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COMMENTARY

Rationale for Further Medical and Health Research on High-Potency Sweeteners

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Abstract

High-potency or artificial sweeteners have historically been considered inert compounds without physiological consequences other than taste sensations. However, recent data suggest that some of these sweeteners have biological effects that may impact human health. Furthermore, there are significant gaps in our current knowledge of the pharmacokinetics of these sweeteners, their potential for "sweetener–drug interactions" and their impact on appetite and body weight regulation. Nine research needs are described that address some of the major unknown issues associated with ingestion of high-potency sweeteners.

Key words: artificial sweeteners, pharmacokinetics, high-potency sweeteners

Introduction

The global market for high-potency sweeteners during 2010 was reported to be $1.146 billion (Leatherhead Food Research 2011). Leatherhead Food Research estimated the relative global market share for the major high-potency sweetener types as follows—aspartame (27.9%), sucralose (27.9%), cyclamate (15.7%), saccharin (13.1%), stevia (8.7%), acesulfame-K (5.2%), and neotame (1.4%). High-potency sweeteners are used in thousands of different food and beverage products (Yang 2010) to reduce caloric content without sacrificing the pleasures of sweetness. Over the last 3 decades, the proportion of the population in the United States that uses products containing these sweeteners has more than doubled (Mattes and Popkin 2009; Calorie Control Council 2010).

Although experimental safety data on high-potency sweeteners have been reviewed by scientific and regulatory agencies prior to introduction into the food supply (Nabors 2012), significant gaps remain in our understanding of the biological effects of these sweeteners. These gaps in knowledge depend in part on the specific sweetener type but include 1) their pharmacokinetics (i.e., absorption, distribution, metabolism, and excretion), 2) their membrane transport, 3) their potential for "sweetener–drug interactions", and 4) their impact on appetite and body weight regulation. These knowledge gaps exist in part because high-potency sweeteners have historically been considered inert compounds devoid of physiological consequences other than taste sensations. An overview of the recent scientific literature, however, suggests that some of these sweeteners may have biological consequences that can affect human health. Additional laboratory and clinical research are necessary to address these concerns. Nine examples of research needs are described below.

Research Need 1: determine the role of transporters in the absorption and disposition of high-potency sweeteners

Intestinal transporters, both efflux and absorptive, are expressed in the gastrointestinal tract and are known to play a major role in the absorption of orally administered compounds, including food chemicals and drugs (Custodio et al. 2008; Shugarts and Benet 2009). However, the precise role of intestinal transporters in the absorption and disposition of high-potency sweeteners is not well understood due to the limited number of experimental studies published in the open scientific literature. An examination of excretion data for the

artificial sweeteners sucralose, neotame, Na saccharin, and acesulfame-K strongly suggests that intestinal transporters are likely involved in their absorption. These 4 sweeteners (sucralose, neotame, Na saccharin, and acesulfame-K) are amphipathic molecules, that is, they possess both hydrophilic and hydrophobic domains as shown in Table 1. Amphipathic molecules are not necessarily expected to require specific transport mechanisms to penetrate or diffuse through phospholipid membrane bilayers of enterocytes (Szakács et al. 2008). This is because phospholipids, like these sweeteners, are also amphipathic molecules—they have a hydrophilic region (polar head groups) and a hydrophobic region (tails in the interior). Recall the well-known chemical mantra, ''like dissolves like.'' Thus, given the fact that sucralose and neotame are amphipathic (and very soluble in alcohol), we would expect these 2 sweeteners to be readily absorbed and ultimately excreted predominantly in the urine. However, this is not the case. Approximately 70–80% of ingested sucralose and neotame is reportedly excreted in the feces with the remainder excreted in the urine (US FDA 1998; WHO 2004). This suggests that efflux transporters must shunt these 2 sweeteners back into the intestinal lumen. Our recent study (Abou-Donia et al. 2008) indicates that the transporter P-glycoprotein (P-gp) plays a role in the efflux of sucralose back to the intestinal lumen. (P-gp also transports many therapeutic drugs, including the cardiac medication digoxin and the immunosuppressant drug cyclosporine that is used in organ transplantation.) Conversely, Na saccharin and acesulfame-K, while amphipathic, are charged and poorly soluble in alcohol (Merck Index 2006); thus, if no transporters were involved, we might expect substantial excretion of these 2 sweeteners in the feces. Yet, approximately 95% of ingested Na saccharin and acesulfame-K is reportedly excreted in the urine and only 5% in the feces (Renwick 1985; Volz et al. 1991); this suggests that uptake transporters may play a role in their absorption.

Although these excretion data in conjunction with the physicochemical properties are strongly suggestive of a role for intestinal transporters in the absorption of high-potency sweeteners, experimental studies in vitro and in vivo are needed to identify the specific intestinal transporters involved. Testing strategies similar to those used in drug research (International Transporter Consortium et al. 2010) can be used to determine which transporters control the entry and exit of each sweetener type through intestinal cellular barriers. In addition, given the prominent role of transporters in the pharmacokinetics of drugs as well as food-drug interactions (Custodio et al. 2008; Shugarts and Benet 2009), it is important to determine if concomitant use of high-potency sweeteners with medications affects the bioavailability of drugs through sweetener–drug interactions that involve transporters. The medications utilized in studies of potential sweetener–drug interactions should be selected from lists of preferred and acceptable drugs recommended by the US FDA (2011).

Research Need 2: identify the metabolites of high-potency sweeteners, the metabolic enzymes involved, and the toxicity of the metabolites

An illustration of this research need is our current lack of knowledge of the metabolites of the organochlorine sweetener sucralose. According to information submitted in the food additive petition to the FDA, sucralose is reportedly excreted unchanged (i.e., not metabolized) in the feces (US FDA 1998). However, thin layer chromatograms (TLCs) of methanolic fecal extracts following oral administration of ^{14}C-sucralose to rats (Sims et al. 2000) and humans (Roberts et al. 2000) do not support this conclusion. Figure 1 is a TLC radiochromagraphic trace from a rat fecal sample (Sims et al. 2000) that shows multiple closely eluting peaks of approximately equal height. The multiple peaks in the trace indicate that at least 2 radioactive chemicals were extracted from the fecal material and that sucralose is indeed metabolized in the gastrointestinal tract. Neither the chemical identity nor the toxicity of these sucralose metabolites has been determined in mammals; however, metabolites of sucralose produced by microorganisms include 1,6-dichloro-l,6-dideoxy-D-fructose (1,6-DCF) and an unsaturated aldehyde of sucralose (Labare and Alexander 1994). 1,6-DCF, a sucralose hydrolysis product, is weakly mutagenic in both the Ames test and the L5178Y TK+/– mutation assay (US FDA 1998). Aldehydes are reactive compounds that can have a broad range of biological effects (O'Brien et al. 2005).

Table 1 Amphipathic properties and solubility characteristics of 4 high-potency sweeteners[a]

Sweetener	Hydrophobic domain	Hydrophilic domain	Solubility in alcohol
Acesulfame-K (charged)	Methyl group and ring of the molecule	Carbonyl group, sulfonyl group	s
Na saccharin (charged)	Benzene ring	Carbonyl group, sulfonyl group	s
Neotame	Phenyl group and 3,3-dimethylbutyl group	Carboxylic group, carbonyl group	**S**
Sucralose	–C–CH_2Cl groups	Hydroxyl groups	**S**

S, readily/freely soluble; s, sparingly/slightly soluble.
[a]For information on substituents in a compound along with their hydrophobic and hydrophilic properties that can affect the permeation through the gastrointestinal membrane, see Smith (2010) and Smith et al. (2012).

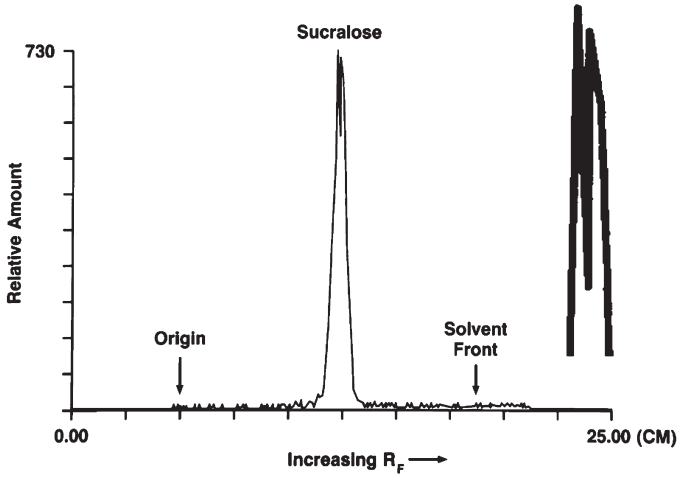

Figure 1 Thin-layer radiochromatographic profile of a methanolic fecal extract from a male rat that received an oral dose of ^{14}C-sucralose (100 mg/kg) (from Figure 2b, Sims et al. 2000). An enlargement of the multiple peaks in the profile is given to the right.

Further experimental studies in both rats and humans are needed for identification and safety assessment of sucralose metabolites in order to determine if the metabolic profile differs between these species. If differences in metabolic profiles are found to occur, historical rat toxicity tests of sucralose (Goldsmith 2000; Mann et al. 2000) may not generalize fully to humans. For example, metabolites may be generated in humans that are absent in rodents or alternatively metabolites may be formed at disproportionately higher levels in humans than in rodents. Metabolites can differ in ADME (absorption, distribution, metabolism, and excretion) and toxicity characteristics from the parent compound sucralose, for example, metabolites may be accumulated or retained differently in humans and rodents leading to different observed toxicity. In the case of drug metabolites, the US FDA (2008) has implemented guidance for safety assessment of metabolites with exposures that are >10% of the administered dose or systemic exposure.

Although the precise identity of the sucralose metabolites has not yet been determined, our data (Abou-Donia et al. 2008) suggest that the enzymes responsible for the metabolism of sucralose in the intestines belong to the cytochrome P450 (CYP) superfamily. We found that oral administration of sucralose at doses approved by the US FDA (1998) and European Union (2004) increased the intestinal expression of 2 members of the CYP family, that is, CYP3A4 and CYP2D1 (rat analog of CYP2D6) that are involved in the metabolism of over 70% of marketed drugs. The increased expression of CYP isozymes in the intestinal tract likely results from "autoinduction" by which sucralose enhances it own metabolism. Autoinduction is a well-recognized biological phenomenon by which xenobiotics induce proteins involved in their own detoxification (Schuetz et al. 1996). The induction of cytochrome P450 (CYP) by sucralose reemphasizes the concern that this organochlorine sweetener (and perhaps some other high-potency sweeteners) may affect the bioavailability of coadministered drugs through sweetener–drug interactions involving metabolic enzymes.

Research Need 3: determine if high-potency sweeteners alter the secretion of drugs in the kidney leading to altered drug clearance

This issue was initially raised (but not answered) over 30 years ago when it was shown that saccharin was excreted in the kidney both by filtration at the glomerulus and by secretion from the peritubular capillaries to renal tubular lumen (Cranmer 1980). The secretory mechanism was found to be saturable, and saccharin was shown to compete with *para*-aminohippurate (PAH) when simultaneously administered; PAH is an organic acid used in blood flow measurements in the kidney. This competition at the same transporter (subsequently identified as an organic anion transporter or OAT) resulted in a reduction in the rate at which both saccharin and PAH were removed by the kidney from the blood and conveyed to the urine. Competitive inhibition at the OAT transporter can have serious toxic effects if it reduces drug elimination. An example is the interaction at OATs between nonsteroidal anti-inflammatory drugs and methotrexate that can result in severe methotrexate toxicity (Uwai et al. 2000). When saccharin coexists in the plasma with drugs that are substrates of OATs (e.g., anti-HIV therapeutics, antitumor drugs, antibiotics, antihypertensives, and anti-inflammatories), it can potentially compete for transport and modulate a drug's pharmacokinetics. It is not yet known if or under what conditions this is clinically relevant in the case of saccharin. OATs have also been implicated in the excretion of steviol (Srimaroeng et al. 2005), the metabolite of steviol glycosides (stevioside and rebaudioside), but the clinical significance is not known. Interestingly, steviol is sold commercially as an OAT inhibitor (Sigma-Aldrich 2012).

Research Need 4: determine the effect of high-potency sweeteners alone and in combination on transporters and hormones involved in nutrient absorption and body weight regulation

In the last several years, studies in rodents have found that sucralose, acesulfame-K, and saccharin, increased the expression of the Na^+–glucose cotransporter called SGLT1 and the diffusive apical GLUT2 pathway via interaction with nonlingual sweet taste receptors located in the gastrointestinal tract (Margolskee et al. 2007; Mace et al. 2007). Interaction of these same 3 high-potency sweeteners with sweet taste receptors expressed in pancreatic β-cells have been reported to induce insulin secretion (Nakagawa et al. 2009). Corkey (2012) also reported that 2 of the 3 sweeteners (sucralose and saccharin) stimulated insulin secretion in dissociated rat islets. Sucralose has also been shown to initiate

glucagon-like peptide-1 (GLP-1) release from human gastrointestinal L cells in vitro (Jang et al. 2007). GLP-1 is an incretin hormone that is involved in physiological processes related to energy homeostasis. Clinical research in humans is necessary to determine if these findings are relevant for persons who consume high-potency sweeteners alone or particularly in combination as typically found in the food supply. One recent study (Brown et al. 2009) showed that GLP-1 was elevated in humans who drank a caffeine-free diet soda sweetened with a combination of sucralose and acesulfame-K 10 min prior to a glucose load. Clinical studies that utilize mixtures of sweetener types are important because many foods and beverages contain multiple high-potency sweeteners (or high-potency sweeteners with nutritive sweeteners) to improve their taste profile and to take advantage of their synergistic interactions with the taste receptor (Schiffman et al. 1995, 2000, 2003; Wolf et al. 2010). Studies should also include recently developed sweet taste enhancers that are selective for specific sweetener types (Servant et al. 2010, 2011; Zhang et al. 2010) to determine if these new enhancers have a clinically relevant effect on transporters and hormones involved in nutrient absorption.

It is not yet known if the interaction of high-potency sweeteners with nonlingual taste receptors in the intestines and pancreas (Mace et al. 2007; Margolskee et al. 2007; Nakagawa et al. 2009) plays a role in the 176% increase in the prevalence of diagnosed diabetes over the last 30 years in the United States (CDC 2011). MacKenzie et al. (2006) reported that adults with diabetes who had one or more diet soft drinks per day had significantly higher levels of glycosylated hemoglobin (Hba1c), a marker of the average plasma glucose concentration over prolonged periods of time, than adults with diabetes who drank no diet soda. However, the MacKenzie et al. finding does not prove a "cause and effect" because the data are cross-sectional. In another study, Grotz et al. (2003) reported that sucralose (667 mg/day) did not increase Hba1c over a period of 3 months in diabetic patients (Grotz et al. 2003). The 667 mg/day dosage is ~2× the ADI in a 70 kg adult and ~1.5× the ADI for obese individuals. In the Grotz et al. study, patients with diabetes were instructed to self-administer capsules of sucralose twice daily over a 3-month period; however, patients were not supervised daily to ensure compliance with the sucralose dosage regimen. Daily supervision of patients with diabetes is prudent to ensure compliance because the World Health Organization (WHO 2003) has reported that diabetes noncompliance is very prevalent in the United States. In addition, the sites of capsule dissolution and release of sucralose in the gastrointestinal tract (e.g., duodenum, ileum, jejunum, colon) in vivo were not described. The site of release of sucralose in the gastrointestinal tract would affect the outcome of the study. Further studies with daily clinical oversight of test article administration are advisable to determine unambiguously if high-potency sweeteners alone or in combination have a clinically significant effect on glucose control in persons with diabetes.

Research Need 5: determine the effect of acute and chronic use of high-potency sweeteners on brain activation, neuroplasticity, and interactions with taste receptors in the brain

Experiments on this topic have been underway in several laboratories in the last few years. In 2009, Ren et al. reported that sucralose altered the expression of *Tas1r2* in hypothalamic murine cells; *Tas1r2* is the gene for taste receptor type 1 member 2 that is relatively specific for sweet taste perception. Ren et al. exposed mouse hypothalamic cells to glucose media at variable concentrations, while maintaining normal L-amino acid concentrations. They found that the expression levels of the sweet-associated gene *Tas1r2* increased when the hypothalamic cells were exposed to low (compared with high) extracellular glucose concentrations, and this was reversed when sucralose was added to the low glucose medium. The addition of sucralose had no effect on other taste receptor genes *Tas1r1* and *Tas1r3*. The reversal by sucralose of the upregulation of *Tas1r2* from exposure to a low glucose medium indicates that *Tas1r2* expression is independent of glucose metabolism. This finding suggests that activation of sweet taste receptors by sucralose in the nutrient-sensing region of the brain may give inaccurate feedback regarding extracellular glucose.

A research question that arises from this discovery is whether altered expression of the sweet-associated taste receptor gene *Tas1r2* occurs for some high-potency sweetener types but not others. Given our current state of knowledge of the absorption and metabolism of the high-potency sweeteners approved by the US FDA, only 3 could potentially reach the hypothalamus as intact sweet compounds after oral ingestion: sucralose (~20% of a dose), saccharin, and acesulfame-K (see Table 1); access of these 3 sweeteners to the hypothalamus would depend on whether they can pass the blood-brain barrier, which is currently unknown. The sweeteners aspartame, neotame, and steviol glycosides do not reach the hypothalamus as intact sweetener molecules because they are metabolized to nonsweet metabolites in the gastrointestinal tract. Thus, one could test the hypothesis that the effects of high-potency sweeteners in the hypothalamus after oral ingestion are compound specific due to differences in their pharmacokinetics.

Neuroimaging techniques have been employed to study neural representation and neuroplasticity after ingestion of high-potency sweeteners. Rudenga and Small (2011) recently reported that routine use of artificial sweeteners alters responses to sucrose in the amygdala and insula as measured by fMRI scanning. The amygdala and the insula are 2 areas of that brain that are implicated in the integration of oral sensory and homeostatic signals. Rudenga and Small (2011) suggested that these brain changes may be related to degradation or uncoupling of the predictive relationship between sweet taste and its postingestive consequences that have been reported in rat models (Swithers et al. 2010). The

Rudenga and Small finding raises many interesting questions. Does this result apply to all high-potency sweeteners equally or does the degree of neuroplasticity vary by sweetener type? Are any differences related to variability in taste properties among the high-potency sweeteners (e.g., lingering, bitter components, delayed onset in taste), their access to taste receptors in the hypothalamus, or to differences in their pharmacokinetics? What is the length of exposure needed to produce this effect? Can the effect be unlearned and if so what length of time is required?

Research Need 6: determine if high-potency sweeteners have clinically relevant genetic effects

Results from comet assays indicate that treatment of rats with high-potency sweeteners (e.g., sucralose, sodium cyclamate, saccharin and its sodium salt, and stevioside) can induce DNA damage (Sasaki et al. 2002; Nunes et al. 2007). The comet assay is a single-cell gel electrophoresis test that is used in the genotoxicity testing of food additives, industrial chemicals, and pharmaceuticals to detect DNA damage in various organs of experimental animals (Speit et al. 2009; Pfuhler et al. 2011). In the case of stevioside, Nunes et al. (2007) suggested that the DNA aberrations found in the liver, spleen, and brain from comet tests could be due to its metabolite, steviol, rather than to stevioside itself. In the case of the organochlorine sweetener sucralose, the findings from the comet test are consistent with previous genotoxicity studies. Sucralose has been reported to be weakly mutagenic in the mouse lymphoma mutation assay, and as noted above, its hydrolysis product 1,6-DCF was found to be weakly mutagenic in both the Ames test and the L5178Y TK+/– assay (US FDA 1998). Further study of long-term ingestion of high-potency sweeteners is necessary to determine if these findings are clinically relevant in humans.

Studies of the epigenetic regulation of transcription are also needed to determine if high-potency sweeteners alter gene expression without changing the underlying DNA sequence. Epigenetics is the study of heritable changes in gene activity caused by mechanisms such as DNA methylation that can suppress gene expression without changing the nucleotide sequence of the silenced genes. One example of a research need is to determine if the chlorinated sucralose hydrolysis product 1,6-DCF, which is an alkylating agent, can alter patterns of gene expression via epigenetic modification. Organochlorine compounds have been shown to induce persistent epigenetic reprogramming that can be transmitted transgenerationally (Stouder and Paoloni-Giacobino 2010; Zama and Uzumcu 2010). Furthermore, dietary variables have also been reported to induce epigenetic changes (Burdge et al. 2007; Vucetic et al. 2010; McKay and Mathers 2011; Feil and Fraga 2012). Thus, additional research is essential to determine if artificial sweeteners (and/or their metabolites) can alter gene expression (along with body phenotype such as obesity) through mechanisms that are independent of the DNA sequence itself.

Research Need 7: determine the long-term consequences of high-potency sweeteners on gastrointestinal bacteria

High-potency sweeteners including saccharin, acesulfame-K, cyclamate, and sucralose have been shown to affect commensal bacteria (normal symbiotic microflora) as well as pathogenic bacteria (Linke 1977; Linke and Doyle 1985; Pfeffer et al. 1985; Oldacay and Erdem 2000; Abou-Donia et al. 2008). Linke and Doyle (1985) studied the effect of Na saccharin on bacterial growth of Gram-positive and Gram-negative rods as well as cocci from the human oral cavity. They found that Na saccharin significantly inhibited Gram-positive rods and Gram-negative cocci with little or no inhibition of Gram-negative rods. Neither the mechanism by which Na saccharin inhibits bacterial growth nor the reason for the variability of the effect by bacterial type is known. However, Pfeffer et al. (1985) reported that acesulfame-K, cyclamate, and saccharin inhibited anaerobic acid production from glucose by intestinal bacteria.

Recently, we found that daily administration of sucralose (delivered in the commercial product Splenda at sucralose dosages approved for use by global regulatory agencies) over a 12-week period to rats produced highly significant reductions in the numbers of total anaerobes, bifidobacteria, lactobacilli, *Bacteroides*, clostridia, and total aerobic bacteria with no significant treatment effect on enterobacteria (Abou-Donia et al. 2008). The number of total anaerobes remained significantly depressed after the 12-week recovery from treatment. The reduction in bacteria during the 12-week treatment period was accompanied by intermittent incidences of unformed or soft feces. In addition, alterations of the intestinal epithelial border were observed, including lymphocytic infiltrates into epithelium, epithelial scarring, mild depletion of goblet cells, and glandular disorganization. Like the findings for saccharin, neither the mechanism by which sucralose inhibits bacterial growth nor the reason for the variability of the effect by bacterial type is known.

Going forward, human studies must now be performed to determine if there are clinically relevant alterations in gut microflora when high-potency sweeteners are consumed habitually on a daily basis. These studies are vital because disruption in the number and relative balance of intestinal bacterial types can potentially impact numerous biological processes, including carbohydrate fermentation and absorption, formation of short-chain fatty acids that serve as a source of useful energy and nutrients, synthesis of vitamins, absorption of calcium and magnesium, maintenance of the intestinal epithelial barrier function, repression of pathogenic bacterial growth, prevention of allergies and inflammatory bowel disease, metabolism of drugs, and expression of host xenobiotic-metabolizing enzymes (Cummings and

Macfarlane 1991; Guarner and Malagelada 2003; Nicholson et al. 2005; Ouwehand and Vaughan 2006; Meinl et al. 2009; Prakash et al. 2011).

Research Need 8: determine the clinical consequences of eating high-potency sweeteners that have been heated

Global regulatory agencies typically permit the use of high-potency sweeteners in food applications that involve elevated temperatures, including bakery products (see American Dietetic Association 2004; EU 2004). However, scientific studies as well as evaluations by culinary experts have reported that the sensory properties of bakery products prepared with high-potency sweeteners differ from those using nutritive sweeteners (Redlinger and Setser 1987; Attia et al. 1993; Ness 2004). Although differences in sensory properties among sweetener types are known to involve formation of new compounds during thermal decomposition at elevated temperatures (e.g., Hutchinson et al. 1999), our knowledge of the full range of chemical interactions that occur during baking with high-potency sweeteners is still incomplete. This contrasts sharply with the vast database on thermal changes that occur with nutritive sweeteners, especially compounds formed during caramelization and Maillard reactions (Mauron 1981; Fayle and Gerrard 2002; Nursten 2005; Purlis 2010). Recently, there has been renewed interest in gaining a better understanding of the effects of elevated temperature on high-potency sweeteners, and in particular sucralose, because historical claims of thermal stability (Barndt and Jackson 1990; US FDA 1998) conflict with data from other laboratories (Hutchinson 1996; Hutchinson et al. 1999; Bannach et al. 2009; Rahn and Yaylayan 2010).

In 1990, Barndt and Jackson performed a radiolabeled baking study in which ^{14}C-sucralose was incorporated into recipes for yellow cake, cookies, and graham crackers. After baking, the ^{14}C-sucralose was extracted from the baked goods and analyzed by TLC. Although Barndt and Jackson concluded that sucralose minimally degrades in baked goods from 180 to 300 °C, their data suggest otherwise. The TLC trace from an ethyl acetate/ethanol/water extract of cookies shows multiple closely eluting peaks that indicate multiple radioactive chemicals were extracted, that is, sucralose underwent thermal degradation during baking. Since the publication by Barndt and Jackson (1990), 3 separate laboratories in the United States (Hutchinson 1996; Hutchinson et al. 1999), Canada (Rahn and Yaylayan 2010), and Brazil (Bannach et al. 2009) have concluded that sucralose degrades at temperatures used in baking. Hutchinson (1996) and Hutchinson et al. (1999) reported that sucralose completely degrades at 180 °C in aqueous solutions at pH 3, 7, and 11 with the release of chloride ions. In addition, Hutchinson et al. (1999) analyzed the volatile compounds released and concluded that dehydrochlorination steps accompanied their production. Bannach et al. (2009) studied the effect of temperature on sucralose using thermoanalytic techniques; they concluded that thermal decomposition of sucralose begins at 119 °C with liberation of water and HCl. Above this temperature, thermal decomposition of sucralose took place in 3 steps up to 550 °C without melting. Rahn and Yaylayan (2010) also found that sucralose undergoes thermal degradation and cautioned that baking with sucralose in the presence of glycerol and or lipids could lead to formation of toxic chloropropanols.

Several other high-potency sweeteners have been also subjected to thermal analysis (de Carvalho et al. 2009). All of the sweeteners evaluated exhibited thermal decomposition, but in some cases, this took place only after dehydration. de Carvalho et al. (2009) ranked the thermal stability of the high-potency sweeteners as follows: aspartame < Na saccharin < Na cyclamate < acesulfame-K. Overall, these findings on the thermal degradation of high-potency sweeteners suggest that more research is required to identify the new compounds generated during baking, including the utilization of liquid chromatography–mass spectrometry. The compounds that are identified can then be evaluated for acute and chronic toxicity.

Research Need 9: determine if bioaccumulation of high-potency sweeteners occurs when administered alone and when coadministered with drugs

In Research Need 3, the potential of high-potency sweeteners to alter renal clearance and trigger bioaccumulation of coadministered drugs was raised. Conversely, the potential of high-potency sweeteners themselves to bioaccumulate after single or multiple doses in the presence of coadministered drugs also requires further study. Historical data show that administration of multiple doses of saccharin to rats and humans can lead to bioaccumulation of saccharin even in the absence of drugs (Cranmer 1980); it is not yet known, however, the degree to which this may be exacerbated by coadministration of drugs. In a study of oral ingestion of sucralose in nonmedicated humans, Roberts et al. (2000) found that excretion of radioactivity was incomplete after 5 days following a single oral dose of 1 mg/kg ^{14}C-sucralose (less than one 12-oz drink); for 2 of the 8 subjects, approximately 12% of the radioactivity from the single dose was still not excreted after 5 days. It is not yet known if this prolonged excretion is simply due to individual variation beyond normal gastrointestinal transit time (~1 to 3 days in healthy individuals) or to bioaccumulation. Coadministration of sucralose with therapeutic drugs that inhibit of P-gp and CYP could potentially elevate the bioaccumulation of sucralose and slow its clearance even further. (As noted above, we reported that sucralose increases the expression of P-gp and CYP when administered without medications in rats [Abou-Donia et al. 2008]; drugs that inhibit P-gp and CYP would counteract this process.)

Overall, additional studies should be performed in medicated humans to quantify the tissue distribution and potential for bioaccumulation of high-potency sweeteners and their metabolites subsequent to long-term ingestion. The medications can be selected from lists of preferred and acceptable substrates, inhibitors, and inducers recommended by the US FDA (2011). For example, in order to determine if inhibition of P-gp promotes bioaccumulation of sucralose, one or more of the following drugs could be selected that are inhibitors of P-gp: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, or verapamil (US FDA 2011). Future studies should include vulnerable populations, for example, patients with diabetes, pregnant women, and young children. This will help determine, for example, if high-potency sweeteners or their metabolites: 1) alter the bioavailability of drugs taken by patients with diabetes, 2) accumulate in the fetus during pregnancy when the prospective mother takes drugs that inhibit P-gp, CYP3A4, or CYP2D6, or 3) affect the body weight of young children.

Final comment

These 9 suggestions of research needs are just some of the areas that require more investigation. It is now time to rethink the historical assumption that all high-potency sweeteners are inert compounds devoid of physiological effects other than peripheral taste responses but rather that some of these molecules can interact with transporters and cytochrome P450 enzymes that play a major role in the disposition of drugs. Furthermore, new toxicity-testing strategies (see International Transporter Consortium et al. 2010; Krewski et al. 2010) have evolved and expanded since the initial approval of high-potency sweeteners by national and international regulatory agencies, and these new approaches should be utilized to further evaluate the safety of these compounds. In conclusion, more research on high-potency sweeteners is required to better understand their biological effects, safety, and potential therapeutic applications. Collaboration between academics, government, and industry will be required to conclusively determine guidelines for the appropriate and safe uses of high-potency sweeteners in the global food supply.

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