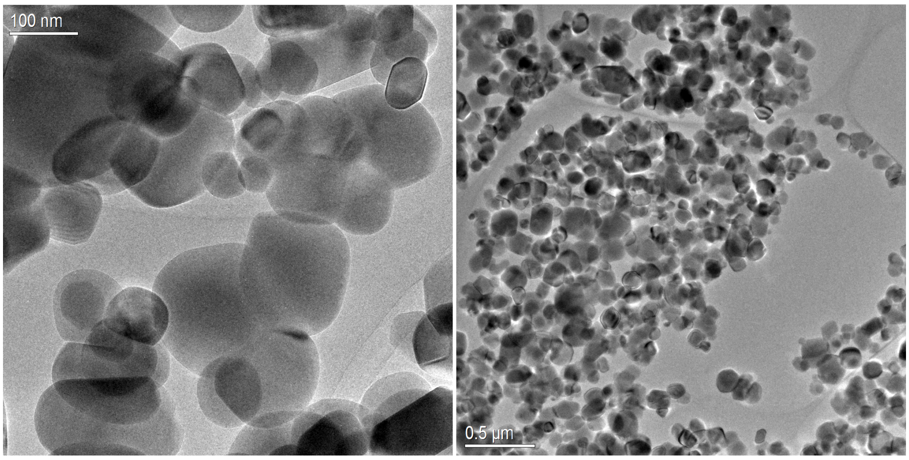

Figure 7: *TEM images of E 171 Titanium Dioxide food colour.*

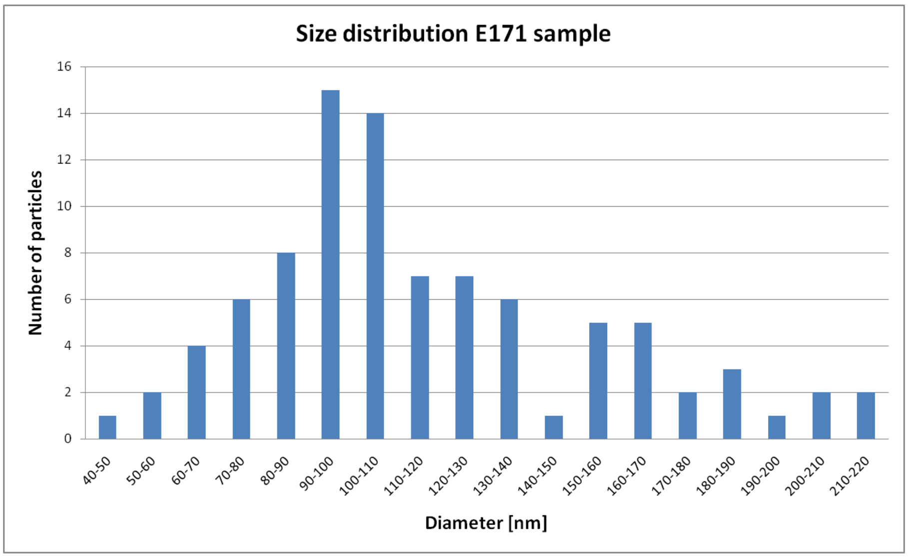

Figure 8: *Size distribution measured from the TEM images using ImageJ.*

The TEM images (figure 7) show a size distribution with a median around 100-110 nm (figure 8). This indicates that at least 50 % of the particles are nanoparticles. When taking agglomoration into account the amount might be even larger.

Model output, case scenarios

The first rough assessment uses a fixed concentration of 1% TiO_2 in all products. This gives a worst case scenario for consumption of TiO_2 as shown in figure 9.

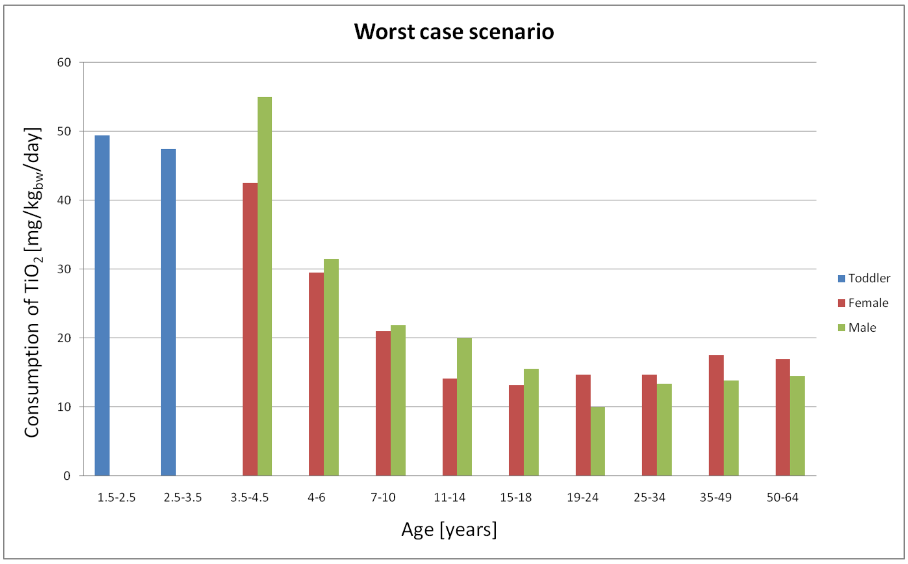

Figure 9: *Histogram of the daily consumption of TiO_2 based on the food consumption of the British population and a TiO_2 concentration in selected food of 1%.*

The output shows that consumption is by far highest among young children and that there is a small increase from the age of 20 to 60. The values vary from 15 to 55 mg/day/kg_{bw}.

Figure 10 is refined using the secondary adjustments and the concentrations used in table 9.

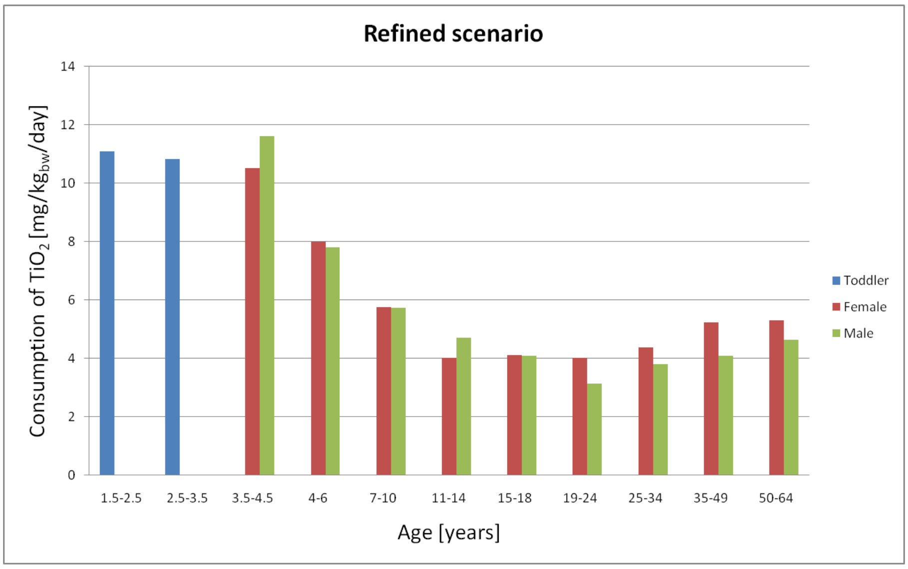

Figure 10: *Histogram of the daily consumption of TiO_2 based on the food consumption of the British population and a TiO_2 concentration in selected food based on scientific data.*

The shape of the output resembles what is seen in figure 9, but the difference between children and adults has been lowered. The values now vary from 3 to 12 mg/day/kg$_{bw}$.

Figure 11 represents the Monte Carlo simulation of the results in figure 10. It shows the mean output with standard deviation for the choice of consumption of a random population of 100.000 for each age group. The model takes into account the probability of a consumer consuming a certain product. The results here (figure 11) represents a realistic case for a whole population, with maximum cases represented in figure 10.

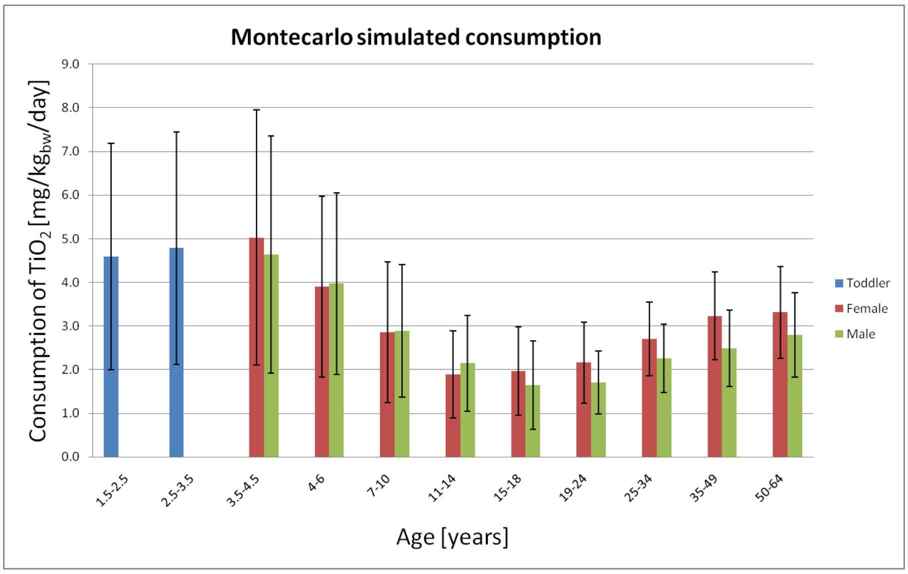

Figure 11: *Histogram of the mean (stdv) daily consumption of* TiO_2 *based on the food consumption of the British population and a* TiO_2 *concentration in selected food based on scientific data.*

As in the previous cases, there is a larger exposure among children than adults, but the difference between the age groups compared to the worst case is again decreased. However, the standard deviation for the children is quite large. The average consumption is approximately 2-5 mg/day/kg_{bw}

Examples of model output

Figure 12 and 13 are examples of the output from the matlab model. Figure 12 shows the consumption of a boy aged 11-14, while figure 13 is for a woman aged 50-64. Both of these results are included in the Monte Carlo simulation.

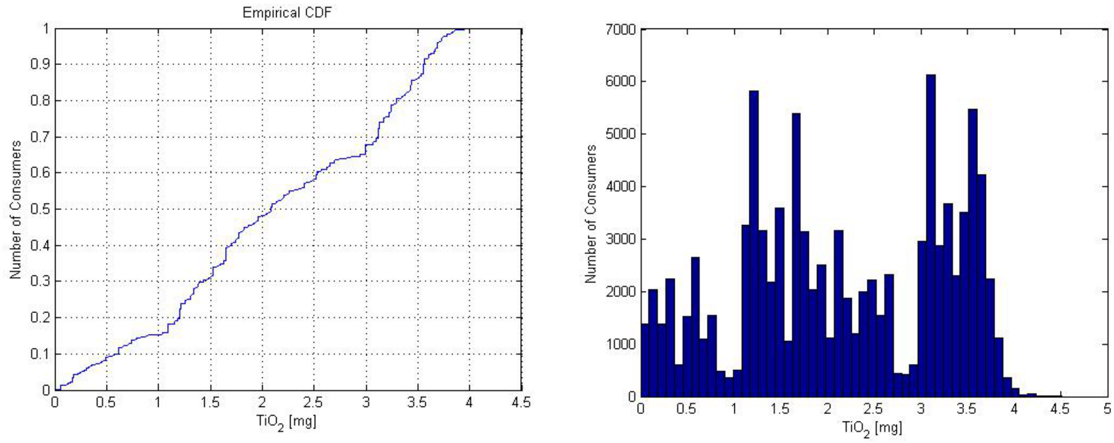

Figure 12: *Output from simulation. Left: Cumulative plot of the TiO_2 consumption of boys aged 11-14. Right: Histogram showing the dispersion in daily consumption of TiO_2 among boys aged 11-14.*

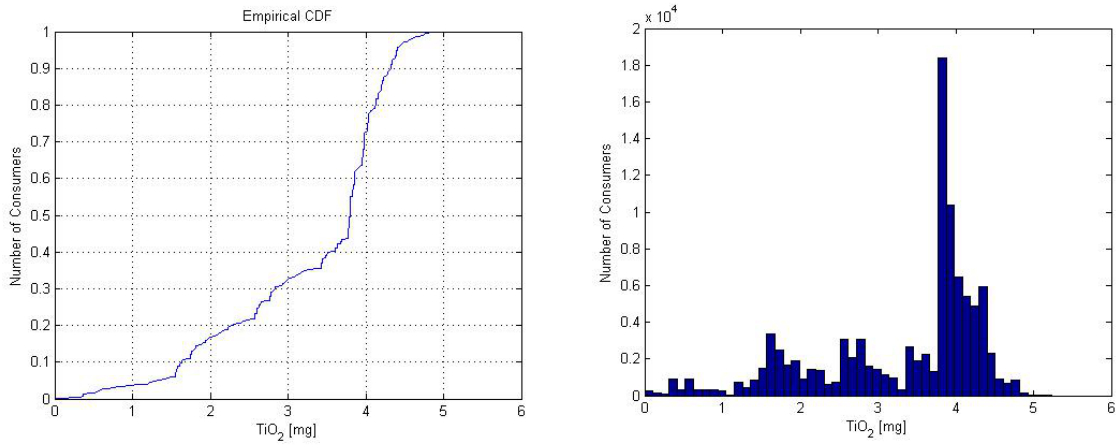

Figure 13: *Output from simulation. Left: Cumulative plot of the TiO_2 consumption of women aged 50-64. Right: Histogram showing the dispersion in daily consumption of TiO_2 among women aged 50-64.*

The two figures show the potential variation that may occur between different consumer groups. The difference in the pattern is a result of different diets, more so because of what people consume rather than the amount. From figure 12 it can be said that the variation in consumption is even and that no specific product stands out. Some consume a little, some a bit more and some a lot. For figure 13 the situation is completely different. One or a few products are very important and a lot of people in this consumer group choose to consume these. Also, for this specific group the tendency is to consume a lot rather than a little of products with TiO_2. These results are available for all consumer groups and enables diet evaluation and recommendations.

Sensitivity analysis

In order to evaluate the results from the modeling it is important to look at uncertainty and sensitivity. By looking at the contribution to the total maximum consumption it is possible to say for which products a reduction or increase in consumption would have the greatest effect. Comparing the percent chance of people choosing to consume a product with eachother indicates which products that are generally most important. By coupling the two it is possible to estimate the sensitivity of the results. In other words, a product containing a lot of TiO_2 which is only consumed by few, might contribute less than a product with less that is consumed by many. However, a small change in the percent consumer for the first will have a dramatic impact on the results, while not for the latter. Likewise, a small change in the concentration in the latter can have a great impact, while it may not in the first.

Figures 14 and 15 represent women while figures 16 and 17 are for men.

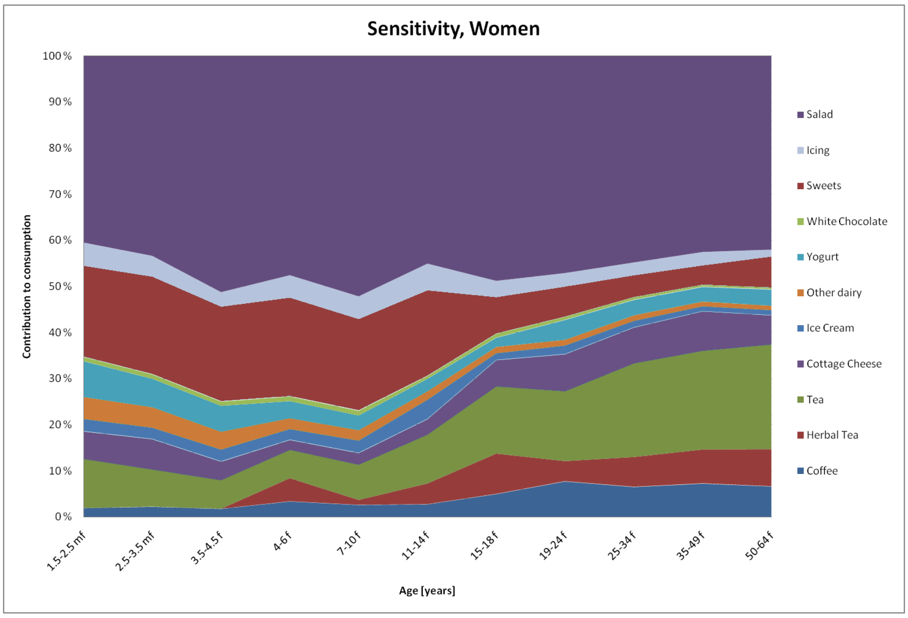

Figure 14: *Contribution to the consumption of TiO_2 by age groups, if the product is consumed for UK women.*

Figure 14 shows that salad and sweets are the most important contributors for children, while consumption of tea replaces sweets for adults.

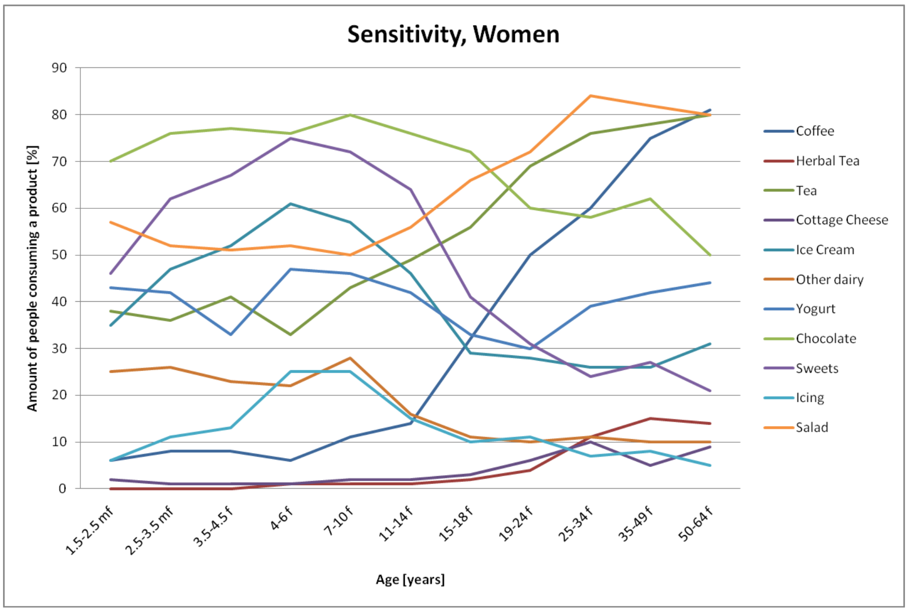

Figure 15: *Chance of a product being consumed by UK women.*

Figure 15 shows that the most important food groups for female children are sweets incl. chocolate, ice cream and salad, while adult women are more likely to consume tea, coffee, salad and chocolate.

Coupling figure 14 and 15 indicate that the main contributers to the consumption of TiO_2 for women is sweets and salad (dressing) for the children and tea (non-dairy creamer) and salad (dressing) dominates for the adults.

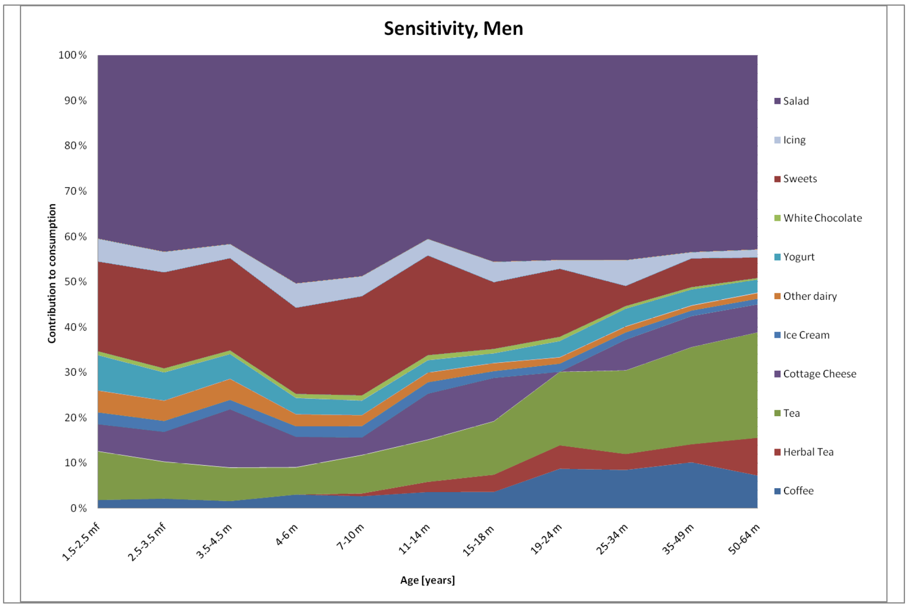

Figure 16: *Contribution to the consumption of TiO_2 if the product is consumed for UK men.*

For young men figure 16 shows that sweets and salad are the most important factors, while adult men are more exposed through tea and salad.

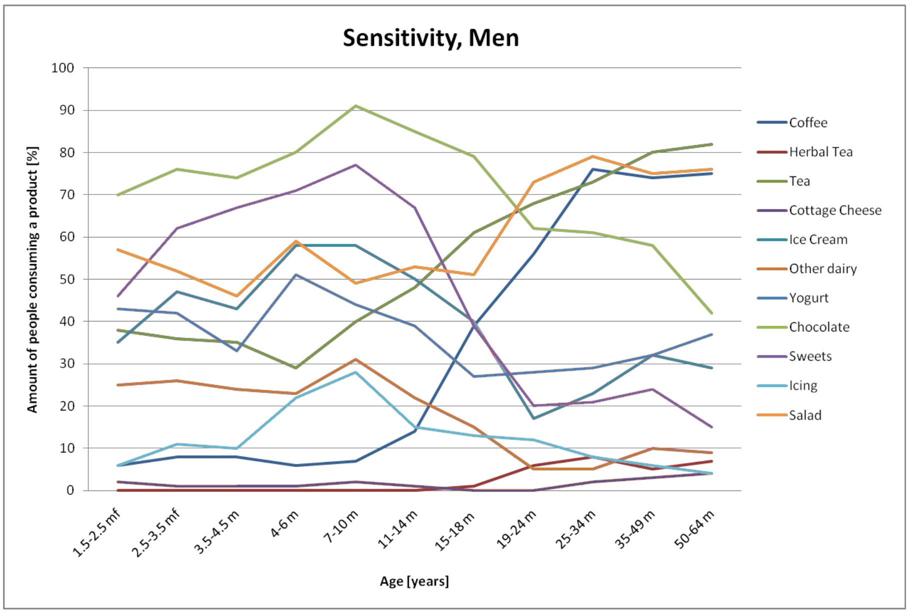

Figure 17: *Chance of a product being consumed by UK men.*

As for the women, figure 17 shows that young men are most likely to consume sweets incl. chocolate as well as salad and ice cream, while adults are more likely to consume coffee, tea, chocolate and salad.

Coupling the two graphs for men show that the product dependence is the same as for the women, indicating small changes between the male and female. The results also show a large dependence on the consumption of products that them self do not contain any TiO_2. This means that in order to model the consumption of TiO_2 it is important to know the fraction where the products of interest, non-dairy creamer and salad dressing, are used.

Special case scenario

In the special case, the consumer fraction that uses a non-dairy creamer and/or salad dressing is set to 10 and 50 %, respectively. This creates an corrected version of the Monte Carlo simulation.

As the percent consumers is reduced for certain products in figure 18, it shows an average consumption between 1 and 3 mg/day/kg$_{bw}$. The results show a large standard deviation for all groups, indicating a large variation in diets between the different consumers.

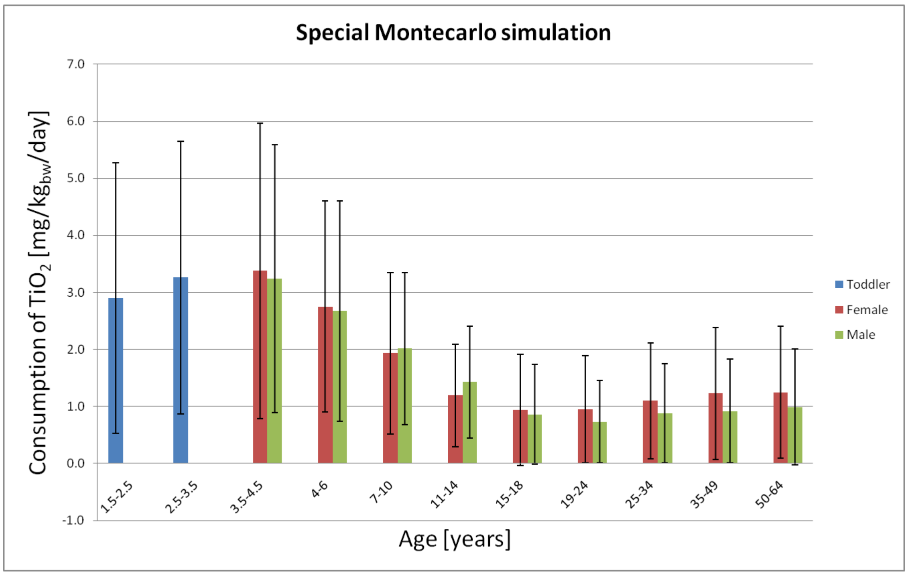

Figure 18: *Histogram of the daily consumption of TiO_2 based on the food consumption of the British population and a TiO_2 concentration in selected food based on scientific data. The output is derived from the random choice of 100.000 people from each age group on whether they consume a product or not and the likelihood of a consumer consuming a product is reduced to 10 % for Tea/Coffee/Herbal Tea and to 50 % for salad.*

3.4 Discussion

Nano or not?

It was only possible to analyse one sample of E171. This does affect the justification of whether it is nanoparticles or not. However, nanosized titanium dioxide is not allowed as a food additive. Although the ideal size for E171 is claimed to be 200-300nm [2], the size distribution in the sample was measured to be around 100nm (figure 7). Thus, even under current legislation, which does not allow nanosized titanium dioxide to be used as a food additive, this sample must be said to contain a large amount of nanoparticles. Nanoparticles might have a greater effect than microparticles and it is of concern that such a large fraction of this sample is smaller than 100nm.

Exposure model

The exposure model is built using the best available consumer data in Europe. The consumption data from the National Diet and Nutritional Survey provides a solid base for the modeling with good data in relevant food groups, knowledge about consumer behavior and the bodyweight of the consumers.

For all the food groups in the model there are a lot of important factors that may limit the validity of the results of the exposure model. While data provided from different sources are correct, interlinking these is very difficult. Relating concentration in a specific product to the consumption of a general product group means that certain assumptions have to be made. The consumption of one product is not equivalent to the consumption of an accompanying product. Thus, for example, coffee and tea consumption is not equivalent to consumption of non-dairy creamer consumption. Likewise, salad consumption is not equivalent to consumption of Caesar salad dressing. However, it is reasonable to assume that a consumer who uses an accompanying product is likely to always use that product. In spite of this, the concentration of titanium dioxide may not be the same in all brands of non-dairy creamer, and consumption of pre-made salad dressings vary between countries.

Data are specific for cottage cheese, a known product to contain titanium dioxide. However, there are many other cheeses that might contain this additive, such as mozzarella. Exposure might vary greatly, as a consumer is also likely not to be consistent in his or her consumption of a specific cheese.

A very critical aspect of the model is that all products within a category are defined as containing TiO_2. In some cases only a few products in a specific category will contain TiO_2, and these specific products might have a low or high fraction of the market. In dairy products such as ice cream, titanium dioxide is used as an additive, but not in all ice creams. Concentrations here are very much unknown as well as whether the source of the TiO_2 is from product recipe or as replacement for milk solids. The model is focused on low-fat products and an estimate that 20 % of the dairy products consumed are of such a sort. Low fat products were chosen as they may contain less milk solids, thus increasing the need for a white colour.

Consumption of white chocolate only accounts for about 5 % of the total consumption of chocolate, but is the only product where TiO_2 is known to be a used additive. Choosing food groups is difficult as knowledge about products containing TiO_2 is limited. This means that sections that are excluded could be more relevant than some that are included. There is data that says chocolate bars and milk chocolate do contain small amounts of TiO_2, but in this case it is used to get a certain texture rather than colour. For other types of sweets one will find a small amount of TiO_2 in a vast amount of products.

The worst case scenario from the model, figure 9, is quite high, showing consumptions up to 1 g TiO_2/day (15-55 mg/day/kg_{bw}). However, the concentrations here are significantly higher than what is found in any product, and the output is probably above what can be expected to be a maximum. The first refinements, figure 10, where the concentrations in the different products are reduced, lowers the daily consumption to approximately 200 mg/day (3-12 mg/day/kg_{bw}). The biggest changes between the two graphs is the concentration in cottage cheese which is artificially high in the worst case scenario. However, these results still do assume that all consumers consume every product. To tackle this problem a population of 100.000 was randomly choosing if they consumed a product or not based on dietary data. This Monte Carlo simulation, shown in figure 11, indicated that consumption is closer to 2-5 mg/day/kg_{bw}). The simulation eliminates unnatural high contributions to the average consumption of TiO_2, as only a few percent will eat and drink products such as cottage cheese and herbal tea.

There are few significant differences between males and females. The only case where this is found is in the worst case scenario where male children have a higher consumption than females (figures 14-17). This value comes from the consumption of cottage cheese and somewhat sweets. It is important to notice that the TiO_2 concentration in the worst case scenario is very high and that likelihood of a 3-4 year old to consume cottage cheese is 1 % which is why this difference is eliminated in the simulated scenarios. The large standard deviations for children is due to that some, but few children are given coffee and tea. In all cases, children consume a lot more TiO_2/ kg_{bw} than adults, which is of concern. Especially products such as sweets, which are known to contain TiO_2 are a significant part of children's consumption. For adults, the consumption relies more on products such as tea and salad. However, the consumption of tea and/or salad is not equivalent to the consumption of TeaMate or premade dressings. The model output shown in figure 18 tries to counteract this problem by reducing the amount of consumers for instance drinking tea with TeaMate. The result show that the average consumption of TiO_2, although still with high product concentrations, can be estimated to 1-2 mg/day/kg_{bw}). However, depending on the diet, consumers can be exposed to up to 2-3 as much. Figure 12 and 13 show how big the difference in dietary behaviour can be between different consumer groups.

The uncertainty is quite large concerning modeling the exposure to titanium dioxide as the sources and consumption is so widespread and unknown. Despite this, it is though quite clear that humans may be exposed to much more of this additive than what is believed.

Model potential

From the model it is possible to get a worst case scenario value and to see the difference between different diets. This gives a value that can be directly coupled to an effect value to estimate if consumption of TiO_2 can be a risk. The model is also easy to adapt, depending on the requests and can provide different scenarios.

Alex Weir has investigated the titanium dioxide content in a vast amount of US products [35]. These yet unpublished data provided by Alex Weir and Prof. Paul Westerhoff can easily be implemented to create a new estimation of the exposure. The exposure modeled so far represents UK and possibly European consumption. With the new data, it will be possible to use US consumer data to assess the exposure for North American consumers. Thus, creating a possibility to evaluate and compare exposure in different parts of the world.

4 Discussion - Exposure assessment

4.1 Human exposure to inorganic nanoparticles

Humans are exposed to engineered inorganic nanoparticles. While many products connected with food may contain nanoparticles the exposure from them varies greatly. For nanotechnology, human exposure has to be assessed on a case by case basis. The choice in this case has been to examine the exposure to silver and titanium dioxide added to food related products or food itself. There are very few similarities between the two products in general, but they do have something incommon. Firstly, addition of nanoparticles to food has a very short history and is a novel field of research. Secondly, they are both added as an aid for food preservation or looks, and in many cases as an undeclared additive. Thirdly, they have no nutritional value. Fourthly, in most cases, the exposure and toxicity is partly or completely unknown and regulation is still up for discussion. Finally there is a general fear that nanoparticles will pass all human barriers and cause damage to vital organs such as the brain and liver.

Considering the products with a long lifetime containing nanosilver, there is very little exposure. Figure 3 shows that there will initially be concentrations that are questionable, but when considering the lifetime of these products, they will after a short period of time be exactly the same as the equivalent container without silver. Compared to the background exposure of 20-80 μg/day [15], the concentrations of silver leaching from the food container are fairly small. However, disposable packaging products used for food and containing silver could be a significant source of silver nanoparticles. Although no leaching measurements have yet been performed, a rough estimation shows that usage of meat pads, such as created by Fernandez et al., can give a dose significantly higher than the background and high enough to be antimicrobial. It is important to remember that intake is not the same as uptake and up to 90 % is believed to leave the body directly through feces. The remaining silver might be absorbed by the body. However, naturally occurring sulphur in the food may bind to the silver creating an insoluble compound, Ag_2S (K_{sp} 10^{-49}), changing the properties of silver and the bioavailability of the biocide.

While nanosilver is a trademark used for advertisement [36], with uncertainties of whether it is actually in the product [17], titanium dioxide is an "E" substance found in a vast amount of products as a food colour or "taste" additive. Nanosilver is also a substance added to utilities and not directly to food, while TiO_2 is an active ingredient added to the food directly.

The TiO_2 model gives data on potential exposure. In all cases the exposure is very diet dependent and small changes can have large impacts. The average consumer will be exposed to a dose that is 5-10 times larger than the background concentration. As a general trend children are exposed to more TiO_2 than adults per kilo bodyweight. The maximum values of a few hundred mg/day is significantly larger than the background (5 mg/day) and represents a large increase in exposure. Another interesting aspect is that despite the manufacturers saying that E171 should ideally be around 200-300 nm in diameter, the sample investigated show an average around 110 nm, making part of this sample nanoform TiO_2, which is illegal in food. If nanoform TiO_2 has a greater toxicological effect than larger particles, these results are of great concern.

It is difficult to link silver and titanium dioxide exposure. But one thing is very clear, nanoparticles added to something as stable as polypropylene will probably not increase exposure significantly, whereas adding the particles directly to the food, irrespective of the purpose, will lead to a large increase in exposure. From this it can be expected that adding TiO_2 to plastic containers to get UV protection is not likely to lead to an increase in exposure, while adding silver to a porous material such as meat pads will give a significant dose in the food. Other materials such as silicates which are added to powders as anticaking agent will, as with the E171, increase the daily exposure to that specific inorganic material.

4.2 Risk

Silver nanoparticles have a very clear and measurable effect as they are an efficient antimicrobial agent. However, incorporating silver nanoparticles into polymers, as in products tested here, it is not likely to lead to an increase in silver exposure, at least not comparable to the background level, as shown in figure 4. It is therefore possible to say that the risk of using such containers is very low and could be considered on the same level as a conventional box after first time use. They can thereby be marked as safe. If, on the other hand, the food is to be packed in disposable packaging with silver nanoparticles from the manufacturer, the exposure levels would increase and thereby also the risk. The rough estimation based on the results from Fernandez et al. show that concentration can be significantly higher than the background and that it might reach concentrations high enough to be antimicrobial.

Unlike the nanosilver, titanium dioxide has been an additive used in large quantities for quite some time. As there is a large variety of food additives in general, it is difficult to link a specific effect to the titanium dioxide. It has been marked as a carcinogenic substance in inhalation studies and although the absorption from the gastro-intestinal tract is smaller than the lungs it might have a potential effect [28]. Generally the exposure might be larger than what is commonly known and if this substance has an adverse effect it should be reconsidered. The relative higher consumption by children is of concern. Sweets and many artificially coloured products are a common part of their diet and contribute significantly to the total exposure.

For all inorganic nanoparticles there is a large uncertainty regarding the absorption of the particles. From a toxicological perspective the gastro-intestinal tract is still the outside of the body and intake may differ greatly from absorption. The ultimate risk when considering nanoparticles is that they will be absorbed into the body and accumulate in vital organs, such as the brain, causing cytotoxic conditions. For nanoparticles up to 90%

passes straight through the gastro-intestinal tract without being absorbed [10]. The remaining may be adapted by the immune system making them inert, leaving only a small fraction bioavailable. However, silver, as an antimicrobial agent, and titanium dioxide, as a strong irritant, may do much damage to bacteria and cells in the gastro-intestinal tract just by passing through. Silver nanoparticles will at high enough concentrations affect the bacteria culture in the intestines, while nanoparticular titanium dioxide can irritate the mucosa and may be carcinogenic.

5 Conclusion

Using full scale containers and ICP-MS, previous results on leaching of silver nanoparticles from food containers to food simulants have been confirmed. Experiments have also shown that leaching will decrease rapidly with repeated use. By analysing the surface of the container with AFM, it is expected that the surface structure have a major effect on the amount of released silver. The concentrations found are significantly lower than what is required for an antimicrobial effect and it is also lower than background concentrations. The exposure from food containers is therefore expected to be low. As a general note they may be considered as safe, while at the same time they will not be functioning different from a normal plastic container, especially when considering a long lifetime. Concerns should be raised with regards to disposable packaging as these may release much more silver and give concentrations above the critical limits.

A sample of E171 Titanium dioxide has been analysed with TEM showing a size distribution around 100 nm. This size was smaller than expected and since nanoparticular TiO_2 is not licensed for food, this specific sample would not be legal for commercial use. It can therefore be expected that consumers are exposed to TiO_2 nanoparticles. By using consumer data from the National Diet and Nutritional Survey on food consumption, several scenarios have been created for the exposure to TiO_2. As a worst case scenario a maximum exposure/day is about 1g. A further refined scenario using Monte Carlo simulation shows that depending on age and diet, humans may on average be exposed to 1-3 mg/kg$_{bw}$/day. The results indicate that children are exposed to more TiO_2 than adults primarily due to their consumption of sweets.

There are many aspects to take into account when analysing exposure to nanoparticles. Nanotechnology is a fairly new field of research and it struggles with a lack of set definitions. Although the definition of a nanoparticle is set now, it might be changed within a few years as further research on the properties of such particles is performed. The TiO_2 sample analysed here contains nanoparticles under current legislation, but is the change in toxicological effect as drastic as the change in regulatory effect? Will another sample containing particles with a mean around 200 nm, which would most likely be legal, have a much higher margin of safety?

Both titanium dioxide and silver are additives used in the food industry. When estimating the exposure there are two very significant difference between the two products. Firstly, silver is added to utilities used for food, while TiO_2 is added directly to the consumed food. As a consequence the PDI of TiO_2 is much larger than silver, which only represents a very small dose. Secondly, silver is coupled to a very specific and measurable toxicological effect and the dose can therefore very easily be considered acceptable or not. For TiO_2, there is only potential effects linked to oral intake and no threshold limit is currently known. It is therefore difficult to evaluate if the potential dose is acceptable or if concerns should be raised. However, a few things are quite certain. Silver added to food containers can only be called a commercial gimmick. There is no indication whatsoever that these containers will have any antimicrobial effect after first time use, neither on the surface, nor in the food, or that they under any circumstances will be a source of a dose that should be of concern. The only point in their lifetime where they represent any threat is when they are disposed, where the complete amount of silver trapped in the polymer may be released to the environment. For the titanium dioxide the lack of a threshold makes it difficult to say if a consumption of a few hundred mg is a lot. However, one thing is again certain; If there is a toxicological effect in the range of what humans are exposed to, children are much more likely to be affected by this as their daily dose is significantly larger.

There are many engineered inorganic nanoparticles directly or indirectly added to the food we daily consume. Most of these may present no danger, with predicted daily intakes lower than the background exposure. This research presents two such nanoparticles, one of which should not be in nanoform. It will be important to investigate both exposure and effect for as many as these additives as possible in order to create a filter, indicating what is safe and what is not. Nanotechnology is here to stay, and it is more likely to see an increase rather than a decrease in food nanotechnology. It is therefore safe to say that nanorisk is real, it is just a question of whether it is an acceptable one.

Outlook

The results of the research that I have been part of this last year has been the source of a few surprises.

We have experiment after experiment confirmed that nanosilver added plastic containers creates a product that has no real positive or for that matter negative effect. It will after first time use be exactly the same as a conventional product. The first time use is also not likely to have any special effect on the microbes in food. Using these products will not be associated with any risk, but they will as well to our surprise be very inefficient as anything but a regular food container. However, the disposal of these containers may pose a new question regarding the environmental exposure.

Another surprise is that the sample of E171, which is not a nanoproduct, actually contained as much as 50 % nanoparticles. As regulation is so precise, the product was legally sold to us as a food additive, but after a trip to the lab it is suddenly strictly forbidden.

Nanotechnology may very well revolutionize the food industry in the years to come. It will help increase production, help increase nutritional values, add artificial taste, texture and colour to food and potentially create more and healthier food. One interesting question remains though. As consumers in Europe increasingly ask for organic food, happy chicken and local cheese, what role will nanotechnology play? Can nanotechnology supply the volume, while the local farmer provide the unique? One thing is certain, adding nanoparticles to products where they have no effect or exposing children to a large dose without knowing the effect is completely unnecessary, and the ethical questions of the gamble are likely to be discussed in time to come.

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A Model Data

Appendix A contains all consumer data used and modified for the titanium dioxide model. The tables include the following groups:

Product of interest: Product known to contain titanium dioxide.

Reference: Product found in the NDNS.

B.W: Body Weight.

Amount: Average amount of the product consumed every day.

Eqv. Portions: Average amount of portions of a product consumed every day.

Portion: Portion size and type.

TiO_2: Worst case titanium dioxide concentration.

TiO_2: Amount of titanium dioxide in each portion in the worst case scenario.

Consumed: Average amount of titanium dioxide consumed in the worst case scenario.

New: Refined titanium dioxide concentration.

Consumed: Average amount of titanium dioxide consumed in the refined case.

Table A.1: Consumer data for female and male aged 1.5-2.5 and 2.5-3.5 years.

Product of interest	Reference	B.W.	Amount	Eqvl. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	MF 1.5-2.5		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	12	5.82	0.023	Cups [250ml]	1	0.045	1.05	0.20	0.2
Milk replacement	Herbal Tea	12	0.00	0.000	Cups [250ml]	1	0.045	0.00	0.75	0.0
Milk replacement	Tea	12	8.80	0.035	Cups [250ml]	1	0.045	1.58	0.75	1.2
Cheese	Cottage Cheese	12	0.66	0.017	tbs [40g]	1	0.4	6.65	0.10	0.7
Dairy dessert	Ice cream	12	0.29	0.003	Bowls [100g]	1	1	2.94	0.10	0.3
Dairy dessert	Other	12	0.53	0.005	Bowls [100g]	1	1	5.34	0.10	0.5
Dairy dessert	Yogurt	12	0.86	0.006	Portion [150g]	1	1.5	8.61	0.10	0.9
Chocolate	White Chocolate	12	0.05	0.002	piece [25g]	1	0.25	0.50	0.20	0.1
Sweets	Sweets	12	1.10	0.022	packet [50g]	1	0.5	10.96	0.20	2.2
Icings, fillings etc.	Icing	12	0.28	0.009	Portion [30g]	1.	0.3	2.80	0.20	0.6
Premade dressings	Salad	12	3.00	0.030	Bowls [100g]	1	0.3	8.99	0.50	4.5
								49.42		11.1
	MF 2.5-3.5									
Milk replacement	Coffee	15	6.58	0.026	Cups [250ml]	1	0.045	1.18	0.20	0.2
Milk replacement	Herbal Tea	15	0.00	0.000	Cups [250ml]	1	0.045	0.00	0.75	0.0
Milk replacement	Tea	15	6.51	0.026	Cups [250ml]	1	0.045	1.17	0.75	0.9
Cheese	Cottage Cheese	15	0.71	0.018	tbs [40g]	1	0.4	7.14	0.10	0.7
Dairy dessert	Ice cream	15	0.26	0.003	Bowls [100g]	1	1	2.64	0.10	0.3
Dairy dessert	Other	15	0.49	0.005	Bowls [100g]	1	1	4.85	0.10	0.5
Dairy dessert	Yogurt	15	0.67	0.004	Portion [150g]	1	1.5	6.67	0.10	0.7
Chocolate	White Chocolate	15	0.05	0.002	piece [25g]	1	0.25	0.51	0.20	0.1
Sweets	Sweets	15	1.14	0.023	packet [50g]	1	0.5	11.45	0.20	2.3
Icings, fillings etc.	Icing	15	0.24	0.008	Portion [30g]	1	0.3	2.45	0.20	0.5
Premade dressings	Salad	15	3.13	0.031	Bowls [100g]	1	0.3	9.39	0.50	4.7
								47.47		10.8

Table A.2: Consumer data for female and male aged 3.5-4.5 years.

Product of interest	Reference	B.W.	Amount	Eqvl. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 3.5-4.5		[g/day/kg_{bw}]	[n/day/kg_{bw}]		[%]	[g]	[mg/kg_{bw}]	[%]	[mg/kg_{bw}]
Milk replacement	Coffee	16	5.04	0.020	Cups [250ml]	1	0.045	0.91	0.20	0.2
Milk replacement	Herbal Tea	16	0.00	0.000	Cups [250ml]	1	0.045	0.00	0.75	0.0
Milk replacement	Tea	16	4.87	0.019	Cups [250ml]	1	0.045	0.88	0.75	0.7
Cheese	Cottage Cheese	16	0.43	0.011	tbs [40g]	1	0.4	4.27	0.10	0.4
Dairy dessert	Ice cream	16	0.27	0.003	Bowls [100g]	1	1	2.68	0.10	0.3
Dairy dessert	Other	16	0.41	0.004	Bowls [100g]	1	1	4.13	0.10	0.4
Dairy dessert	Yogurt	16	0.59	0.004	Portion [150g]	1	1.5	5.92	0.10	0.6
Chocolate	White Chocolate	16	0.05	0.002	piece [25g]	1	0.25	0.48	0.20	0.1
Sweets	Sweets	16	1.08	0.022	packet [50g]	1	0.5	10.80	0.20	2.2
Icings, fillings etc.	Icing	16	0.17	0.006	Portion [30g]	1.	0.3	1.66	0.20	0.3
Premade dressings	Salad	16	3.60	0.036	Bowls [100g]	1	0.3	10.79	0.50	5.4
								42.52		10.5
	M 3.5-4.5									
Milk replacement	Coffee	17	5.31	0.021	Cups [250ml]	1	0.045	0.96	0.20	0.2
Milk replacement	Herbal Tea	17	0.00	0.000	Cups [250ml]	1	0.045	0.00	0.75	0.0
Milk replacement	Tea	17	6.32	0.025	Cups [250ml]	1	0.045	1.14	0.75	0.9
Cheese	Cottage Cheese	17	1.50	0.037	tbs [40g]	1	0.4	14.97	0.10	1.5
Dairy dessert	Ice cream	17	0.25	0.002	Bowls [100g]	1	1	2.46	0.10	0.2
Dairy dessert	Other	17	0.54	0.005	Bowls [100g]	1	1	5.35	0.10	0.5
Dairy dessert	Yogurt	17	0.63	0.004	Portion [150g]	1	1.5	6.30	0.10	0.6
Chocolate	White Chocolate	17	0.05	0.002	piece [25g]	1	0.25	0.49	0.20	0.1
Sweets	Sweets	17	1.18	0.024	packet [50g]	1	0.5	11.79	0.20	2.4
Icings, fillings etc.	Icing	17	0.18	0.006	Portion [30g]	1	0.3	1.81	0.20	0.4
Premade dressings	Salad	17	3.23	0.032	Bowls [100g]	1	0.3	9.68	0.50	4.8
								54.95		11.6

Table A.3: Consumer data for female and male aged 4-6 years.

Product of interest	Reference	B.W.	Amount	Eqvl. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 4-6		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	21	7.44	0.030	Cups [250ml]	1	0.045	1.34	0.20	0.3
Milk replacement	Herbal Tea	21	2.98	0.012	Cups [250ml]	1	0.045	0.54	0.75	0.4
Milk replacement	Tea	21	3.67	0.015	Cups [250ml]	1	0.045	0.66	0.75	0.5
Cheese	Cottage Cheese	21	0.17	0.004	tbs [40g]	1	0.4	1.74	0.10	0.2
Dairy dessert	Ice cream	21	0.18	0.002	Bowls [100g]	1	1	1.84	0.10	0.2
Dairy dessert	Other	21	0.19	0.002	Bowls [100g]	1	1	1.92	0.10	0.2
Dairy dessert	Yogurt	21	0.45	0.003	Portion [150g]	1	1.5	2.97	0.10	0.3
Chocolate	White Chocolate	21	0.04	0.002	piece [25g]	1	0.25	0.40	0.20	0.1
Sweets	Sweets	21	0.86	0.017	packet [50g]	1	0.5	8.56	0.20	1.7
Icings, fillings etc.	Icing	21	0.19	0.006	Portion [30g]	1.	0.3	1.95	0.20	0.4
Premade dressings	Salad	21	2.54	0.025	Bowls [100g]	1	0.3	7.62	0.50	3.8
								29.53		8.0
	M 4-6									
Milk replacement	Coffee	21	6.72	0.027	Cups [250ml]	1	0.045	1.21	0.20	0.2
Milk replacement	Herbal Tea	21	0.00	0.000	Cups [250ml]	1	0.045	0.00	0.75	0.0
Milk replacement	Tea	21	3.45	0.014	Cups [250ml]	1	0.045	0.62	0.75	0.5
Cheese	Cottage Cheese	21	0.53	0.013	tbs [40g]	1	0.4	5.26	0.10	0.5
Dairy dessert	Ice cream	21	0.18	0.002	Bowls [100g]	1	1	1.84	0.10	0.2
Dairy dessert	Other	21	0.21	0.002	Bowls [100g]	1	1	2.08	0.10	0.2
Dairy dessert	Yogurt	21	0.42	0.003	Portion [150g]	1	1.5	2.78	0.10	0.3
Chocolate	White Chocolate	21	0.04	0.001	piece [25g]	1	0.25	0.37	0.20	0.1
Sweets	Sweets	21	0.74	0.015	packet [50g]	1	0.5	7.41	0.20	1.5
Icings, fillings etc.	Icing	21	0.21	0.007	Portion [30g]	1	0.3	2.08	0.20	0.4
Premade dressings	Salad	21	2.62	0.026	Bowls [100g]	1	0.3	7.87	0.50	3.9
							0	31.52		7.8

Table A.4: Consumer data for female and male aged 7-10 years.

Product of interest	Reference	B.W.	Amount	Eqvl. portion	Portion	TiO_2	TiO_2	Consumed	New	Consumed
	F 7-10		[g/day/kg_{bw}]	[n/day/kg_{bw}]		[%]	[g]	[mg/kg_{bw}]	[%]	[mg/kg_{bw}]
Milk replacement	Coffee	31	4.13	0.017	Cups [250ml]	1	0.045	0.74	0.20	0.1
Milk replacement	Herbal Tea	31	0.45	0.002	Cups [250ml]	1	0.045	0.08	0.75	0.1
Milk replacement	Tea	31	3.29	0.013	Cups [250ml]	1	0.045	0.59	0.75	0.4
Cheese	Cottage Cheese	31	0.15	0.004	tbs [40g]	1	0.4	1.46	0.10	0.1
Dairy dessert	Ice cream	31	0.15	0.002	Bowls [100g]	1	1	1.53	0.10	0.2
Dairy dessert	Other	31	0.13	0.001	Bowls [100g]	1	1	1.33	0.10	0.1
Dairy dessert	Yogurt	31	0.28	0.002	Portion [150g]	1	1.5	1.84	0.10	0.2
Chocolate	White Chocolate	31	0.03	0.001	piece [25g]	1	0.25	0.30	0.20	0.1
Sweets	Sweets	31	0.57	0.011	packet [50g]	1	0.5	5.71	0.20	1.1
Icings, fillings etc.	Icing	31	0.14	0.005	Portion [30g]	1.	0.3	1.42	0.20	0.3
Premade dressings	Salad	31	2.01	0.020	Bowls [100g]	1	0.3	6.02	0.50	3.0
								21.02		5.8
	M 7-10									
Milk replacement	Coffee	31	4.35	0.017	Cups [250ml]	1	0.045	0.78	0.20	0.2
Milk replacement	Herbal Tea	31	0.26	0.001	Cups [250ml]	1	0.045	0.05	0.75	0.0
Milk replacement	Tea	31	3.58	0.014	Cups [250ml]	1	0.045	0.64	0.75	0.5
Cheese	Cottage Cheese	31	0.22	0.006	tbs [40g]	1	0.4	2.23	0.10	0.2
Dairy dessert	Ice cream	31	0.15	0.001	Bowls [100g]	1	1	1.47	0.10	0.1
Dairy dessert	Other	31	0.14	0.001	Bowls [100g]	1	1	1.38	0.10	0.1
Dairy dessert	Yogurt	31	0.27	0.002	Portion [150g]	1	1.5	1.83	0.10	0.2
Chocolate	White Chocolate	31	0.03	0.001	piece [25g]	1	0.25	0.34	0.20	0.1
Sweets	Sweets	31	0.63	0.013	packet [50g]	1	0.5	6.27	0.20	1.3
Icings, fillings etc.	Icing	31	0.13	0.004	Portion [30g]	1	0.3	1.25	0.20	0.3
Premade dressings	Salad	31	1.87	0.019	Bowls [100g]	1	0.3	5.60	0.50	2.8
							0	21.86		5.7

Table A.5: Consumer data for female and male aged 11-14 years.

Product of interest	Reference	B.W.	Amount	Eqvl. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 11-14		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	50	3.03	0.012	Cups [250ml]	1	0.045	0.55	0.20	0.1
Milk replacement	Herbal Tea	50	1.33	0.005	Cups [250ml]	1	0.045	0.24	0.75	0.2
Milk replacement	Tea	50	3.16	0.013	Cups [250ml]	1	0.045	0.57	0.75	0.4
Cheese	Cottage Cheese	50	0.14	0.003	tbs [40g]	1	0.4	1.36	0.10	0.1
Dairy dessert	Ice cream	50	0.08	0.001	Bowls [100g]	1	1	0.83	0.10	0.2
Dairy dessert	Other	50	0.08	0.001	Bowls [100g]	1	1	0.75	0.10	0.1
Dairy dessert	Yogurt	50	0.16	0.001	Portion [150g]	1	1.5	1.08	0.10	0.1
Chocolate	White Chocolate	50	0.02	0.001	piece [25g]	1	0.25	0.24	0.20	0.0
Sweets	Sweets	50	0.37	0.007	packet [50g]	1	0.5	3.71	0.20	0.7
Icings, fillings etc.	Icing	50	0.12	0.004	Portion [30g]	1.	0.3	1.16	0.20	0.2
Premade dressings	Salad	50	1.20	0.012	Bowls [100g]	1	0.3	3.61	0.50	1.8
								14.11		4.0
	M 11-14									
Milk replacement	Coffee	48	4.77	0.019	Cups [250ml]	1	0.045	0.86	0.20	0.2
Milk replacement	Herbal Tea	48	0.79	0.003	Cups [250ml]	1	0.045	0.14	0.75	0.1
Milk replacement	Tea	48	3.23	0.013	Cups [250ml]	1	0.045	0.58	0.75	0.4
Cheese	Cottage Cheese	48	0.48	0.012	tbs [40g]	1	0.4	4.79	0.10	0.5
Dairy dessert	Ice cream	48	0.12	0.001	Bowls [100g]	1	1	1.21	0.10	0.1
Dairy dessert	Other	48	0.10	0.001	Bowls [100g]	1	1	0.99	0.10	0.1
Dairy dessert	Yogurt	48	0.19	0.001	Portion [150g]	1	1.5	1.27	0.10	0.1
Chocolate	White Chocolate	48	0.03	0.001	piece [25g]	1	0.25	0.27	0.20	0.1
Sweets	Sweets	48	0.52	0.010	packet [50g]	1	0.5	5.17	0.20	1.0
Icings, fillings etc.	Icing	48	0.09	0.003	Portion [30g]	1	0.3	0.86	0.20	0.2
Premade dressings	Salad	48	1.27	0.013	Bowls [100g]	1	0.3	3.82	0.50	1.9
							0	19.97		4.7

Table A.6: Consumer data for female and male aged 15-18 years.

Product of interest	Reference	B.W.	Amount	Eqvl. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 15-18		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	63	5.66	0.023	Cups [250ml]	1	0.045	1.02	0.20	0.2
Milk replacement	Herbal Tea	63	2.67	0.011	Cups [250ml]	1	0.045	0.48	0.75	0.4
Milk replacement	Tea	63	4.46	0.018	Cups [250ml]	1	0.045	0.80	0.75	0.6
Cheese	Cottage Cheese	63	0.24	0.006	tbs [40g]	1	0.4	2.36	0.10	0.2
Dairy dessert	Ice cream	63	0.06	0.001	Bowls [100g]	1	1	0.59	0.10	0.1
Dairy dessert	Other	63	0.06	0.001	Bowls [100g]	1	1	0.58	0.10	0.1
Dairy dessert	Yogurt	63	0.12	0.001	Portion [150g]	1	1.5	0.81	0.10	0.1
Chocolate	White Chocolate	63	0.02	0.001	piece [25g]	1	0.25	0.17	0.20	0.0
Sweets	Sweets	63	0.16	0.003	packet [50g]	1	0.5	1.63	0.20	0.3
Icings, fillings etc.	Icing	63	0.07	0.002	Portion [30g]	1.	0.3	0.73	0.20	0.1
Premade dressings	Salad	63	1.34	0.013	Bowls [100g]	1	0.3	4.02	0.50	2.0
								13.20		4.1
	M 15-18									
Milk replacement	Coffee	71	4.15	0.017	Cups [250ml]	1	0.045	0.75	0.20	0.1
Milk replacement	Herbal Tea	71	1.15	0.005	Cups [250ml]	1	0.045	0.21	0.75	0.2
Milk replacement	Tea	71	3.55	0.014	Cups [250ml]	1	0.045	0.64	0.75	0.5
Cheese	Cottage Cheese	71	0.39	0.010	tbs [40g]	1	0.4	3.91	0.10	0.4
Dairy dessert	Ice cream	71	0.06	0.001	Bowls [100g]	1	1	0.62	0.10	0.1
Dairy dessert	Other	71	0.07	0.001	Bowls [100g]	1	1	0.72	0.10	0.1
Dairy dessert	Yogurt	71	0.13	0.001	Portion [150g]	1	1.5	0.86	0.10	0.1
Chocolate	White Chocolate	71	0.02	0.001	piece [25g]	1	0.25	0.21	0.20	0.0
Sweets	Sweets	71	0.30	0.006	packet [50g]	1	0.5	2.99	0.20	0.6
Icings, fillings etc.	Icing	71	0.09	0.003	Portion [30g]	1	0.3	0.91	0.20	0.2
Premade dressings	Salad	71	1.24	0.012	Bowls [100g]	1	0.3	3.72	0.50	1.9
							0	15.53		4.1

Table A.7: Consumer data for female and male aged 19-24 years.

Product of interest	Reference	B.W	Amount	Eqv. Portion	Portion	TiO_2	TiO_2	Consumed	New	Consumed
	F 19-24	[kg]	[g/day/kg_{bw}]	[n/day/kg_{bw}]		[%]	[g]	[mg/kg_{bw}]	[%]	[mg/kg_{bw}]
Milk replacement	Coffee	66	8.6	0.0345	Cups [250ml]	1	0.045	1.55	0.20	0.3
Milk replacement	Herbal Tea	66	1.3	0.0052	Cups [250ml]	1	0.045	0.23	0.75	0.2
Milk replacement	Tea	66	4.5	0.0181	Cups [250ml]	1	0.045	0.82	0.75	0.6
Cheese	Cottage Cheese	66	0.3	0.0081	tbs [40g]	1	0.4	3.25	0.10	0.3
Dairy dessert	Ice cream	66	0.1	0.0007	Bowls [100g]	1	1	0.74	0.10	0.1
Dairy dessert	Other	66	0.1	0.0005	Bowls [100g]	1	1	0.52	0.10	0.1
Dairy dessert	Yogurt	66	0.2	0.0011	Portion [150g]	1	1.5	1.72	0.10	0.2
Chocolate	White Chocolate	66	0.0	0.0005	piece [25g]	1	0.25	0.13	0.20	0.0
Sweets	Sweets	66	0.1	0.0026	packet [50g]	1	0.5	1.32	0.20	0.3
Icings, fillings etc.	Icing	66	0.1	0.0020	Portion [30g]	1	0.3	0.59	0.20	0.1
Premade dressings	Salad	66	1.3	0.0127	Bowls [100g]	1	0.3	3.80	0.50	1.9
								14.67		4.0
	M 19-24									
Milk replacement	Coffee	79	7.64	0.0306	Cups [250ml]	1	0.045	1.37	0.20	0.3
Milk replacement	Herbal Tea	79	1.21	0.0048	Cups [250ml]	1	0.045	0.22	0.75	0.2
Milk replacement	Tea	79	3.77	0.0151	Cups [250ml]	1	0.045	0.68	0.75	0.5
Cheese	Cottage Cheese	79	0.00	0.0000	tbs [40g]	1	0.4	0.00	0.10	0.0
Dairy dessert	Ice cream	79	0.06	0.0006	Bowls [100g]	1	1	0.57	0.10	0.1
Dairy dessert	Other	79	0.04	0.0004	Bowls [100g]	1	1	0.43	0.10	0.0
Dairy dessert	Yogurt	79	0.11	0.0007	Portion [150g]	1	1.5	1.11	0.10	0.1
Chocolate	White Chocolate	79	0.02	0.0006	piece [25g]	1	0.25	0.15	0.20	0.0
Sweets	Sweets	79	0.24	0.0047	packet [50g]	1	0.5	2.35	0.20	0.5
Icings, fillings etc.	Icing	79	0.03	0.0010	Portion [30g]	1	0.3	0.30	0.20	0.1
Premade dressings	Salad	79	0.95	0.0095	Bowls [100g]	1.	0.3	2.84	0.50	1.4
								10.03		3.1

Table A.8: Consumer data for female and male aged 25-34 years.

Product of interest	Reference	B.W	Amount	Eqv. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 25-34		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	67	7.9	0.0316	Cups [250ml]	1	0.045	1.42	0.20	0.3
Milk replacement	Herbal Tea	67	2.1	0.0084	Cups [250ml]	1	0.045	0.38	0.75	0.3
Milk replacement	Tea	67	6.6	0.0264	Cups [250ml]	1	0.045	1.19	0.75	0.9
Cheese	Cottage Cheese	67	0.3	0.0085	tbs [40g]	1	0.4	3.41	0.10	0.3
Dairy dessert	Ice cream	67	0.1	0.0006	Bowls [100g]	1	1	0.61	0.10	0.1
Dairy dessert	Other	67	0.1	0.0005	Bowls [100g]	1	1	0.54	0.10	0.1
Dairy dessert	Yogurt	67	0.1	0.0010	Portion [150g]	1	1.5	1.44	0.10	0.1
Chocolate	White Chocolate	67	0.0	0.0005	piece [25g]	1	0.25	0.12	0.20	0.0
Sweets	Sweets	67	0.1	0.0021	packet [50g]	1	0.5	1.04	0.20	0.2
Icings, fillings etc.	Icing	67	0.1	0.0020	Portion [30g]	1	0.3	0.61	0.20	0.1
Premade dressings	Salad	67	1.3	0.0131	Bowls [100g]	1	0.3	3.92	0.50	2.0
								14.69		4.4
	M 25-34									
Milk replacement	Coffee	83	8.97	0.0359	Cups [250ml]	1	0.045	1.62	0.20	0.3
Milk replacement	Herbal Tea	83	0.99	0.0040	Cups [250ml]	1	0.045	0.18	0.75	0.1
Milk replacement	Tea	83	5.18	0.0207	Cups [250ml]	1	0.045	0.93	0.75	0.7
Cheese	Cottage Cheese	83	0.26	0.0065	tbs [40g]	1	0.4	2.58	0.10	0.3
Dairy dessert	Ice cream	83	0.06	0.0006	Bowls [100g]	1	1	0.62	0.10	0.1
Dairy dessert	Other	83	0.05	0.0005	Bowls [100g]	1	1	0.48	0.10	0.0
Dairy dessert	Yogurt	83	0.15	0.0010	Portion [150g]	1	1.5	1.47	0.10	0.1
Chocolate	White Chocolate	83	0.01	0.0005	piece [25g]	1	0.25	0.12	0.20	0.0
Sweets	Sweets	83	0.08	0.0017	packet [50g]	1	0.5	0.84	0.20	0.2
Icings, fillings etc.	Icing	83	0.11	0.0036	Portion [30g]	1	0.3	1.08	0.20	0.2
Premade dressings	Salad	83	1.14	0.0114	Bowls [100g]	1	0.3	3.43	0.50	1.7
								13.35		3.8

Table A.9: Consumer data for female and male aged 35-49 years.

Product of interest	Reference	B.W.	Amount	Eqv. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 35-49		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	70	10.5	0.0421	Cups [250ml]	1	0.045	1.89	0.20	0.4
Milk replacement	Herbal Tea	70	2.8	0.0114	Cups [250ml]	1	0.045	0.51	0.75	0.4
Milk replacement	Tea	70	8.3	0.0332	Cups [250ml]	1	0.045	1.49	0.75	1.1
Cheese	Cottage Cheese	70	0.4	0.0112	tbs [40g]	1	0.4	4.49	0.10	0.4
Dairy dessert	Ice cream	70	0.1	0.0006	Bowls [100g]	1	1	0.56	0.10	0.1
Dairy dessert	Other	70	0.1	0.0006	Bowls [100g]	1	1	0.55	0.10	0.1
Dairy dessert	Yogurt	70	0.2	0.0011	Portion [150g]	1	1.5	1.64	0.10	0.2
Chocolate	White Chocolate	70	0.0	0.0004	piece [25g]	1	0.25	0.11	0.20	0.0
Sweets	Sweets	70	0.1	0.0022	packet [50g]	1	0.5	1.10	0.20	0.2
Icings, fillings etc.	Icing	70	0.1	0.0026	Portion [30g]	1.	0.3	0.77	0.20	0.2
Premade dressings	Salad	70	1.5	0.0148	Bowls [100g]	1	0.3	4.44	0.50	2.2
								17.55		5.2
	M 35-49									
Milk replacement	Coffee	85	11.53	0.0461	Cups [250ml]	1	0.045	2.08	0.20	0.4
Milk replacement	Herbal Tea	85	1.21	0.0048	Cups [250ml]	1	0.045	0.22	0.75	0.2
Milk replacement	Tea	85	6.47	0.0259	Cups [250ml]	1	0.045	1.16	0.75	0.9
Cheese	Cottage Cheese	85	0.28	0.0070	tbs [40g]	1	0.4	2.80	0.10	0.3
Dairy dessert	Ice cream	85	0.05	0.0005	Bowls [100g]	1	1	0.51	0.10	0.1
Dairy dessert	Other	85	0.04	0.0004	Bowls [100g]	1	1	0.44	0.10	0.0
Dairy dessert	Yogurt	85	0.14	0.0009	Portion [150g]	1	1.5	1.42	0.10	0.1
Chocolate	White Chocolate	85	0.01	0.0004	piece [25g]	1	0.25	0.11	0.20	0.0
Sweets	Sweets	85	0.13	0.0026	packet [50g]	1	0.5	1.29	0.20	0.3
Icings, fillings etc.	Icing	85	0.03	0.0009	Portion [30g]	1	0.3	0.28	0.20	0.1
Premade dressings	Salad	85	1.18	0.0118	Bowls [100g]	1	0.3	3.54	0.50	1.8
								13.85		4.1

Table A.10: Consumer data for female and male aged 50-64 years.

Product of interest	Reference	B.W.	Amount	Eqv. portion	Portion	TiO2	TiO2	Consumed	New	Consumed
	F 50-64		[g/day/kg$_{bw}$]	[n/day/kg$_{bw}$]		[%]	[g]	[mg/kg$_{bw}$]	[%]	[mg/kg$_{bw}$]
Milk replacement	Coffee	71	9.7	0.0390	Cups [250ml]	1	0.045	1.75	0.20	0.4
Milk replacement	Herbal Tea	71	3.2	0.0126	Cups [250ml]	1	0.045	0.57	0.75	0.4
Milk replacement	Tea	71	8.9	0.0357	Cups [250ml]	1	0.045	1.61	0.75	1.2
Cheese	Cottage Cheese	71	0.3	0.0084	tbs [40g]	1	0.4	3.35	0.10	0.3
Dairy dessert	Ice cream	71	0.1	0.0006	Bowls [100g]	1	1	0.58	0.10	0.1
Dairy dessert	Other	71	0.1	0.0005	Bowls [100g]	1	1	0.52	0.10	0.1
Dairy dessert	Yogurt	71	0.2	0.0012	Portion [150g]	1	1.5	1.84	0.10	0.2
Chocolate	White Chocolate	71	0.0	0.0004	piece [25g]	1	0.25	0.09	0.20	0.0
Sweets	Sweets	71	0.2	0.0036	packet [50g]	1	0.5	1.79	0.20	0.4
Icings, fillings etc.	Icing	71	0.0	0.0013	Portion [30g]	1.	0.3	0.40	0.20	0.1
Premade dressings	Salad	71	1.5	0.0148	Bowls [100g]	1	0.3	4.45	0.50	2.2
								16.96		5.3
	M 50-64									
Milk replacement	Coffee	87	9.37	0.0375	Cups [250ml]	1	0.045	1.69	0.20	0.3
Milk replacement	Herbal Tea	87	2.86	0.0114	Cups [250ml]	1	0.045	0.52	0.75	0.4
Milk replacement	Tea	87	7.98	0.0319	Cups [250ml]	1	0.045	1.44	0.75	1.1
Cheese	Cottage Cheese	87	0.29	0.0072	tbs [40g]	1	0.4	2.87	0.10	0.3
Dairy dessert	Ice cream	87	0.06	0.0006	Bowls [100g]	1	1	0.58	0.10	0.1
Dairy dessert	Other	87	0.06	0.0006	Bowls [100g]	1	1	0.58	0.10	0.1
Dairy dessert	Yogurt	87	0.13	0.0009	Portion [150g]	1	1.5	1.33	0.10	0.1
Chocolate	White Chocolate	87	0.01	0.0004	piece [25g]	1	0.25	0.09	0.20	0.0
Sweets	Sweets	87	0.11	0.0021	packet [50g]	1	0.5	1.05	0.20	0.2
Icings, fillings etc.	Icing	87	0.04	0.0014	Portion [30g]	1	0.3	0.41	0.20	0.1
Premade dressings	Salad	87	1.33	0.0133	Bowls [100g]	1	0.3	3.98	0.50	2.0
							0	14.53		4.6

Table A.11: Percent women consuming a product for different age groups.

Age [years]	1.5-2.5 mf	2.5-3.5 mf	3.5-4.5	4-6	7-10	11-14	15-18	19-24	25-34	35-49	50-64
Coffee	6	8	8	6	11	14	32	50	60	75	81
Herbal Tea	0	0	0	1	1	1	2	4	11	15	14
Tea	38	36	41	33	43	49	56	69	76	78	80
Cottage Cheese	2	1	1	1	2	2	3	6	10	5	9
Ice Cream	35	47	52	61	57	46	29	28	26	26	31
Other dairy	25	26	23	22	28	16	11	10	11	10	10
Yogurt	43	42	33	47	46	42	33	30	39	42	44
Chocolate	70	76	77	76	80	76	72	60	58	62	50
Sweets	46	62	67	75	72	64	41	31	24	27	21
Icing	6	11	13	25	25	15	10	11	7	8	5
Salad	57	52	51	52	50	56	66	72	84	82	80

Table A.12: Percent men consuming a product for different age groups.

Age [years]	1.5-2.5 mf	2.5-3.5 mf	3.5-4.5	4-6	7-10	11-14	15-18	19-24	25-34	35-49	50-64
Coffee	18	17	8	6	7	14	39	56	76	74	75
Herbal Tea	0	0	0	0	0	0	1	6	8	5	7
Tea	0	0	35	29	40	48	61	68	73	80	82
Cottage Cheese	8	8	1	1	2	1	0	0	2	3	4
Ice Cream	0	0	43	58	58	50	40	17	23	32	29
Other dairy	36	41	24	23	31	22	15	5	5	10	9
Yogurt	1	1	33	51	44	39	27	28	29	32	37
Chocolate	47	52	74	80	91	85	79	62	61	58	42
Sweets	26	23	67	71	77	67	39	20	21	24	15
Icing	42	33	10	22	28	15	13	12	8	6	4
Salad	11	13	46	59	49	53	51	73	79	75	76

B Matlab model

Appendix B includes the matlab model used for the Montecarlo simulation.

clear all
close all
tic

%Input data
load 'data.mat'

%Model

% Consumption values
$x = [];$
% Consumer percentage
$p = [];$

$r = [(rand(1, 100000) <= p(1, 1));$
$(rand(1, 100000) <= p(2, 1));$
$(rand(1, 100000) <= p(3, 1));$
$(rand(1, 100000) <= p(4, 1));$
$(rand(1, 100000) <= p(5, 1));$
$(rand(1, 100000) <= p(6, 1));$
$(rand(1, 100000) <= p(7, 1));$
$(rand(1, 100000) <= p(8, 1));$
$(rand(1, 100000) <= p(9, 1));$
$(rand(1, 100000) <= p(10, 1));$
$(rand(1, 100000) <= p(11, 1));$
$];$

$xt = diag(x);$

$y = xt * r;$

$z = sum(y);$

$hist(z, 50);$

$[h, stats] = cdfplot(z)$
xlabel('TiO_2 [mg]')
ylabel('Number of Consumers')

toc