applied sciences

MDPI

*Review*

# Sources, Bioavailability, and Safety of Silicon Derived from Foods and Other Sources Added for Nutritional Purposes in Food Supplements and Functional Foods

**Anna Sadowska * and Franciszek Świderski**

Department of Functional and Organic Food, Institute of Human Nutrition Sciences, Warsaw University of Life Sciences, Nowoursynowska Str. 159c, 02-776 Warsaw, Poland; franciszek_swiderski@sggw.edu.pl
* Correspondence: anna_sadowska@sggw.edu.pl

Received: 9 August 2020; Accepted: 4 September 2020; Published: 9 September 2020

**Abstract:** Silicon is a microelement that performs a number of important functions in the human body, being involved in the formation and maintenance of normal osteocartilaginous connective tissue, such as skin, hair, and nails, and having beneficial effects in the prevention of cardiovascular and neurodegenerative diseases. Natural sources of silicon include fruits, vegetables, cereals, and mineral water. European and North American diets are generally low in silicon, which correlates with a diet high in processed foods. Dietary silicon deficiency can be overcome by the consumption of high bioavailability silicon-rich foods and the use of silicon supplements. A good form of supplementation is orthosilicic acid (OSA), usually stabilized by the introduction of a methyl group, choline, or vanillin. OSA is naturally found in diatomaceous earth in the form of amorphous silica and extracts from silicon-rich plants, e.g., horsetail (*Eguiseti herba* L.) and nettles (*Urtica dioica* L.). This article presents the characteristics of the various sources of silicon and their bioavailability and safety of use, with particular reference to the sources used in functional foods and dietary supplements. There is a great need to produce functional foods containing dietary silicon, together with other scarce mineral components.

**Keywords:** dietary silicon; diatomite; silicon supplements

## 1. Introduction

In recent decades, there has been a strong interest in silicon (Si) as a trace element, which plays an important role in physiological and metabolic function in both plants and humans. Silicon is present in all organisms (including plants and humans) and also in soil [1]. Silicon is involved in the metabolism of connective tissue and is important for the biosynthesis of collagen and glycosaminoglycan, which are needed for bone formation [2–4]. Silicon is also required for the function of polyhydroxylase, which is responsible for the formation of collagen, elastane, cartilage, and other connective tissues. Si deficiency causes weak and malformed bones, osteoporosis, Alzheimer's disease, bone decalcification, cardiovascular disease, and atherosclerosis. Silicon is also involved in the maintenance and growth of hair and nails [5–7]. There is approximately 1 g of Si in the human body, which is the third most abundant trace element after iron and zinc [8]. Si is deposited and stored in the connective tissue of the aorta, trachea, tendons, bones, and skin, and stored silicon has been found to decline with age [9–11]. One of the most important silicon compounds is silica (silicon dioxide, $SiO_2$), which is the basic component of many minerals used in the industry. Silicon in the form of orthosilicic acid (OSA) and salts (silicates) have the greatest importance in nutrition and are considered the best sources of silicon. Natural sources of silicon include cereals, fruits, and vegetables. The essentiality and precise functional roles of Si for humans have not been fully established, and a recommended intake for this element has not been set [12–15]. In 2004, the European Food Safety Authority (EFSA) was unable to establish a tolerable upper level (UL) for silicon intake as there was no suitable dose–response data nor data on adverse effects of silicon available [14]. However, given the available research results, a silicon intake level was set at 20–50 mg per day, and a safe upper level was set at 700 mg per day for adults over a lifetime. Such quantity should not cause any undesirable effects [12,16]. The consumption of silicon by people living in Europe and North America is much lower than in societies whose diets are based on vegetables, fruits, and unprocessed cereals, e.g., in India and China, where the consumption is 140–204 mg/day. In these populations, a lower incidence of bone fractures has been observed, suggesting that increasing the intake of silicon above the recommended intake may have a beneficial effect. The primary sources of silicon in the diet are food products of plant origin, water and beverages, and to a lesser extent, animal products. Silicon may also appear in the diet as part of processed products in which the additive (excipient) E551, an anticaking and antifoaming agent that is high in silicon, is used [17,18]. In recent years, dietary supplements and functional foods containing silicon compounds have become available on the market in various forms, with varying bioavailability, and have become increasingly popular, claiming numerous health-promoting effects. However, these are frequently poorly documented and sometimes not confirmed by the EFSA. Therefore, the purpose of this publication is to present up-to-date data on the various sources of silicon, their bioavailability and safety, and to characterize the silicon-containing chemical compounds used in the production of dietary supplements and functional foods. This data will help to guide consumer selection of silicon-enriched products and may also help in the selection of appropriate compounds by functional food manufacturers. This paper may also provide guidance to nutritionists and physicians who are involved in the prevention and complementary therapy of widely occurring osteoarticular diseases and people interested in the promotion of healthy skin, hair, and nails.

### 1.1. Sources and Bioavailability of Silicon from Foods

Silicon compounds of greatest nutritional importance include silicic acids and their salts (silicates). Among them, OSA is considered to be the best form due to its high absorption rate and bioavailability [19]. OSA is characterized by a high absorption rate equal to about 43%; however, at a concentration of more than 0.1%, polysilicic acids are formed, which show a much lower bioavailability [12,20]. It is believed that for the majority of the population, the main source of Si is food. This is because Si is naturally present in the diet in the form of silicic acid, silicon dioxide (silica), and silicates, and higher levels are found in food of plant origin than in food of animal origin [21]. Silicic acid is naturally present in food, mainly in water and beverages, particularly beer [22,23]. Plants naturally absorb silicic acid, where it is polymerized as solid silica bodies, silica cells, or phytoliths [24]. In these phytoliths, hydrogen and cellulose bond within the cell walls as silicon dioxide, $SiO_{2n}H_2O$ [25]. Tables 1 and 2 show the content and average intake of silicon from various common sources. Drinking water is considered to be an important source of silicon; however, silicon content depends on its geological origin. The consumption of silicon in water can account for up to 20% of the total consumption [26]. In vivo and in vitro studies of the bioavailability of silicon in water have shown that at least 50% of the silicon present in mineral water is absorbed; therefore, it is a good source of this compound [27]. Beer is also important in the dietary pool of silicon sources due to the presence of barley and hops, which are abundant in silicon. In addition, the processes involved in beer production cause the decomposition of silicon compounds into OSA, an easily absorbable form [26]. As a result, up to 55% of the silicon in beer can be absorbed. However, it should be noted that increasing the consumption of alcoholic beer should not be considered a sensible way of increasing the dietary intake of Si; however, nonalcoholic beer might be considered [28]. Cereals, such as barley, oats, wheat, and rice bran, as well as rice and some herbaceous plants, account for 30% of dietary silicon intake, followed by fruits (especially apple and banana), vegetables (particularly carrot, potato, green beans), beverages, nuts, and some dried fruits [26,29,30]. Collectively, these foods provide more than 75% of dietary silicon intake [31]. Grain products such as bread, cake, rice, pasta, breakfast cereals, and flour are also high dietary sources of silicon. Other sources of silicon include fish and animal meat, eggs, milk, juices, drinking water, alcoholic beverages, and many pharmaceutical supplements [32]. However, food processing can cause significant losses of silicon (up to 50%), so unprocessed whole-grain products contain much higher quantities. It is generally accepted that after consuming silicon-rich foods, the level of this element in blood serum increases significantly [33]. Silicon is most effectively absorbed from cereal products and, to a lesser extent, green beans and dried fruits. On the other hand, Si that is present in bananas in significant quantities (5 mg/portion) is only 5% absorbed. Bananas are thought to contain a highly polymerized form of silicon that is not effectively hydrolyzed and absorbed in the gut [34]. Sripanyakor et al. (2004) [28] and Bellia et al. (1994) [35] studied the absorption of silicon from beer, where 80% of the overall silicon content is in the form of OSA. The absorption of silicon from beer was 55%, and 42–72% of Si was excreted in urine. Reffitt et al. (1999) [36] studied Si intake as OSA from water and reported that OSA excretion in urine was between 21% and 74%.

**Table 1.** Silicon content in food products [27,34].

| **Product Group** | **Silicon Content (mg/100 g or mg/100 mL)** |
|---|---|
| **Cereal and Related Products (Highest Concentration of Silicon in Grain Husk, Especially in Oat Bran)** | |
| Breakfast cereals | 7.79 |
| Cornflakes | 2.42 |
| Biscuits | 1.56 |
| Other wheat cakes | 2.78 |
| White rice | 1.24 |
| Brown rice | 2.07 |
| Pasta | 0.60 |
| Bran | 10.17 |
| Wheat bread | 1.69 |
| Whole-grain bread | 2.25 |
| Brown bread | 4.47 |
| Croissant | 1.67 |
| Fruit | |
| Banana | 5.44 |
| Orange | 0.32 |
| Strawberries | 0.12 |
| Mango | 2.00 |
| Raisins | 8.25 |
| Dried dates | 16.61 |
| Nuts and seeds | 0.78 |
| Vegetables | |
| Carrots (peeled, raw) | 0.29 |
| Potatoes (peeled, cooked) | 0.34 |
| Iceberg lettuce | 0.41 |
| Chickpeas | 0.76 |
| Green beans (cooked) | 2.44 |
| Drinks | |
| Beer | 2.19 |
| Wine | 1.24 |
| Black tea | 0.86 |
| Mineral water | 0.69 |

**Table 2.** Meals, portion sizes, and silicon content [34].

| Product Group | Portion | Silicon Content (mg/100 g or mg/100 mL) |
|---|---|---|
| Cornflakes | 100 g | 2.42 |
| High-bran cereal | 100 g | 10.17 |
| Lady's fingers | 2.78 g | 2.78 |
| White rice | 200 g | 2.48 |
| Brown rice | 200 g | 4.14 |
| Pasta | 250 g | 1.50 |
| Wheat bread | 200 g | 3.38 |
| Whole-grain bread | 200 g | 8.94 |
| Brown bread | 200 g | 4.50 |
| Croissant | 100 g | 1.67 |
| Fruit | | |
| Peeled banana | 250 g | 13.60 |
| Peeled orange | 210 g | 0.67 |
| Strawberries | 200 g | 0.24 |
| Vegetables | | |
| Carrots (peeled, raw) | 200 g | 4.58 |
| Potatoes (young, cooked) | 200 g | 0.58 |
| Iceberg lettuce | 250 g | 1.03 |
| Green beans (cooked) | 250 g | 6.10 |
| Mineral water | 0.5 L | 3.44 |

The richest source of silicon in the plant world is horsetail (25% of its dry weight is silica), which has been used for thousands of years as a herbal remedy, and current scientific evidence supports most of its potential benefits [37]. Horsetail has multiple potential health benefits, including improved bone, skin, hair, and nail health. It is most commonly consumed in the form of herbal teas, capsules, and tinctures. Despite being a widely recognized and used herb and supplement, horsetail is not approved by the Food and Drug Administration (FDA) as with most herbal supplements [38].

### 1.2. Sources of Silicon of Mineral Origin Used in Functional Foods and Food Supplements

Although silicon is present in nutritionally significant amounts in many foods, the increasing domination of processed foods in the diet makes usual dietary intake insufficient. This may be remedied by supplementation. Silicon can be added to functional foods and supplements in various forms, with varying degrees of bioavailability. Products commercially recommended as concentrated sources of silicon, produced industrially with the best-known health-promoting effects, use OSA solutions and its stabilized forms. During the manufacture of functional foods and dietary supplements, the polymerization of silicic acid to polysilicic acid is often prevented to aid bioavailability. To prevent polymerization, several methods of stabilization have been developed, for example, introducing a methyl group to obtain monomethylsilanetriol (MMST) or "organic silicon" [39,40], stabilization with choline to form choline-stabilized orthosilicic acid (ch-OSA) [39,41], or combining with vanillin to form orthosilicic acid vanillin complex (OSA-VC) [41,42]. In addition, amorphous diatomaceous earth is of great interest both as a source of organic silicon and as an additive with multidirectional health-promoting effects [1]. Silicon dioxide and silicates are of lesser importance as a source of silicon due to their low bioavailability. However, they are widely used in food as the additive E551. Extracts of silicon compounds from silicon-rich plants, such as from horsetail (*Eguisetum arvense* L.) and nettles (*Urtica dioica* L.), have been used for a long time in cosmetics and natural medicine, and nowadays, they are produced in various forms (concentrated liquid, powders, capsules, and tablets) using various carriers and as part of combination products with other added vitamins and minerals. They are marketed mainly as dietary supplements to strengthen the hair, skin, and nails [39].

### 1.2.1. Silicic Acids and Their Stabilized Forms

Silicic acids are considered the best sources of silicon due to their high bioavailability (approx. 40%) and natural occurrence in food [43,44]. Orthosilicic acid (OSA) is the natural form of Si formed by the hydration of silicon dioxide ($SiO_2$). OSA plays an important role in providing elemental silicon to human and animal cells. In the industry, OSA is formed by the thermal fusion of $SiO_2$ with NaOH. The reaction results in soluble silicates and then silicic acids. OSA is the main water-soluble silicon compound. Supersaturation causes OSA to polymerize into less water-soluble forms. The degree of polymerization of orthosilicic acid is positively correlated with its intestinal absorption [20,23,27,45]. OSA is a neutral-charged monomeric silica, which is easily absorbed in the digestive tract, while larger types of colloids and polymers must be broken down to water-soluble monomer in the lumen of the digestive tract before being absorbed [23,27,45]. Beverages such as water and beer predominantly contain soluble monomeric species that are readily absorbed [33]. At higher silicon concentrations (above 2–3 mM, in most supplements), less absorbable and larger colloids or polymers are present, with the exception of methylsilanetriol (MMST), in which one hydroxyl group of OSA is replaced by one methyl group, raising the solubility limit and maintaining the silicon in well-absorbed forms [40]. Ch-OSA (choline stabilized orthosilicic acid) contains polymerized silicon in a highly concentrated solution; however, extensive aggregation and polymerization of Si particles are prevented by the presence of choline in the solution [43]. The solubility of silicon depends on the pH of the environment. It dissolves more easily in an almost neutral environment (which is characteristic of the intestinal pH) compared with acidic conditions (i.e., in the stomach) [39]. The availability of silicon compounds depends on their specificity and solubility [46]. The available literature does not provide much comparative data on silicon absorption from different sources. Sripanyakorn et al. (2009) [43] examined the absorption (based on urinary silicon excretion) from eight sources containing high concentrations of silicon: OSA (control), alcohol-free beer, green beans, bananas, ch-OSA, supplemental colloidal silica (CS), MMST, and magnesium trisilicate (MTBP). The highest absorption was obtained for MMST and beer (64%), followed by green beans (44%), OSA (43%), ch-OSA (17%), bananas and MTBP (4%), and CS (1%). It was noticed that with increasing polymerization, the silicates were less well absorbed [43]. In other studies, assessment of individual substances or in relation to another (usually OSA) was mainly made. The data obtained will be discussed further when discussing the EFSA opinion on the evaluation of these substances. The silicon sources currently approved for use in the production of dietary supplements are listed in Directive 2002/46/EC. These are ch-OSA, $SiO_2$, OSA gel, and MMST (Table 3) [47]. In addition, the EFSA provided opinions on OSA-VC and MMST as novel food ingredients used in food supplements and also an opinion on the bioavailability and safety of ch-OSA added for nutritional purposes as a source of silicon in food supplements (Table 3). In 2017, the EFSA provided a re-evaluated opinion on the safety of $SiO_2$ (E551), used as a food additive (Table 3) [48].

**Table 3.** Opinion on the safety and bioavailability of silicon of mineral origin approved for use in the production of food supplements and as a food additive [39–41,47,48].

| Documents | Sources of Silicon Compounds | Opinion |
|---|---|---|
| Directive 2002/46/EC of the European Parliament and Council relating to Food Supplements.<br>EFSA opinion on the safety and bioavailability of silicone from ch-OSA added for nutritional purposes in food supplements. | ch-OSA, $SiO_2$, OSA gel, and MMST | currently approved for use in the production of food supplements |
| EFSA opinion on OSA-VC as a novel food ingredient used in food supplements | OSA-VC | approved as novel food ingredients used in food supplements |
| EFSA opinion on MMST as a novel food ingredient used in supplements. | MMST | approved as novel food ingredients used in food supplements |
| EFSA, re-evaluation of silicon dioxide (silica, E551) as a food additive. | silica only in synthetic amorphous silica (E551), without colloidal silica | approved as a food additive, including food supplement |

EFSA = the European Food Safety Authority; ch-OSA = choline-stabilized orthosilicic acid; OSA = orthosilicic acid; OSA-VC = orthosilicic acid vanillin complex and MMST = monomethylsilanetriol.

#### 1.2.2. EFSA Opinion on OSA-VC as a Novel Food Ingredient Used in Food Supplements

OSA-VC is produced by completely dissolving vanillin powder in 40% ethanol solution at 40 °C. The solution is then diluted with water and acidified to a pH of 1.5–2.5 using phosphoric acid. The potassium orthosilicate is then added to the solution. The final pH is adjusted to the value according to the proposed specifications [41]. The EFSA assessed the bioavailability of Si from OSA-VC, taking into account available studies, among others, the Marcowycz et al. (2015) [49] research. This study demonstrated a significant increase of silicon concentration in plasma after oral ingestion of OSA-VC by human volunteers, with maximum concentrations obtained after 3 hours from intake. Urinary excretion after 6 hours was about 21% of the taken dose of Si, which was significantly different from the control group. The EFSA concluded that OSA is bioavailable after intake of OSA-VC, and its bioavailability is similar to values given in the literature for other recognized OSA sources (measured as Si). The EFSA concluded that there would be no safety concerns with the use of OSA as a novel food ingredient in dietary supplements for the adult population in a dose that provides an additional Si intake of about 10–18 mg per day [41].

#### 1.2.3. EFSA Opinion on MMST as a Novel Food Ingredient Used in Supplements

According to Directive 2002/46/EC [43,47], MMST is one of the sources of Si that can be used in dietary supplement production in the form of an aqueous solution at a concentration of 4.1 mM. A daily recommended intake of MMST in the amount of 60–90 mL corresponds to a Si content of approximately 7–10 mg. The receiving of MMST has two stages. In the first stage, potassium methylsiliconate is synthesized under highly alkaline conditions. After that, the obtained material is diluted, and the pH is adjusted to the value of 6.6 [40]. The solubility of MMST in water is up to 21 mM (about 588 mg silicon/L) at 21 °C and does not irreversibly polymerize after 2 months. Studies by Popplewell et al. (1998) [50] and Pruksa et al. (2014) [51], conducted in humans with the use of silicon, showed that most of the silicon is excreted. With regard to MMST, it is known that when this compound is ingested, most Si is rapidly excreted in the urine, but a small proportion of Si is stored for a longer period, and then bioconversion of MMST to orthosilicic acid occurs. These and other studies [52–56] would support the metabolism of MMST to OSA. In Jugdaohsingh et al.'s study (2013) [57], total silicon was measured twice in fasting serum and urine samples at baseline and after 4 weeks of supplementation with MMST. The results showed an increase in total silicon. Urinary MMST accounted for about 10.3% of the increase in the total silicon excreted, consistent with the conversion of MMST to OSA in the body. In addition, this study concluded that there were no significant changes in any of the biochemical measurements taken or changes in well-being after 4 weeks of the maximum daily dosage of MMST (i.e., consumption of 10.5 mg Si per day). Sripanyakorn et al. (2009) [43] conducted a study comparing the absorption of silicon from eight sources with high silicon levels: bananas, alcohol-free beer, green beans, MMST, ch-OSA, supplemental CS, and magnesium trisilicate (MTBT) compared with OSA (positive control). Urinary excretion of silicon was the highest for MMST (64%), followed by OSA (43%), ch-OSA (17%), MTBP (4%), and CS (1%). Taking into account the available information in the literature studies and the results cited above, the EFSA concluded that MMST is unlikely to raise any safety concerns as a novel food ingredient for the proposed single-use and that OSA is released from MMST and is likely to have comparable or higher bioavailability from MMST than from other sources [40].

#### 1.2.4. EFSA Opinion on the Safety and Bioavailability of Silicon from ch-OSA That Is Added for Nutritional Purposes in Food Supplements

Ch-OSA consists of orthosilicic acid (OSA) and choline chloride (CAS) and occurs in both liquid and pellet form with the silicon content (mainly as OSA) of 1.7–2.39% (*w*/*v*) and 0.6–1.0% (*w*/*v*), respectively [35,39]. Vanden Berghe (2000) [58] showed that incubated solutions of ch-OSA dissolved in water contain Si primarily in the form of OSA. During the manufacturing process of ch-OSA liquid, choline chloride is subjected to a chemical reaction with dry hydrochloric acid and silicon tetrachloride, and, after that, water is added. Sodium hydroxide is then added to the ch-OSA solution for neutralization, followed by the concentration of the entire solution by distillation under vacuum. At the end, glycerol is added. Ch-OSA pellets are formed by adding microcrystalline cellulose to the concentrated solution. After adding water, the mass is extruded, and the resulting pellets are dried. The absorption of Si from ch-OSA was investigated in human studies using a crossover method. Each fasting subject received ch-OSA, herbal silica, CS, or mineral water as a placebo. For ch-OSA, a significant increase in serum silicon concentration was observed, which was achieved earlier compared to the placebo. After ch-OSA supplementation, urinary silicon excretion was also significantly higher than the placebo [59]. The ch-OSA absorption was faster and higher compared to herbal silica and CS. No side effects related to ch-OSA were observed.

Vanden Berghe (2001) [60] studied the bioequivalence of choline-stabilized orthosilicic acid in liquid and pellet forms. The increase in serum Si content was comparable for both forms of ch-OSA. In another comparative crossover study [46], the bioavailability of Si from ch-OSA, herbal extract (Equisetum arvense), and silicon-rich diet was compared. There was no increase in urinary Si levels after eating a silicon-rich diet. Urinary silicon excretion increased significantly after supplementation with the dry herbal extract. Consuming a ch-OSA solution resulted in an increase in serum silicon content and excretion of urinary silicon, reflecting the high bioavailability of ch-OSA. The study also demonstrated that the bioavailability of Si is strongly dependent on the chemical form and matrix of consumed silicon sources. A further study on the bioavailability of ch-OSA was performed, in which women with damaged facial skin were given 10 mg of silicon daily in the form of ch-OSA pellets or placebo for 20 weeks. The serum silicon concentration increased after 20 weeks in the ch-OSA group but was unchanged in the placebo group [61]. Spector (2003) [62] conducted a study in women with osteopenia who consumed ch-OSA supplements. The authors concluded that taking quite high doses of choline-stabilized orthosilicic acid orally for 5 weeks and for long periods (even up to 12 months) did not significantly change the biochemical blood parameters. In these two clinical studies, no serious adverse events related to ch-OSA were observed. The subchronic toxicity studies on choline-stabilized orthosilicic acid were conducted in both humans (supplementation studies) and animals (rodents and mammals). No adverse effects of ch-OSA administration have been observed in these studies. The proposed dose of choline-stabilized orthosilicic acid in dietary supplements is between 5 and 10 mg per day. The EFSA concluded that the bioavailable of silicon in ch-OSA used in supplements, at these levels, is of no safety concern as long as the choline ceiling is not exceeded [39].

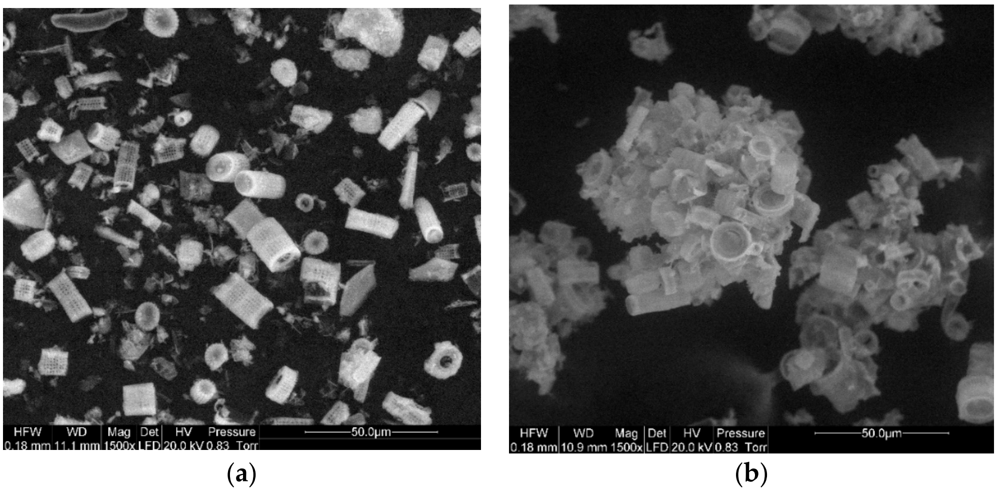
#### 1.2.5. Re-Evaluation of Silicon Dioxide (Silica, E551) as a Food Additive

In 1974, the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) committee established an “unlimited acceptable intake” for silicon dioxide and some silicates. Based on the available research results, the committee concluded that the oral administration of silicon dioxide and silicates appears to be biologically inert and that there is no evidence of toxic accumulation of silicates in the body due to their easy excretion in the urine. Safe upper levels (SUL) for silica has been set at 25 mg/kg/day for lifelong consumption [16]. This amount was determined based on a study of mice and rats using amorphous silica [63]. The EFSA assessed that using up to 1500 mg of silicon dioxide per day for nutritional purposes in dietary supplements is safe. Therefore, silicon dioxide can be used in the production of dietary supplements. In 2004, the EFSA concluded that silicon in the form of silica, silicates, and dimethylpolysiloxane can be added to food and dietary supplements as an anticaking and antifoam agent. The Si availability from the abovementioned sources varies but is quite low. The EFSA stated that there is no adequate dose–response data, and, therefore, an UL cannot be established. In 2017, the EFSA re-assessed the safety of $SiO_2$ (E551), used as a food additive. The forms of synthetic amorphous silica (SAS) used as E551 include fumed silica and hydrated silica (precipitated and hydrous silica and silica gel). According to Regulation (EU) No. 231/2012 [60,64], silicon dioxide (E551) is defined as an amorphous substance that is produced synthetically by vapor-phase hydrolysis to give a fumed silica or by a wet process to give precipitated or hydrated silica or silica gel. According to Fruijtier-Poelloth (2012) [65], there are three main types of silicon dioxide: (1) crystalline silica, (2) amorphous silica (naturally occurring or as a byproduct), and (3) synthetic amorphous silica (SAS), including silica gel, precipitated silica, pyrogenic (fumed) silica, and colloidal silica. Among these three types of silicon dioxide, only synthetic SAS is authorized as a food additive (E551) but without "colloidal silica". Authorized uses and maximum permitted levels of silicon dioxide (E551) have been defined in Regulation (EC) No. 1333/2008 [66]. $SiO_2$ and silicates are characterized by a maximum level of additive, oscillating from 2000 to 30,000 mg/kg, and, in some food categories, can also be used at "quantum satis". Silicon dioxide (E551) can also be authorized together with silicates (E552, E553a, and E553b). Silicon dioxide (E551) and calcium silicate (E552) can also be used as food additives in nutrients, with the exception of those that are used for infants and young children (mentioned in Regulation (EC) No. 1333/2008) in dry powdered formulas containing all nutrients, which have the maximum level of 50,000 mg/kg [67]. Silicon dioxide (E551) is authorized in potassium chloride preparations (used in salt substitutes) up to the maximum level of 50,000 mg/kg and is also used as a food additive in foods for infants and young children in a dry powdered form up to the maximum level of 10,000 mg/kg. Silicon dioxide (E551) is on the labels of nearly 5000 food products: half of them are dietary supplements, others are, for example, meal replacements, creamers, instant noodles, malt, and drinks. The percentage of foods in each subcategory labeled as containing silicon dioxide (E551) ranged from less than 0.1% to 24.5% in the "vitamins and dietary supplements" subcategory [48]. There are few toxicological studies on silicon, including those in which nano silicon dioxide was examined. In the few available animal studies, the content of silicon in the liver, kidneys, and spleen was slightly increased after the oral administration of SAS. Studies using rats showed no accumulation of Si after multiple oral intakes of silica. There are few signs of SAS being absorbed after human consumption; however, silicon dioxide has been found in liver and spleen tissue. Overall, there is no evidence of the acute oral toxicity of SAS. No adverse clinical effects have been observed with doses up to 20,000 mg of SAS per kg. In subchronic toxicity studies, no side effects were observed in rats fed with a diet containing SAS at a level of 4000 mg/kg/day for 13 weeks. There were no effects on food consumption, food efficiency, and weight gain. Hematology, urinalysis, clinical chemistry, and macroscopical and microscopical pathology also did not reveal any abnormal findings [67,68]. Similarly, no adverse effects were detected in female rats fed a diet containing silica gel at doses up to 8980 mg/kg/day for 6 months [69]. In a further subchronic toxicity study in rats fed a diet with up to 3500 mg/kg/day of fumed silica for 90 days, the low toxicity of the applied doses was confirmed [70]. Other studies used lower doses that were not sufficient to assess repeat-dose toxicity [71,72]. The in-vitro and in-vivo studies of SAS used as a food additive do not indicate its genotoxic potential. Synthetic amorphous silica, characterized by various physicochemical properties, is allowed for use based on the EU specifications for silicon dioxide (E551). SAS does not appear to induce genotoxicity when used as a food additive, and there is no evidence of carcinogenic effects in long-term studies, with the highest tested doses at 7500 and 2500 mg silica gel/kg/day, respectively, in mice and rats.

However, due to the lack of long-term studies on silicon dioxide containing nanoparticles, the EFSA was unable to transfer the results from the available silicon dioxide studies due to the lack of data for the nanoparticle sizes that may be present in E551. The EFSA considered that the current specifications for E551 are not sufficient to adequately characterize silicon dioxide that possibly contains nanoparticles. These specifications should include the characteristics of nanoscale particles. ADI for silicon dioxide has not been confirmed due to insufficient data. Silicon dioxide seems to be poorly absorbed; however, Si, considered to be in the form of silicon dioxide, was found in some tissues. Overall, there are no signs of adverse effects, and SAS does not raise any concern for genotoxicity or carcinogenicity when used as a food additive [48].

### 1.3. Diatomaceous Earth as a Supplement

A good form of organic silicon supplementation is diatomaceous earth or amorphous diatomaceous earth, e.g., Fossil Shell Flour® (FSF), obtained from diatoms. Dating back to the Jurassic, Cretaceous, and even Devonian periods, diatoms are a group of single-celled algae that form diatomic sediments. These deposits occur in the form of slate or loose diatomaceous earth and, in its pure, unprocessed form, comprises, on average, of 85–90% of silicon dioxide in amorphous form. The basic element of the silica structure is the silicon-oxygen tetrahedron $(SiO_4)^{4-}$, with the molecular formula $SiO_2$. The amorphous form, as opposed to the crystalline one, results from the lack of an ordered spatial arrangement of these tetraeders. Figure 1a,b shows the microstructure of diatoms from amorphous diatomaceous earth containing $SiO_2$ in amorphous form and saltwater diatomaceous earth, with a high content of $SiO_2$ in crystalline form. In amorphous diatomaceous earth (a), single forms of diatoms are clearly visible, and in saltwater sources (b), they are joined into large clusters with a poorly preserved diatomaceous shape. Its unique porosity (between 10 and 200 µm), chemical inertness, small particle size, large surface area, good permeability, and low heat conduction properties make it very popular among naturally occurring materials [73].



(**a**) (**b**)

**Figure 1.** Images of the microstructure of diatoms from diatomaceous earth containing silica (**a**) in amorphous form and (**b**) from diatomaceous earth, with a high content of crystalline silicon. (Own research, images were taken with a scanning electron microscope Quanta 200 XL, FEI, Oregon, USA).

Diatomaceous earth of saltwater origin, due to its high content of crystalline silica (up to 60%) and arsenic admixtures, serves only as a technical product and should not be approved for use in the food industry as it may pose a real health risk [74]. Amorphous diatomaceous earth originating from freshwater consists mainly of amorphous silica, and the content of the crystalline form is negligible (0.5–2%). As a result, this product is considered completely safe and suitable for ingestion. There are several types of food-grade diatomaceous earth on the market, differing in chemical composition and origin, of which Fossil Shell Flour® is the most studied. The product comes from four Melosira Preicelanica freshwater reservoirs and is certified by the FDA as the purest food quality (Food Grade Codex). During manufacturing, this product is subjected to a purification process that uses hot air and water vapor and has a high amorphous silica content (89–95%), with the proportion of crystalline silica not exceeding 1% (average 0.3%). The content of other minerals is negligible. Amorphous silica, the main constituent of amorphous diatomaceous earth, including Fossil Shell Flour®, is an approved food additive of the E551 silicate group (silicon dioxide, amorphous). Amorphous diatomaceous earth is insoluble in water. However, it is presumed that when silica is hydrated in the body, it is converted to OSA, which is, in turn, soluble in water, increasing its bioavailability and facilitating absorption in the gastrointestinal tract [30]. In the available literature, there is no data on the bioavailability of diatomic organic silicon in amorphous and crystalline forms. There is not enough evidence that the structure of silica affects bioavailability. It is assumed that both forms are similar to SAS E551. However, the crystalline form of silica is not strictly approved by the EFSA as a food additive, which may be due to its safety.

It should be assumed that its safety is similar to or higher than silicon from synthetic silica (SAS). Diatomic earth is of great interest not only as a supplement of organic silicon but also as an additive with a significant, multidirectional health-promoting effect, confirmed by studies on its use in animal nutrition. The physicochemical properties of FSF allow it to play an important role in animal production. It may have a good application as a food supplement for animals, thus contributing to the productivity of livestock [75,76]. Previous authors [77,78] have found that the diatom surfaces have many porous nanostructured silica cell walls or frustules, increasing its surface and enabling it to be used as a carrier for other substances; for example, FSF has been successfully used to control gastrointestinal parasites in ruminants and poultry. FSF has numerous other uses, including increasing the efficiency of livestock, as a mycotoxin binder, and for pest control of stored grain. On the basis of the studies of Adebiyi et al. (2009) [79], it was found that a 6% addition of FSF® to rooster feed for 16 weeks significantly improved mean weight gain, feed conversion efficiency, and bone development. Similarly, in another study, FSF® improved the intake of feed, body weight gain, as well as the productive efficiency index ratio of feed conversion in cockerels exposed to aflatoxin B1. FSF® has also been found to improve serum albumin and the action of serum lactate dehydrogenase [74]. Modirsane et al., in 2008 [80], conducted a study of piglets supplemented with silicon dioxide, which is the major component of FSF®, and found improvement of mean daily weight gain during the early period, as compared to a control group. Therefore, this supplement can contribute to significant financial gain for farmers. In other studies, it was found that chickens supplemented with FSF® had bigger combs and thicker legs relative to their body size, compared to chickens not supplemented. This highlights the potential use of FSF® for growth performance and maturity in chickens [74].

## 2. Conclusions

There is a strong case for increasing the consumption of silicon, both through a higher proportion of products that are its source and through an increase in silicon-containing foods with a targeted health-promoting effect, i.e., functional foods and dietary supplements. Silicon should be included as an important component in mineral premixtures and supplements. The different forms of silicon (liquid, solid) allow for a wide application in various products. Of the discussed silicon sources, the most important is organic silicon (MMST), as it has such high bioavailability. However, due to its form, it can only be used in liquid products; ch-OSA, which has a lower bioavailability but a wider application, can be used in both liquid and solid products. Due to the high silicon content and promising multidirectional health-promoting effects of amorphous organic silica from diatoms, commercially available diatomaceous earth products may become an important component of functional foods and dietary supplements for humans and also for use in livestock to maximize productivity.

**Author Contributions:** A.S. and F.Ś. conceived and designed the content of the manuscript; A.S. analyzed the literature data; A.S. and F.Ś. wrote the paper. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** All authors declare that they have no conflict of interest.

**Human and animal rights statement:** This article does not contain any studies with human or animal subjects.

## References

1. Farooq, M.A.; Dietz, K.J. Siliconas versatile playerin plantand human biology: Overlooked and poorly understood. *Front. Plant Sci.* **2015**, *6*, 994. [CrossRef]

2. Hott, M.; Pollak, C.D.; Modrowski, D.; Marie, P.J. Short-term effects of organic silicon on trabecular bone in mature ovariectomised rats. *Calcif. Tissue Int.* **1993**, *53*, 174–179. [CrossRef]
3. Prescha, A.; Zabłocka-Słowinska, K.; Grajeta, H. Dietary silicon and its impact on plasma silicon levels in the Polish population. *Nutrients* **2019**, *11*, 980. [CrossRef] [PubMed]
4. Ratcliffe, S.; Jugdaohsingh, R.; Vivancos, J.; Marron, A.; Deshmukh, R.; Ma, J.F.; Mitani-Ueno, N.; Robertson, J.; Wills, J.; Boekschoten, M.V.; et al. Identification of a mammalian silicon transporter. *Am. J. Physiol. Cell Physiol.* **2017**, *312*, 550–561. [CrossRef] [PubMed]
5. Nielsen, F.H. Update on the possible nutritional importance of silicon. *J. Trace Elem. Med. Biol.* **2014**, *28*, 379–382. [CrossRef] [PubMed]
6. Reffitt, D.M.; Ogston, N.; Jugdaosingh, R.; Cheung, H.F.; Evans, B.A.; Thompson, R.P.H.; Powell, G.N. Orthosilicic acid stimulates collagen type 1 synthesis and osteoblastic differentiation in human osteoblast-like cells in vitro. *Bone* **2003**, *32*, 127–135. [CrossRef]
7. Macdonald, H.M.; Hardcastlea, A.C.; Jugdaohsingh, R.; Fraserc, W.D.; Reida, D.M.; Powell, J.J. Dietary silicon interacts with oestrogen to influence bone health: Evidence from the Aberdeen Prospective Osteoporosis Screening Study. *Bone* **2012**, *50*, 681–687. [CrossRef] [PubMed]
8. Arora, M.; Arora, E. The promise of silicon: Bone regeneration and increased bone density. *J. Arthrosc. Jt. Surg.* **2017**, *4*, 103–105. [CrossRef]
9. Adler, A.J.; Etzion, Z.; Berlyne, G.M. Uptake, distribution, and excretion of 31 silicon in normal rats. *Am. J. Physiol.* **1986**, *251*, 670–673.
10. Carlisle, E.M. Silicon. In *Handbook of Nutritionally Essential Mineral Elements*; O'Dell, B.L., Sunde, R.A., Eds.; Marcel Dekker Inc.: New York, NY, USA, 1997; pp. 603–618.
11. Carlisle, E.M. Silicon. In *Biochemistry of the Essential Ultratrace Elements*; Freiden, E., Ed.; Plenum Press: New York, NY, USA, 1984; Volume 3, pp. 257–291.
12. EFSA (European Food Safety Authority). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of silicon. *EFSA J.* **2004**, *60*, 1–11.
13. SCF (Scientific Committee for Food). Nutrient and energy intakes for the European Community. In *Reports of the Scientific Committee for Food (Thirty-First Series)*; European Commission: Luxembourg, 1993.
14. IOM (Institute of Medicine). Food and Nutrition Board. In *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*; National Academy Press: Washington, DC, USA, 2000.
15. Jurkić, L.M.; Cepanec, I.; Kraljević Pavelić, S.; Pavelić, K. Biological and therapeutic effects of ortho-silicic acid and some ortho-silicic acid-releasing compounds: New perspectives for therapy. *Nutr. Met.* **2013**, *10*. [CrossRef] [PubMed]
16. EVM (Expert Group on Vitamins and Minerals). Silicon. In *Safe Upper Levels for Vitamins and Minerals*; Food Standards Agency: London, UK, 2003.
17. Chen, F.; Cole, P.; Wen, L.; Mi, Z.; Trapido, E.J. Estimates of trace element intakes in Chinese farmers. *J. Nutr.* **1994**, *124*, 196–201. [CrossRef] [PubMed]
18. Anasuya, A.; Bapurao, S.; Paranjape, P.K. Fluoride and silicon intake in normal and endemic fluorotic areas. *J. Trace Elem. Med. Biol.* **1996**, *10*, 149–155. [CrossRef]
19. Węglarzy, K.; Bereza, M. Biologiczne znaczenie krzemu oraz jego interakcje z innymi pierwiastkami. *Wiad. Zootech.* **2007**, *4*, 67–70.
20. Meija, J.; Coplen, T.B.; Berglund, M.; Brand, W.A.; De Bièvre, P.; Gröning, M.; Holden, N.E.; Irrgeher, J.; Loss, R.D.; Walczyk, T.; et al. Atomic weights of the elements 2013 (IUPAC Technical Report). *Pure Appl. Chem.* **2016**, *88*, 265–291. [CrossRef]
21. EFSA (European Food Safety Authority). Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. Calcium silicate and silicon dioxide/silicic acid gel added for nutritional purposes to food supplements. *EFSA J.* **2009**, *1132*, 1–24.
22. Carlisle, E.M. Silicon as an essential trace element in animal nutrition. *Ciba Found. Symp.* **1986**, *121*, 123–139. [CrossRef]
23. Royal Society of Chemistry. Silicon–Element Information, Properties and Uses. Available online: https://www.rsc.org/periodic-table/element/14/silicon (accessed on 3 August 2020).

24. Ma, J.F.; Yamaji, N. Silicon uptake and accumulation in highe rplants. *Trends Plant Sci.* **2006**, *11*, 392–397. [CrossRef]
25. Tripathi, D.; Dwivedi, M.M.; Tripathi, D.K.; Chauhan, D.K. Silicon bioavailability in exocarp of Cucumis sativus Linn. *3 Biotech* **2017**, *7*, 386. [CrossRef]
26. Jugdaohsingh, R. Silicon and bone health. *J. Nutr. Health Aging* **2007**, *11*, 99–110.
27. Prescha, A.; Zabłocka, K.; Naduk, J.; Grajeta, H. Naturalne wody mineralne i źródlane oraz soki owocowe jako źródło krzemu w pożywieniu. *Rocz. PZH* **2011**, *62*, 289–293.
28. Sripanyakorn, S.; Jugdaohsingh, R.; Elliott, H.; Walker, C.; Metha, P.; Shoukru, S.; Thompson, R.P.H.; Powel, J.J. The silicon content of beer and its bioavailability in healthy volunteers. *Br. J. Nutr.* **2004**, *91*, 403–409. [CrossRef] [PubMed]
29. Pennington, J.A. Silicon in foods and diets. *Food Addit. Contam.* **1991**, *8*, 97–118. [CrossRef] [PubMed]
30. Montesano, F.F.; D'Imperio, M.; Parente, A.; Cardinali, A.; Renna, M.; Serio, F. Green bean biofortification for Si through soilless cultivation: Plant response and Si bioaccessibility in pods. *Sci. Rep.* **2016**, *6*, 31662. [CrossRef] [PubMed]
31. McNaughton, S.A.; Bolton-Smith, C.; Mishra, G.D.; Jugdaosingh, R.; Powell, J.J. Dietary silicon intake in post-menopausal women. *Br. J. Nutr.* **2005**, *94*, 813–817. [CrossRef]
32. Powell, J.J.; McNaughton, S.A.; Jugdaosingh, R.; Anderson, S.H.C.; Dear, J.; Khot, F.; Mowatt, L.; Gleason, K.L.; Sykes, M.; Thompson, R.P.H.; et al. A provisional database for the silicon content of foods in the United Kingdom. *Br. J. Nutr.* **2005**, *94*, 804–812. [CrossRef]
33. Spripanyakorn, S.; Jugdaohsingh, R.; Richard, P.; Thompson, H.; Powell, J.J. Dietary silicon and bone health. *Nutr. Bull.* **2005**, *30*, 222–230. [CrossRef]
34. Jugdaohsingh, R.; Anderson, S.H.C.; Tucker, K.L.; Elliott, H.; Kiel, D.P.; Thompson, R.P.H.; Powell, J.J. Dietary silicon intake and absorption. *Am. J. Clin. Nutr.* **2002**, *75*, 887–893. [CrossRef]
35. Bellia, J.P.; Birchall, J.D.; Roberts, N.B. Beer: A dietary source of silicon. *Lancet* **1994**, *343*, 235. [CrossRef]
36. Reffitt, D.M.; Jugdaohsingh, R.; Thompson, R.P.H.; Powell, J.J. Silicic acid: Its gastrointestinal uptake and urinary excretion in man and effects on aluminum excretion. *J. Inorg. Biochem.* **1999**, *76*, 141–147. [CrossRef]
37. Vasanthi, N.; Lilly, M.S.; Raj, S.A. Silicon in Day Today Life. *World Appl. Sci. J.* **2012**, *17*, 1425–1440.
38. © Cosmetic Ingredient Review. Safety Assessment of Equisetum Arvense-Derived Ingredients as Used in Cosmetics. Available online: https://www.cir-safety.org/sites/default/files/equise062020slr.pdf (accessed on 2 August 2020).
39. EFSA (European Food Safety Authority). Choline-stabilised orthosilicic acid added for nutritional purposes to food supplements. *EFSA J.* **2009**, *7*. [CrossRef]
40. EFSA (European Food Safety Authority). Safety of organic silicon (monomethylsilanetriol, MMST) as a novel food ingredient for use as a source of silicon in food supplements and bioavailability of orthosilicic acid from the source. *EFSA J.* **2016**, *14*, 4436. [CrossRef]
41. EFSA (European Food Safety Authority). Safety of orthosilicic acid-vanillin complex (OSA-VC) as a novel food ingredient to be used in food supplements as a source of silicon and bioavailability of silicon from the source. *EFSA J.* **2018**, *16*, e05086. [CrossRef]
42. Rahman, A. *Studies in Natural Products Chemistry*; Elsevier: Amsterdam, The Netherlands, 1988; ISBN 978-0-444-42970-4.
43. Sripanyakorn, S.; Jugdaohsingh, R.; Dissayabutr, W.; Anderson, S.H.; Thompson, R.P.; Powell, J.J. The comparative absorption of silicon from different foods and food supplements. *Br. J. Nutr.* **2009**, *102*, 825–834. [CrossRef]
44. Choi, M.K.; Kim, M.H. Dietary silicon intake of Korean young adult males and its relation to their bone status. *Biol. Trace Elem. Res.* **2017**, *176*, 89–104. [CrossRef]
45. Greenwood, N.N.; Earnshaw, A. Silicon. In *Chemistry of the Elements*, 2nd ed.; Butterworth-Heinemann: Oxford, UK, 1997; pp. 328–367. [CrossRef]
46. Van Dyck, K.; Van Cauwenbergh, R.; Robberecht, H.; Deelstra, H. Bioavailability of silicon from food and food supplements. *Fresenius J. Anal. Chem.* **1999**, *363*, 541–544. [CrossRef]
47. *Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the Approximation of the Laws of the Member States Relating to Food Supplements. Official Journal of the European Communities*; 12.7.2002, L 183/51-57; European Parliament: Brussels, Belgium, 2002.
48. EFSA (European Food Safety Authority). Re-evaluation of silicon dioxide (E 551) as a food additive. *EFSA J.* **2018**, *16*, 50088. [CrossRef]

49. Marcowycz, A.; Housez, B.; Maudet, C.; Cazaubiel, M.; Rinaldi, G.; Croizet, K. Digestive absorption of silicon, supplemented as orthosilicic acid-vanillin complex. *Mol. Nutr. Food Res.* **2015**, *59*, 1584–1589. [CrossRef]
50. Popplewell, J.F.; King, S.J.; Day, J.P.; Ackrill, P.; Fifield, R.G.; Cresswell, M.L.; di Tada, M.L.; Liu, K. Kinetics of uptake and elimination of silicic acid by a human subject: A novel application of 32Si and accelerator mass spectrometry. *J. Inorg. Biochem.* **1998**, *69*, 177–180. [CrossRef]
51. Pruksa, S.; Siripinyanond, A.; Powell, J.J.; Jugdaohsingh, R. A silicon balance study in human volunteers; a study to establish the variance in silicon excretion versus intake. *Nutr. Metab.* **2014**, *11*, 4. [CrossRef] [PubMed]
52. Tacke, R.; Linoh, H. Bioorganosilicon chemistry. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons Ltd.: Hoboken, NJ, USA, 1989; pp. 1143–1206.
53. Sabourin, C.L.; Carpenter, J.C.; Leib, T.K.; Spivack, J.L. Biodegradation of dimethylsilianediol in soils. *Appl. Environ. Microb.* **1996**, *62*, 4352–4360. [CrossRef] [PubMed]
54. Hirner, A.V.; Flassbeck, D.; Gruemping, R. Organosilicon compounds in the environment. In *Organometallic Compounds in the Environment*; Craig, P.J., Ed.; John Wiley & Sons Ltd.: Hoboken, NJ, USA, 2003; pp. 305–351.
55. Graiver, D.; Farminer, K.W.; Narayan, R. A review of the fate and effects of silicones in the environment. *J. Polym. Environ.* **2003**, *11*, 129–136. [CrossRef]
56. Varaprath, S.; McMahon, J.M.; Plotzke, K.P. Metabolites of hexamethyldisiloxane and decamethylcyclopentasil oxane in Fischer 344 rat urine—A comparison of a linear and cyclic siloxane. *J. Polym. Environ.* **2003**, *31*, 206–214. [CrossRef] [PubMed]
57. Jugdaohsingh, R.; Hui, M.; Anderson, S.H.C.; Kinrade, S.D.; Powell, J.J. The silicon supplement 'Monomethylsilanetriol' is safe and increases the body pool of silicon in healthy Pre-menopausal women. *Nutr. Metab. Lond.* **2013**, *10*, 37. [CrossRef] [PubMed]
58. Vanden Berghe, D.A. *Expert Report: Analysis of Choline-stabilised Orthosilicic Acid with the Colorimetric Silicic Molybdate Method*; Laboratory of Microbiology, Parasitology, Hygiene, University of Antwerp: Antwerp, Belgium, 2000.
59. Calomme, R.; Cos, P.; D'Haese, P.C.; Vingerhoets, R.; Lamberts, L.V.; De Broe, M.E.; Van Hoorebeke, C.; Vanden Berghe, D.A. Absorption of silicon in healthy subjects. In *Metal Ions in Biology and Medicine*; Collery, P., Brätter, P., de Brätter, V.N., Khassanova, L., Etienne, J.C., Eds.; John Libbey Eurotext: Paris, France, 1998; Volume 5, pp. 228–232.
60. Vanden Berghe, D.A. *Expert Report: Bioequivalence of Two Galenic Forms of Cholinestabilised Orthosilisic Acid: Ch-OSA Liquid Versus ch-OSA Pellets*; Laboratory of Microbiology, Parasitology, Hygiene, University of Antwerp: Antwerp, Belgium, 2001.
61. Barel, A. *Expert report: Anti-ageing Effect of Choline-stabilised (ortho)silicic Acid in Healthy Volunteers with Photo-damaged Skin*; Free University of Brussels (VUB), Laboratory of General and Biological Chemistry: Brussels, Belgium, 2004.
62. Spector, T. *Expert Report: Assessment of Stabilised Orthosilicic Acid on Bone Turnover Inpatients with Osteopenia: Adverse Events*; St. Thomas' Hospital, Twin Research & Genetic Epidemiology Unit: London, UK, 2003.
63. Takizawa, Y.; Hirasawa, F.; Noritomi, E.; Aida, M.; Tsunoda, H.; Uesugi, S. Oral ingestion of syloid to mice and rats and its chronic toxicity and carcinogenicity. *Acta Med. Biol.* **1988**, *36*, 27–56.
64. *Commission Regulation (EU) No 231/2012 of 9 March 2012 Laying Down Specifications for Food Additives Listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA Relevance*; European Environment Agency: Copenhagen, Denmark, 2012.
65. Fruijtier-Pölloth, C. The toxicological mode of action and the safety of synthetic amorphous silica—A nanostructured material. Review Article. *Toxicology* **2012**, *294*, 61–79. [CrossRef]
66. *Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on Food Additives (Text with EEA Relevance). Official Journal of the European Union, 31.12.2008, L 354/16-33*; European Parliament: Copenhagen, Denmark, 2008.
67. Degussa, A.G. *Study Summary. Subchronic (13 Week) Oral Toxicity Study with SIPERNAT 22 in Rats*; Degussa, A.G., Ed.; US-IT-No. 81-0016; European Food Safety Authority: Parma, Italy, 1981; unpublished report.
68. Til, H.P.; Hollanders, V.M.H.; Beems, R.B. *Sub-Chronic (13-Week) Oral Toxicity Study with Sipernat 22 in Rats*; Degussa, H., Ed.; Civo Institutes TNO: Frankfurt, Germany, 1981; unpublished report, V 81.268/201741.
69. Grace, GmbH. *6-Monate-Toxizit Rats Untersuchung Mit Syloid an Ratten Bei Oraler Applikation (Futteruntersuchung)—Part:1*; Report Inbifo A0386 1103; European Food Safety Authority: Parma, Italy, 1975; Confidential Report—unpublished.

70. Cabot, CAB-O-SIL. *90-day Dietary Feeding*; Final Report dated 11th July 1958; European Food Safety Authority: Parma, Italy, 1958.
71. Leuschner, F. *Uber die chronische Toxizit€at von AEROSIL*; Bericht vom 2; European Food Safety Authority: Parma, Italy, 1963; unpublished report.
72. Newberne, P.M.; Wilson, R.B. Renal damage associated with silicon compounds in dogs. *Proc. Natl. Acad. Sci. USA* **1970**, *65*, 872–875. [CrossRef]
73. Ikusika, O.O.; Mpendulo, C.T.; Zindove, T.J.; Okoh, A.I. Fossil shell flour in livestock production: A Review. *Animals* **2019**, *9*, 70. [CrossRef]
74. Maciejewska, A. Krzemionka krystaliczna: Kwarc i krystobalit—Frakcja respirabilna. Dokumentacja proponowanych dopuszczalnych wielkości narażenia zawodowego. *Podst. Metod. Ocen. Środowiska Pr.* **2014**, *4*, 67–128. [CrossRef]
75. Bennett, D.C.; Yee, A.; Rhee, Y.J.; Cheng, K.M. Effect of diatomaceous earth on parasite load, egg production, and egg quality of free-range organic laying hens. *Poult. Sci.* **2011**, *90*, 1416–1426. [CrossRef] [PubMed]
76. Koster, H. Diatomite in Animal Feeds. 2013. Available online: https://agrisilica.co.za/pdf/eng/Diatoms%20in%20Animal%20Feeds%20HH%20Koster.pdf (accessed on 20 June 2018).
77. Wang, Z.Y.; Jang, Y.X.; Zhang, L.P. Structural Investigation of some important Chinese diatomites. *Glass Phys. Chem.* **2009**, *35*, 673–679. [CrossRef]
78. Aw, M.S.; Bariana, M.; Yu, Y.; Addai-Mensah, J.; Losic, D. Surface-functionalized diatom microcapsules for drug delivery of water-insoluble drugs. *J. Biomater. Appl.* **2013**, *28*, 163–174. [CrossRef] [PubMed]
79. Adebiyi, O.A.; Sokunbi, O.A.; Ewuola, E.O. Performance Evaluation and Bone Characteristics of Growing Cockerel Fed Diets Containing Different Levels of Diatomaceous Earth. *Middle East J. Sci. Res.* **2009**, *4*, 36–39.
80. Modirsanei, M.; Mansoori, B.; Khosravi, A.R.; Kiaei, M.M.; Khazraeinia, P.; Farkhoy, M.; Masoumi, Z. Effect of diatomaceous earth on the performance and blood variables of broiler chicks during experimental aflatoxicosis. *Sci. Food Agric.* **2008**, *632*, 626–632. [CrossRef]