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Highly Processed Foods Can Be Considered Addictive Substances Based on Established Scientific Criteria

Running Title: Highly Processed Foods Can Be Addictive

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Abstract

Background: There is growing evidence that an addictive-eating phenotype may exist. There is significant debate about whether highly processed foods (HPFs; foods with refined carbohydrates and/or added fats) are addictive. The lack of scientifically grounded criteria to evaluate the addictive nature of HPFs has hindered the resolution of this debate.

Analysis: The most recent scientific debate as to a substance's addictive potential centered around tobacco. In 1988, the Surgeon General issued a report identifying tobacco products as addictive based on three primary scientific criteria: their ability to 1) cause highly controlled or compulsive use, 2) cause psychoactive (i.e., mood-altering) effects via their effect on the brain, and 3) reinforce behavior. Scientific advances have now identified the ability of tobacco products to 4) trigger strong urges or craving as another important indicator of addictive potential. Here, we propose that these four criteria provide scientifically valid benchmarks that can be used to evaluate the addictiveness of HPFs. Then, we review the evidence regarding whether HPFs meet each criterion. Finally, we consider the implications of labeling HPFs as addictive.

Conclusion: Highly processed foods (HPFs) can meet the criteria to be labeled as addictive substances using the standards set for tobacco products. The addictive potential of HPFs may be a key factor contributing to the high public health costs associated with a food environment dominated by cheap, accessible, and heavily marketed HPFs.

Keywords: highly processed foods, food addiction, carbohydrates, fat, tobacco, nicotine, reinforcement, smoking, addiction criteria, compulsion

There is evidence that an eating phenotype exists that reflects the hallmarks of addiction (e.g., loss of control over intake, intense cravings, inability to cut down, continued use despite negative consequences)(1). Based on meta-analyses, approximately 14% of adults and 12% of children exhibit this addictive-like eating phenotype, commonly called food addiction(2, 3). Although some question the utility of applying an addiction framework to food intake(4-7), food addiction is associated with mechanisms implicated in other addictive disorders (e.g., impulsivity, reward dysfunction, emotion dysregulation), as well as lower quality of life and poorer response to weight-loss treatments(1, 8, 9). Controversy exists surrounding the role of the food in triggering this addictive-like eating phenotype. Some propose that it is the act of eating regardless of the type of food consumed that is addicting(10) or that while the type of food is important, it is impossible to classify food as addictive due to the complex nature of foods and the lack of a single addictive agent/compound(4, 5). Food is necessary for survival and a key evolutionary pressure that has shaped reward and motivation systems across species(11, 12). Addictive drugs that deliver high doses of reinforcing substances through rapid delivery systems tap into these systems, potentially activate them, and can lead to maladaptive patterns of behavior(13). Highly-processed foods (HPFs) are evolutionarily novel products made possible through modern food technology that provide refined and rapidly delivered primary reinforcers, specifically calories in the form of refined carbohydrates and added fats(1, 14-16). The debate that remains is whether a refined and optimized delivery system of calories can produce comparative effects to a refined and optimized delivery system of addictive drugs.

The ability to resolve the debate about whether certain foods are addictive is hindered by a lack of identified scientifically based criteria with which to evaluate the addictiveness of certain *foods*. In contrast, there is a general consensus around the criteria for identifying whether *someone* is exhibiting an addictive phenotype(17), which has allowed for clearer criteria to guide the investigation into whether certain individuals exhibit addictive-like eating(2, 3). There is not a comparable standard for evaluating if a *substance* is addictive, which contributes to the conflicting explanations for why certain foods are (or are not) addictive(18).

To allow for progress on this debate, we propose a set of scientifically based criteria for the evaluation of whether certain foods are addictive. Specifically, we propose the primary criteria used to resolve one of the last major controversies over whether a substance, tobacco products, was addictive. In 1988, the Surgeon General (SG) released a report outlining scientific evidence that tobacco products were addictive. This report acknowledged no singular criterion is sufficient to determine that a substance is addictive and frequent (or even excessive) intake alone does not necessarily indicate addiction(19). Rather, the SG report laid out a set of primary criteria that were identified as being necessary and sufficient to establish the addictive nature of tobacco products: 1) they trigger compulsive use, 2) they have psychoactive effects, and 3) they are reinforcing(19). A recent review confirmed that the main conclusions of this report have held up to over 30 years of

scientific evaluation with some important updates based on advances in addiction science, specifically that tobacco products 4) trigger strong urges and craving(20). The 1988 SG report was a watershed moment that bolstered the scientific recognition of tobacco products as addictive and shifted the public's perception about their addictive nature(20). This helped lay the groundwork for the development of new treatments that target addictive mechanisms and effective public health campaigns about the risks of tobacco products.

In this analysis, we consider the evidence that HPFs (i.e., foods with refined carbohydrates and/or added fats)(1, 14-16) can meet all the primary scientific criteria from the 1988 SG report on the addictiveness of tobacco (updated to include the ability to trigger urges and cravings). We propose that the 1988 SG report criteria used for tobacco products are ideal for evaluating the addictive nature of HPFs, as both of these products are legal, easily accessible, inexpensive, lack an intoxication syndrome, and are major causes of preventable death. Based on the established scientific criteria on the addictiveness of tobacco, we conclude that HPFs can meet all of the criteria for an addictive substance. Below we outline the evidence for this conclusion, highlight scientific gaps, provide a roadmap for future research, and consider the implications of labeling HPFs as addictive.

Parallels in the industrialization of food and cigarette production

A number of terms are used to refer to foods that are prone to excessive intake (e.g., highly processed, hyperpalatable, ultra-processed) and there is significant debate about which approach is most appropriate(21-24). We will focus on food categorized as HPF based on the presence of refined carbohydrates and/or added fats, as these ingredients have been most implicated in addictive-like eating(1, 14-16). Commonly consumed HPFs include carbonated soft drinks, sweet or savory snacks, chocolate, candies, ice cream, cakes, cookies, bread, and pizza (among many others)(25). Although processed ingredients (e.g., white flour, sugar, butter) have long been available for purchase to allow for the creation of homemade HPFs (e.g., freshly baked bread, homemade cookies), a marked increase in cheap, easily accessible, and heavily marketed industrialized HPFs foods began in the 1980s and preceded increases in obesity and diet-related disease (e.g., Type II diabetes)(26). The dominance of industrial HPFs is the result of these products being 1) inexpensive due to the use of cheap, but potent industrial substances (e.g., high fructose corn syrup, trans fats), 2) highly accessible and convenient due to additives that allow them to stay self-stable and ready-to-eat, 3) enhanced through additives that amplify somatosensory properties related to smell, taste, and texture through substances not available to the home cook (e.g., flavorants, monosodium glutamate, guar gum), and 4) the focus of marketing campaigns that create positive associations and brand loyalty from a young age(25-27).

There are clear parallels between industrial HPFs and industrial tobacco products. Although dried tobacco leaves have been consumed through smoking or chewing since at least 800 AD, the

development of industrial cigarette-rolling machines in the 1880s revolutionized the tobacco industry(28). Cigarettes could now be rolled at over 10,000 a minute (compared to just a few a minute when hand rolled). This technological shift allowed for the mass production of inexpensive industrial cigarettes and the development of the modern tobacco industry(28). As with industrial HPFs, industrial cigarettes are convenient, accessible, and heavily marketed(29). Although hand-rolled cigarettes made from processed tobacco can still be addictive and damaging to health, it was the marked increase in cheap, convenient, accessible, and heavily marketed industrial tobacco cigarettes that led to a >1000% increase in cigarette consumption and a marked increase in smoking-related disease (e.g., lung cancer)(30). Similarly, while homemade HPFs that include processed ingredients (e.g., sugar, fat) can be consumed addictively and damage health, the rise of cheap, accessible, convenient and heavily marketed industrial HPFs in the food supply is the major driver of excessive food intake, obesity, and diet-related disease(25-27). In contrast, intake of minimally processed foods (MPFs) that promote health, like fruit, vegetables, and legumes, fails to reach recommended levels despite well-funded public health campaigns to promote their consumption(31).

Primary scientific criteria for evaluating the addictiveness of a substance

Criterion 1: Compulsive use

We will now consider whether HPFs meet all criteria outlined in the SG report as necessary and sufficient to identify tobacco products as addictive. The first criterion in the SG report is the ability of the substance to trigger compulsive use, defined by “drug-seeking and drug-taking behavior that is driven by strong, often irresistible urges. It can persist despite a desire to quit or even repeated attempts to quit”(19). Intake alone is not sufficient to identify compulsive use, as only a subset (one-third) of tobacco smokers develop addictive patterns of use(32). Compulsive use for tobacco in the SG report was demonstrated by evidence that most smokers would like to quit, but most were unable to do so. The report notes that compulsive nature is most clear in extreme cases where individuals who are experiencing significant smoking-related disease (e.g., cancer, cardiovascular disease) continue smoking(19).

It is clear that HPFs are capable of triggering compulsive use. Even in the face of significant diet-related health consequences (e.g., diabetes, cardiovascular disease), the majority of patients are unable to adhere to medically recommended dietary plans that require a reduction in HPF intake and a commonly cited obstacle for low dietary adherence is cravings for HPFs(33-37). Failure in response to gastric bypass surgery (i.e., a significant surgery that results in the division of the stomach to treat severe obesity) provides an extreme case of compulsive HPF intake. Approximately 20-50% of individuals who undergo this surgery regain a significant amount of weight(38) and excessive HPF intake is a factor in this weight regain(38-40). This intake persists despite HPFs

triggering immediate aversive physical symptoms (e.g., cramping, vomiting, diarrhea) when consumed after surgery(38-40).

Binge eating (i.e., the experience of a loss of control when consuming a large amount of food) also provides evidence of compulsive HPF intake(41). The type of food predominantly consumed in binges are HPFs, whereas MPFs (like fruits and vegetables) are less likely to be consumed during binges(42-44). Higher dietary intake of MPFs, including high-fat nuts, is inversely associated with binge eating disorder(45). In contrast, higher dietary intake of HPFs, like sweets and baked goods, is positively associated with binge eating disorder(45). Similarly, rodents will risk aversive experiences (e.g., electric shock) to consume industrially produced cheesecake, pound cake, frosting, and chocolate when other calorie sources (i.e., standard chow) are easily available to them(46). Rats even show greater resistance to punishment (foot shock) when working for a “preferred pellet” reward (i.e., chow with added corn syrup) than when methamphetamine is used as the reinforcer(47). In sum, HPFs, but not MPFs, appear to meet the criterion of triggering compulsive intake consistent with addictive substances.

Criterion 2: Psychoactivity

Another primary criterion outlined in the SG report is that the substance needs to cause psychoactive effects(19). Psychoactivity was defined as “produces transient alterations in mood that are primarily mediated by effects in the brain”(19). The ability of tobacco to alter mood is more subtle than intoxicating substances, like opioids and alcohol. However, tobacco products can cause detectable subjective increases in pleasure and reductions in negative affect(19, 48). These mood-altering effects are related to the ability of tobacco products to deliver high doses of nicotine rapidly to the brain(19). It is important to note that at the time of the SG report exact knowledge of how nicotine impacted the brain, particularly in humans, was limited and mostly focused on the ability of the drug to bind to nicotinic receptors and increase glucose utilization in the rat brain(19). Those studies identified a host of brain regions, now known to be dense in nicotinic receptors, but of those, only the medial habenula and ventral tegmental area are established as key mediators of nicotine self-administration and use(49). In the SG report, the ability of centrally acting nicotinic antagonist to alter tobacco smoking also provided evidence about the important role of the brain in the use of tobacco products(19).

Advances in addiction science the last 30 years have yet to lead to the discovery of a specific biomarker to identify whether a substance is addictive or not, but there is a consensus that all addictive substances increase dopamine in the striatum(50). Relative to dopamine agonists such as amphetamine which can increase striatal dopamine release by 1000%(51), nicotine administration causes more modest increases in dopamine efflux (150-250% over baseline), which is similar to other addictive drugs like ethanol (also 150-200% over baseline) (51, 52). However, despite this lower magnitude, nicotine is still capable of triggering compulsive intake and changing mood. Since the SG

report, it has been demonstrated that the amount of subjective pleasure experienced in response to tobacco products is weakly associated with relapse and may be less central to its addictive nature(20). In contrast, the ability of tobacco products to trigger strong urges and cravings appears to be a bigger mediator of addictive patterns of intake, which will be reviewed in more detail in Criterion 4(20).

Based on the standards above, HPFs can be considered psychoactive substances. HPFs are capable of increasing positive affect and reducing negative affect (16, 53-57). For example, intake of white chocolate and 38% cocoa chocolate are associated with “euphoria” ratings on a measure of psychoactive drug effects of 7.0 and 6.4, respectively(53), which is similar to the “euphoria” scores on the same measure after the administration of 1.5 mg of intravenous nicotine to smokers (score of ~6) and much higher than scores by non-smokers (~1) (48). Intake of HPFs, relative to MPFs, is associated with greater subjective experiences of enjoyment (21.69 points higher on a visual analog scale) and the magnitude of this effect is greater for individuals with addictive-like eating(57). Further, HPF intake is often motivated by a desire to alter mood (e.g., experience pleasure, reduce negative affect) rather than to address homeostatic needs and this tendency is associated with addictive eating(1, 58). Further research is warranted to directly compare the magnitude of the psychoactive effects of a wider range of HPFs to known addictive substances and MPFs, but existent research supports the psychoactive nature of HPFs.

Regarding the brain, HPFs and their components increase dopamine in the striatum at a similar magnitude as nicotine when delivered orally (150-200%)(59-62). These substances increase striatal dopamine (~150%) and dopaminergic firing rates even when oral somatosensation is bypassed and nutrients are delivered directly to the gut(63-66). Whereas MPFs are predominantly high in either carbohydrates (e.g., fruit) or fat (e.g., nuts), HPFs are unique in their tendency to rapidly deliver a combination of refined carbohydrates and fat. The combination of refined carbohydrates (like sugar) and fat appears to have supra-additive effect on reward encoding in the striatum in humans(67). Opioid antagonists are also capable of reducing HPF (including chocolate candies and cookies) intake in humans(68-71). In animal models, opioid antagonists reduce consumption of chocolate chip cookies, but not laboratory chow(68, 72), which further highlights the importance of reward systems in the brain in driving HPF intake. As with tobacco, the experience of subjective liking of foods may be less central to their tendency to maintain compulsive intake, but rather their ability to trigger strong urges and cravings may be more central to their addictive potential(73, 74). However, there is sufficient evidence to label HPFs as psychoactive substances based on the SG report.

Criterion 3: Reinforcing

The final criterion in the SG report was that tobacco was a reinforcing substance, as defined by “being sufficiently rewarding to maintain self-administration”(19). Clearly, humans will self-administer tobacco products, although not all humans find tobacco products reinforcing(48, 75). Nicotine was identified as a key factor in the reinforcing nature of tobacco products, as animals would self-administer nicotine, work to gain access to nicotine, prefer places where nicotine was administered, and conditioned cues paired with nicotine became secondary reinforcers(19). Compared to other addictive drugs (like cocaine), nicotine was a relatively weak reinforcer and was only self-administered under a narrow range of conditions (e.g., intermittent reinforcement schedules, food-restriction, combined with food delivery, paired with cues) (19). However, this level of evidence was sufficient for the SG report to conclude that tobacco products were reinforcing due to their ability to deliver nicotine.

Scientific evidence suggests that the reinforcing nature of HPFs is high. Both adults and children will self-administer HPFs (e.g., potato chips, candy, cookies) even when satiated(76, 77). The tendency to consume MPFs when satiated appears to be lower. For example, when children are provided with post-meal access to a MPF (fruit) rather than a HPF (sweet/savory snack), energy intake is reduced by an average of 60%(78). Both adults and children will work on an operant responding paradigm (a classic measure of reinforcement) to gain access to HPF relative to non-food reinforcers(79). Adults, adolescents, and children who find HPFs more reinforcing (as indicated by a greater willingness to work to gain access to them) are more likely to have obesity and are prone to weight gain(80-83). In contrast, the reinforcing value of MPF (e.g., fruit, vegetables, cottage cheese) is not associated with higher body weight in adults, adolescents and children(80, 84, 85). Daily exposure to HPFs (e.g., candy, cookies, chips) appears to sensitize the reinforcing value of these foods (as indicated by an increased willingness to work to gain access to HPFs over time) and larger portions of HPFs lead to greater sensitization(84-87). In contrast, daily exposure to MPFs, such as vegetables and fruits, does not sensitize reinforcement and may even reduce it(85, 88). Although more research is needed to directly compare the reinforcing nature of a wider variety of HPFs to MPFs in humans, there is preliminary evidence that HPFs have a high reinforcement value (particularly for individuals prone to obesity).

In animal models, the strength of reinforcement for HPFs relative to nicotine is very clear. The majority of animal studies that administer food as a primary reinforcer use sucrose or flavored sucrose pellets, an HPF(89, 90). From this extensive literature, we know animals will self-administer HPF in a much wider range of conditions than nicotine, in fact it is often the behavior trained first before attempting to train an animal to self-administer a drug(91). Cues presented with HPFs rapidly become secondary reinforcers and places where HPFs are administered become strongly preferred(92-94). The ability of HPFs to rapidly deliver refined carbohydrates, fat, and sweet tastes appears to play a key role in their reinforcing nature, as these factors are all highly reinforcing even when studied in isolation(95-97). Animals will self-administer sweet tastes over cocaine more than 80% of the time(98, 99). In contrast, animals choose to self-administer nicotine over cocaine less

than 20% of the time(100). While it is clear that animals will overwhelmingly self-administer HPFs over standard laboratory chow (which provides complete nutrition through refined ingredients)(46, 101, 102), there is a need for animal models to directly compare the reinforcing nature of HPFs to MPFs (especially those naturally high in sugar or fat - like fruits and nuts). However, existing research highlights the high reinforcing nature of HPFs even when compared to other addictive substances.

Criterion 4: Strong urges or cravings

In the 1988 SG report, craving for the substance was listed as a secondary criterion that was not considered necessary for identifying tobacco as addictive. However, the report states that the primary criterion of compulsive use “is driven by strong, often irresistible urges”(19). In the 30 years since the report, the ability of tobacco products to trigger strong, recurrent urges or cravings has been identified as a central factor underlying their addictive nature(20). The cues paired with tobacco use and nicotine delivery quickly become salient incentive drivers of behavior(103). Consistent with this finding, cravings in response to tobacco-associated cues are a major driver of use in humans and urges to smoke are predictive of relapse during quit attempts(20). Further, “craving, or a strong desire or urge to use tobacco” is now a diagnostic indicator of a tobacco use disorder(17). Based on this updated science, we propose that the ability of a substance to trigger strong cravings or urges should be a primary criterion for evaluating the addictiveness of a substance.

While experiencing a strong urge or craving for high-calorie food may be adaptive when calorically depleted, craving for HPFs commonly occur even when individuals are satiated(104, 105). The most commonly craved foods are all common HPFs (e.g., chocolate, sweets, pizza) (104, 105) and the neural substrates underpinning cravings for HPFs and other addictive substances largely overlap(106). As with tobacco, stimuli paired with HPFs become salient motivational cues and cue-induced craving for HPFs is implicated in more frequent HPF intake, loss of control over HPF intake (e.g., binge episodes), difficulty losing weight and a failure to reduce HPF intake in the face of serious health conditions(33-37, 104, 107-109). In contrast to HPFs, cravings for MPFs (e.g., fruits, vegetables) are less frequent and are associated with positive health outcomes (e.g., higher diet quality, longer sleep duration, successful weight loss)(105, 110-112). Thus, there is evidence that HPFs (but not MPFs) meet the criterion of triggering strong urges or cravings in a manner consistent with an addictive substance. Future research is needed to investigate whether the intensity of cravings for HPFs is comparable to that for other addictive substances, like tobacco.

Secondary criteria

The SG report did list secondary criteria in their evaluation of the addictiveness of tobacco products, including withdrawal and tolerance(19). These secondary criteria were not considered

necessary, nor sufficient, for determining the addictive nature of tobacco(19). Science on tobacco addiction since the report further supports the secondary nature of withdrawal and tolerance. Many aspects of the withdrawal syndrome (e.g., difficulty concentrating, increased appetite) are only weakly related to relapse and the development of tolerance to the pleasurable effects of nicotine is limited(20). While there is evidence of both a withdrawal and tolerance in HPF intake(113-116), in parallel to the SG report, we do not include them as primary criteria.

A Roadmap for Future Directions

Based on the criteria used to establish the addictive nature of tobacco, we conclude there is sufficient evidence that HPFs can be considered addictive substances. It has been the status quo to treat industrial HPFs as food, not as the highly refined *substances* they are, whose properties and components must be studied. Progress has been made identifying ingredients that amplify the effects of nicotine, such as menthol and sweeteners(117, 118). To identify the key addictive components in HPFs, the same care and control employed in understanding the addictive potential of drugs needs to be applied to studies of foods.

In the case of industrial tobacco products, their complexity and inclusion of thousands of chemicals made identifying a single addictive agent challenging. In the SG report, nicotine was identified as the key addictive component in tobacco products as it was psychoactive, reinforcing, and consumed compulsively(19), but at the time of the SG report (and still today), the specific dose or absorption rate at which nicotine becomes addictive is unknown(119, 120). The presence of nicotine alone in a product is not sufficient for it to be addictive. For example, some foods naturally contain low levels of nicotine, but do not trigger addictive consumption (e.g., eggplant, cauliflower). Products, like nicotine patches, that deliver nicotine at lower doses and at a lower rate also have low addictive potential. It is the ability of tobacco products, like cigarettes, to deliver nicotine rapidly and in high doses that is key to their addictive potential.

Like industrial tobacco products, HPFs are complex substances that are psychoactive, highly reinforcing, strongly craved, and consumed compulsively. The foods that people report being most likely to consume in an addictive manner are all HPFs that deliver both refined carbohydrates and added fats (i.e., chocolate, ice cream, French fries, pizza), followed by HPFs that contain refined carbohydrates without high levels of fat (i.e., breakfast cereal, gummy candy, soda)(14, 16). Further, these HPFs are designed to rapidly deliver these unnaturally high doses of refined carbohydrates and fats due to significant changes to the food matrix during processing that removes ingredients that would slow down eating rate and absorption (e.g., water, fiber)(25). These HPFs are energy-dense substances that quickly deliver bioavailable calories into the body, which then activates the reward systems through the gut-brain axis(121). The exact dose and absorption rate at which refined carbohydrates and added fats become capable of triggering an addictive process is unknown, just as

it is for nicotine(119, 120). This is an important area of future research that may aid in the reformulation of HPFs to reduce addictive potential.

Investigating the role of additives that enhance the somatosensory properties of HPFs is also an important area of future research. In the 1970s, additives to industrial cigarettes became more common with hundreds of additives acknowledged by the tobacco industry(122). The typical industrial cigarette in the United States is 10% additives by weight with sugar, and other taste-based ingredients (e.g., menthol, cocoa, licorice) as main additives(122). These additives enhance the somatosensory appeal, taste, and smell of industrial tobacco products. Smokers develop strong brand loyalty and are reluctant to switch to other industrial brands(123) or to new products, even if they deliver high doses of nicotine (e.g., electronic cigarettes; (20)). Denicotinized cigarettes that deliver the somatosensory experience of smoking, but no nicotine, reduce cigarette craving and are even chosen over intravenous nicotine administration(124). Further evidence for the importance of somatosensory properties is demonstrated by the recent proposal to remove menthol-flavored cigarettes and flavored cigars from the marketplace in the United States. The change to the somatosensory profile is estimated to lead hundreds of thousands of people to quit smoking or to never initiate smoking, despite no reduction in the nicotine levels in the products(125). Thus, tobacco products are addictive, not just because of the existence of nicotine, but because they are industrial products that have been optimized to deliver nicotine rapidly at high doses and are enhanced through additives to have unique somatosensory signatures.

Industrial HPFs are also optimized through additives that pair specific somatosensory properties (e.g., taste, smell, texture, mouthfeel) with the delivery of high doses of refined carbohydrates and added fats(25). These additives are unlikely to be reinforcing on their own, but when combined with refined carbohydrates and added fats, they likely play a key role in amplifying the addictive nature of industrial HPFs. Of concern, many industrial additives (e.g., flavor enhancers like nucleotides and artificial flavors, texturizers like emulsifiers) are not typically used in home cooking. Many somatosensory properties that become powerful drivers of intake (e.g., artificial cheese flavoring, chewiness of gummy candy) are typically only available in industrial HPFs. As with personal tobacco product preferences(123), individual differences in the experience of specific somatosensory profiles paired with the delivery of rapidly absorbed carbohydrates and/or added fats may contribute to personal preferences or brand loyalty for specific HPFs. There are also additives, like non-nutritive sweeteners, that mimic the effects of sugar by intensely activating sweet taste receptors on the tongue without delivering calories. Non-nutritive sweeteners are reinforcing and increase activity in reward centers of the brain (although possibly to a lesser degree than nutritive sweeteners)(126). Non-nutritive sweeteners are frequently included in HPFs alongside refined carbohydrates and/or fat(127), but some products (like diet sodas) include only non-nutritive sweeteners that are often combined with reinforcing ingredients like caffeine. While some randomized control trials have found limited effects of non-nutritive sweeteners on energy intake or body weight, overall there are numerous gaps in the evidence base on the impact of non-nutritive

sweeteners on health outcomes(128). Thus, the understanding of the addictive potential of non-nutritive sweeteners (when consumed alongside caloric ingredients and when amplified by additives like caffeine) is an important area of future study.

Another important question is whether certain MPFs (or MPF combinations) can trigger addictive responses in some circumstances. Although some MPFs have naturally high levels of carbohydrates (e.g., fruit) or fat (e.g., salmon), people report these foods are unlikely to be consumed in an addictive manner(1, 14-16, 42) As reviewed above, MPFs (like fruits and vegetables) are rarely consumed compulsively, are less prone to reinforcement sensitization, and cravings for MPFs are associated with better health(42-45, 80, 84, 85, 105, 110-112). However, MPFs are also diverse. Naturally high in fat MPFs that typically also have high levels of added sodium (e.g., bacon, cheese, salted nuts) are associated with higher subjective ratings of loss-of-control, craving, and enjoyment relative to other MPFs (e.g., avocados, eggs, apples, bananas)(16). Thus, it is important to investigate whether high-fat MPFs with high levels of added sodium have addictive properties. Additionally, MPFs may be altered and combined in ways that may increase their addictive potential. For example, the blending together of high-sugar fruits and high-fat yogurt into a smoothie creates an MPF that delivers high levels of rapidly absorbed carbohydrates combined with fat akin to a HPF. It will be important for future research to investigate the boundary at which some MPFs (or MPF combinations) may meet the criteria for addictive substances based on the proposed criteria.

Conclusion

Here, we provide evidence that HPFs meet the three criteria of an addictive substance as outlined by the 1988 SG report on the addictive nature of tobacco products. Like tobacco, HPFs 1) trigger compulsive use, 2) have psychoactive effects, and 3) are highly reinforcing (19). In addition, HPFs 4) trigger strong urges and cravings, which has emerged as a strong predictor of addictive use(20). These HPFs are highly complex substances that cannot be simplified to a single chemical agent acting through a specific central mechanism. This is also true of industrial tobacco products, which contain thousands of chemicals (in addition to nicotine), an optimized pharmacokinetic profile, and unique somatosensory properties that enhance their addictive nature(122). A dose and rate profile of a single addictive chemical was not used to identify tobacco products as addictive. However, HPFs meet the actual scientific criteria used to determine that tobacco products are addictive. More research into the exact properties and components is needed, but their ability to rapidly deliver high doses of refined carbohydrates and/or fat appear key to their addictive potential. Thus, we conclude that HPFs can be considered addictive substances based on scientifically established criteria.

The scientific evidence that tobacco products are addictive supported the advancement of new treatment, policy, and public health approaches that helped significantly reduce their use. We

must consider the huge public health costs of misclassifying an addictive substance as non-addictive. When tobacco was misclassified, this led the public to be ill-informed about the risks of tobacco products, reduced the likelihood that addiction mechanisms were targeted in treatments, allowed the industry to develop more addictive products with limited oversight, and to target vulnerable populations, including children and racial and ethnic minorities(29). Identifying tobacco products not just as unhealthy, but also as addictive undermined the industry's claim that smoking was solely an act of free will and an "adult choice"(129). The SG report supported increased scrutiny of industry practices, contributed to the success of legal proceedings against the tobacco industry and increased public support for policy initiatives that aimed to protect children (e.g., restrictions in tobacco marketing to minors) and alter the tobacco environment (e.g., taxation, reducing vending machine access)(29).

Tobacco companies (i.e., Philip Morris, RJ Reynolds) bought food and beverage companies (e.g., Kraft General Foods, Nabisco) and became some of the biggest producers of HPFs in the world from 1980 through the mid-2000s(130, 131). Tobacco industry documents demonstrate they applied their playbook from tobacco to increase the profits from their food and beverage portfolios, including the use of flavored additives and marketing strategies to target children and racial/ethnic minorities(130, 131). Currently, poor diets dominated by HPFs are contributing to preventable deaths to a comparable degree as tobacco products(132). Understanding whether addiction contributes to HPF intake may lead to new treatments, as preliminary research finds that behavioral and pharmacological interventions that target addictive mechanisms may reduce compulsive HPF intake(133, 134). Importantly, if the science supports that HPFs are not just unhealthy, but addictive, this challenges the assertion that excessive HPF intake is purely a matter of choice. This may increase scrutiny of industrial practices in the development and marketing of HPFs (particularly to children). At the time of the SG report, tobacco products were the largest cause of preventable death, however, there was still some resistance to accepting their addictive and harmful nature. This was due in large part to industry efforts to undermine confidence in the science on the addictive nature of tobacco(29), and because tobacco products were "so familiar they [had] lost their saliency"(135). This delayed the implementation of effective strategies to address this public health crisis, which cost millions of lives. Unlike smoking, we all need to eat. In the past 40 years, HPFs have become familiar substances that dominate the food environment, but we cannot lose the saliency of their potential to be addictive and harmful.

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