

# Dynamic Interplay Among Homeostatic, Hedonic, and Cognitive Feedback Circuits Regulating Body Weight

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Obesity is associated with a prolonged imbalance between energy intake and expenditure, both of which are regulated by multiple feedback processes within and across individuals. These processes constitute 3 hierarchical control systems—homeostatic, hedonic, and cognitive—with extensive interaction among them. Understanding complex eating behavior requires consideration of all 3 systems and their interactions.

Existing models of these processes are widely scattered, with relatively few attempts to integrate across mechanisms. We briefly review available empirical evidence and dynamic models, discussing challenges and potential for better integration.

We conclude that developing richer models of dynamic interplay among systems should be a priority in the future study of obesity and that systems science modeling offers the potential to aid in this goal. (*Am J Public Health*. 2014;104:1169–1175. doi:10.2105/AJPH.2014.301931)

**THE WORLDWIDE OBESITY EPIDEMIC** is characterized by a gradual increase in mean body weight of the population over a time scale of decades.<sup>1</sup> At its most basic level, development of obesity occurs when intake of calories exceeds the calories expended to maintain life and perform physical work.<sup>2</sup> This statement should not be confused with an explanation of obesity because it is merely a reiteration of the first law of thermodynamics, also known as the principle of energy balance. Nevertheless, the energy balance framework provides a useful way to evaluate the relative contribution of the multiple interacting components of energy intake and expenditure and their contribution to body weight change.<sup>3</sup>

Energy intake and expenditure, the core components of energy balance, are regulated by a series of feedback processes within and across individuals, and influenced by environmental, economic, and social drivers. Increased mechanization and the transition from energetically expensive to more sedentary occupations have certainly resulted in decreased individual energy needs and may have contributed to obesity epidemic.<sup>4</sup> However, many of these occupational changes began to take place long before the onset of the obesity epidemic and the per capita food availability correspondingly decreased in the early part of the 20th century.<sup>1</sup> These observations, along with little direct evidence of decreased physical activity from the late 1970s, suggest that increased food intake is likely to be the primary driver of obesity.<sup>1,5–7</sup>

We therefore focus our discussion on the feedback mechanisms regulating food intake.

Great progress has been achieved in the past decade delineating the molecular mechanisms and the powerful homeostatic physiology that helps regulate food intake.<sup>8</sup> These homeostatic feedback control circuits—sufficient for body weight regulation over the course of most of human history—are likely still functioning perfectly normally, but have been recently overwhelmed by a changing food environment that frequently activates 2 other major processes—hedonic feedback and cognitive feedback. Actual food intake in humans is governed by the interaction and joint function of these 3 hierarchical control systems “below the skin,”<sup>9,10</sup> any of which may be affected by environmental, economic, and social contextual factors “above the skin.”

The determinants of obesity are widely recognized to be complex, including important factors across multiple levels of scale.<sup>11,12</sup> In this article, we argue that quantitative frameworks integrating the neurobiological feedback mechanisms through which many of these factors are processed is likely to yield important new insights for understanding obesity and assessing alternative interventions and policies. Although the concept of energy balance lies at the heart of most quantitative models of weight change, the existing work on modeling the feedback processes governing food intake and energy expenditure is widely

scattered and there are relatively few attempts to integrate across mechanisms. We will briefly review available empirical evidence and dynamic models for each of these systems (including research conducted as part of the National Collaborative on Childhood Obesity Research Envision network), and will discuss the challenges and potential for computational modeling and “systems science” to facilitate better integration across multiple feedback systems.

## HOMEOSTATIC FEEDBACK

Body weight regulation is often described in terms of control engineering terminology where a set point<sup>13</sup> is believed to be controlled under the influence of endocrine feedback signals that are correlated to body weight.<sup>8</sup> Enormous progress has been made in unraveling the molecular mechanisms of homeostatic food intake regulation through complex feeding circuits in the brainstem and various hypothalamic nuclei. These advances have been achieved through basic scientific investigation, primarily in rodent models.

For example, the molecule leptin is secreted by adipose tissue in proportion to its mass, and mice that lack a functional leptin gene cannot sense their energy stores and likely perceive a state of starvation. Therefore, leptin-deficient mice are always hungry and become massively obese.<sup>14,15</sup> Leptin also plays a primary role in the homeostatic regulation of human body weight. People with leptin mutations are morbidly obese but

can be cured by exogenous leptin administration.<sup>16</sup> However, leptin mutations in humans are extremely rare, as are mutations in other genes that play a role in the homeostatic feedback control of food intake.<sup>17</sup> Thus, defective homeostatic regulation of food intake is unlikely to explain common obesity.

Energy expenditure is also subject to balancing feedback loops. As people gain weight, their energy expenditure increases both because of increased metabolism and energy costs of activity, slowing down further increases in weight.<sup>18</sup> Furthermore, there are metabolic adaptations to a reduced-calorie diet when both resting and total energy expenditure decrease to an extent greater than expected on the basis of the measured body weight and composition change.<sup>19,20</sup> Other homeostatic feedback mechanisms may also exist, including nonexercise activity thermogenesis, that may partially compensate for extra energy intake.<sup>21</sup> These metabolic adaptations act to resist weight change and have been hypothesized to play a role in weight regain after loss.

## HEDONIC FEEDBACK

The brain's reward system evolved to promote behaviors that are beneficial to survival and procreation, such as sexual intercourse and eating. Activation of the brain's reward system can lead to food consumption well beyond homeostatic needs<sup>22,23</sup> via "hedonic hunger"<sup>10,24</sup> that operates even in the presence of satiety signals. This system operates through the mesolimbic system<sup>25</sup> and has a neurobiological basis in parallel with homeostatic feedback system.

An important feedback process in the hedonic reward system is conditioning or "reward learning."<sup>26–28</sup> This refers to the

process by which previously neutral cues (such as food images in TV advertisements) gain incentive properties through association with primary reward (such as palatable food consumption). In this way, the reward system "learns" how to effectively seek reward and habitual patterns are developed. The brain regions responsible for inferring primary reward values from food cues are now beginning to be elucidated.<sup>29</sup>

Empirical evidence from laboratory assessments, functional brain imaging, and surveys suggests an important link between strong hedonic attraction to high-calorie foods and obesity.<sup>10,30–34</sup> Interestingly, brain reward regions in obese individuals are particularly responsive to palatable food cues compared with lean controls, but show decreased activation upon receipt of primary food rewards.<sup>35</sup> Reward learning defines a feedback loop in which exposure to rewarding foods, as well as cues that accurately predict receipt of such foods, increases motivational desire for rewarding foods. In some cases, this can take the form of compulsive food-seeking behaviors comparable to drug addiction,<sup>34,36,37</sup> and indeed involves similar sensory and motivational processes.<sup>10</sup>

Differential activation and "training" of this feedback system, resulting in different patterns of sensitization or desensitization of the hedonic system to specific cues, may help explain individual differences in eating patterns.<sup>10,38</sup> Environmental exposures (including the built environment), social context, and economic factors can all play a role in shaping the emergence of such differences in activation and training of reward. Reward system dynamics are also shaped by differences in individual biology (including genetics).

Together, the homeostatic and hedonic systems define "reflexive" eating, with motivational states that may be subconscious.<sup>9</sup> By contrast, "reflective" eating is driven by dynamic processes largely housed in the prefrontal cortex and associated with purposive, conscious behavior—these include several forms of cognitive feedback.

## COGNITIVE FEEDBACK

Cognitive mechanisms linked to eating behavior comprise several distinct subtypes, including self-regulation, social feedback, and environmental feedback. Self-regulatory processes that influence food intake and physical activity include an individual's conscious efforts to close the gap between desired and actual weight, as well as unconscious mechanisms moderated by stress, emotional appeal of eating, and several other factors.<sup>39–42</sup> Conscious self-regulation is exemplified by dieting: an individual seeks to achieve and maintain a desired body weight (or image) by attempting to change food intake patterns. Perspectives on behavior change such as self-determination theory are well-aligned with this cognitive view of self-regulation.<sup>42</sup> Cognitive restraint of eating may be an effective strategy for weight management, but it requires effort and vigilance to track and control food intake in an obesogenic environment.<sup>43</sup> Because of the degree of variability in typical day-to-day food intake,<sup>44</sup> along with unreliable nutrition information,<sup>45,46</sup> it can be difficult for an individual to know how many calories are being eaten on a regular basis. It is little wonder that self-reported measurements are notoriously inaccurate.<sup>47</sup> Thus, cognitive restraint of eating is

generally a qualitative process that employs heuristic strategies such as limiting portion sizes, choosing foods with low energy density, and avoiding food cues and situations associated with overeating high-calorie foods. Cognitive restraint, and goal-oriented eating behavior in general, is also constrained by broader economic and environmental determinants that affect feasibility.

Social feedback mechanisms include the processes through which other people influence an individual's food intake and physical activity behavior, and in return are impacted by the individual's actions. These influence pathways flow through social networks,<sup>48,49</sup> media,<sup>50</sup> and other social interaction processes,<sup>51</sup> and are typically manifested in social norms. In the obesity context, norms related to desired body weight,<sup>52</sup> eating,<sup>53</sup> and physical activity behavior influence individual action. Norms and their effects are sustained through compliance pressure (e.g., social costs and rewards, peer pressure, stigmatization, and regulations), identification (e.g., learning about new behaviors, following role models), and internalization of value systems consistent with those norms.<sup>54</sup> In return, individuals following the norms enact and reinforce them, closing a feedback loop that operates across multiple individuals.<sup>55</sup>

Social influence has an impact on the dynamics of obesity at the population level by leading to widespread diffusion of new norms, interventions, and behavior patterns.<sup>56</sup> For example, many food products rely on word of mouth to become established in the market; similarly, diets have sprung up and gained momentum, only to be replaced by others,<sup>57</sup> and health information spreads

through social networks.<sup>58</sup> The reinforcing mechanism integral to social influence can speed up change as people influence each other and start a cascade.

On the other hand, social influence is also a source of inertia. Norms constrain the actions individuals consider and channel them in socially sanctioned directions. As a result the individuals' actions can settle into a pseudo-equilibrium in which each individual does not change his or her eating or activity pattern when following peers, and norms remain stable in the absence of individual change. Models in which individual eating and exercise level are influenced by peers or social group averages represent this inertial effect of social influence. As a result of this feedback, social influence acts as an anchor slowing behavioral change under other pressures. For example, overweight individuals may be motivated to lose weight because of health risks, yet, seeing a growing number of others with similar weight, they may slowly increase their sense of acceptable weight and find less motivation for weight loss.<sup>59</sup> On the other hand, norms of food preparation and family meals may have slowed down the economically motivated changes toward eating out, and the resulting excess energy intake.<sup>60</sup>

The third category of cognitive feedback involves the interaction between individuals and their living environment. It is increasingly recognized that obesogenic environments, with increases in sedentary activities (from video-gaming to desk work), stress, eating out and portion sizes, access to low-cost calories, limits to physical activity opportunities, among others, are key to obesity trends.<sup>1,7,61,62</sup> At this level, the actions of any single individual

have little impact, and much of the change in the environment is driven by technological shifts and economic imperatives. Yet, by influencing norms, regulations, and market incentives for economic actors, individuals collectively set in motion the forces that shape the food and built environment and consequently society's eating and activity routines. This feedback mechanism unfolds over long time horizons and tends to create further inertia in obesity trends. For example, even if a diverse group of nutritious, more palatable, less expensive, and less energy-dense food items appeared overnight, it would take years before they would be known, accepted, and incorporated into popular recipes. This group of feedback processes could be potentially important to the societal obesity trends and feasible policies for changing those trends. For example Struben et al.<sup>63</sup> analyzed opportunities for food market transformation in the interaction between consumers, producers, and policymakers, and found significant challenges to coordinated action among producers to improve nutritional value of their supply.

## DYNAMIC INTERACTION AMONG FEEDBACK TYPES

Several times every day, we decide when, where, what, with whom, and how much to eat. This complex eating behavior is determined by dynamic interactions among homeostatic, hedonic, and cognitive processes. Our cognitive choices about when to eat are modulated by homeostatic hunger as well as the availability of food, the social context, our response to environmental food cues, and our habitual eating times. Food choice and how much we eat are also

under cognitive control, but strongly influenced by appetite, food variety, portion size, social context, habits, satiety, and the reward value of the food. Homeostatic hunger enhances, and satiety attenuates, both food and nonfood rewards<sup>64,65</sup> and activation of hedonic circuits may override homeostatic satiety signals thereby facilitating eating in the absence of physiological hunger.

When an obese individual attempts to change habitual eating patterns to lose weight, cognitive self-regulation strategies can be used to restrain food intake, at least temporarily.<sup>43</sup> However, reward value plays an important role in decision-making,<sup>66</sup> and the delayed reward associated with the possibility of future weight loss is likely to be strongly discounted compared to the immediate primary reward of eating palatable foods.<sup>10</sup> Furthermore, the social and environmental factors that originally facilitated development of obesity often remain unchanged when one is trying to lose weight. Habitual eating patterns are thereby promoted and reinforced by their associated environmental and social cues.

In addition to these impediments to obese persons consciously changing their eating patterns, there is evidence that the brain's reward circuitry in obesity is altered similarly to drug addiction and is associated with decreased activation in prefrontal brain regions associated with executive function and self-control.<sup>37</sup> Such brain changes could limit obese individuals' ability to resist palatable food cues and may lead to compulsive overeating and thereby sabotage their self-regulatory weight-control efforts.

These multiple pathways of dynamic interplay among the 3 major feedback systems imply that

a sufficiently rich understanding of eating behavior through time is likely to require dynamic models that can capture multiple interacting mechanisms. Systems modeling methods offer such an approach.

## SYSTEMS MODELING OF BODY WEIGHT REGULATION

Metabolic adaptations to alterations in diet and physical activity and the resulting changes in body weight and composition have been subject to intensive modeling efforts over the past several years.<sup>2</sup> Although most such models have focused on adults, recently normal childhood growth and the development and treatment of childhood obesity have been modeled within an energy balance framework.<sup>67,68</sup> These models have typically focused on changes in metabolism and body composition that occur under controlled diet and physical activity interventions that are used as model inputs. Recently, it has been suggested that these validated models can be inverted to use repeated body weight measurements over a period of months to calculate long-term average changes in diet.<sup>69,70</sup> Such methodologies may help address our inability to accurately measure food intake behavior outside a short-duration laboratory setting.<sup>47,71</sup>

Systems modeling of food intake regulation began in the 1970s when investigators attempted to capture the homeostatic feedback regulation of hunger, primarily in rodents.<sup>72</sup> Models have recently been developed that include molecular mechanisms of homeostatic food intake regulation in rodents.<sup>73,74</sup> However, homeostatic regulation of human food intake may not be necessary

to explain body weight stability.<sup>18</sup> Recent conceptual models of food intake have ascribed a more limited role of homeostatic feedback in determining eating behavior, with more emphasis on hedonic and cognitive factors that are modulated by homeostatic signals.<sup>13,75</sup>

At the cognitive self-regulation level, computational models of individuals can be developed by quantifying the desired body weight (or image), the salience and precision of perceived weight, the availability and knowledge of effective interventions to close the gap, and the strength of motivation to implement an intervention. Simple goal-seeking formulations<sup>76</sup> would provide a solid starting point, but more complex models can take into account the history of eating and physical activity by the individual and how they influence compensatory reactions (e.g., to get back on diet) and habit formation. Some of these variables are coupled with other feedback mechanisms. For example, success in achieving the desired weight, as well as the costs and discomfort induced by the selected self-regulatory strategies, likely have an impact on future adherence and choice of interventions.<sup>77,78</sup> Studies that quantify this feedback mechanism can inform more successful intervention design by incorporating the endogenous motivation change. Moreover, the goal toward which the individual self-regulates (desired body weight) is not exogenous, but is often a function of the current weight of peers and other reference groups.<sup>79</sup> This dependence creates additional feedback loops crossing multiple individuals, as the desired weight of each person is partially a function of the weight of others, whose eating is influenced by the weight of others. Such feedback processes could

operate at the level of cohesive social groups (e.g., family and friends) or more diffusely in the society and over long time periods.<sup>55,80</sup>

Social influences have long been identified with a diffusion mechanism<sup>81</sup> and many computational models have analyzed these processes in sociology,<sup>82</sup> marketing,<sup>83</sup> and health communication.<sup>84</sup> Analogous processes have long been the cornerstone of mathematical epidemiology,<sup>85</sup> although application to eating and obesity has been limited. A few researchers have modeled obesity to follow similar diffusion patterns using individual-level<sup>80</sup> and compartmental formulations,<sup>86</sup> but have not included detailed representation of the interacting feedback mechanisms described previously.

Energy intake variations from equilibrium can be modeled by considering the balance between 2 potential goals: toward the average intake for the same age, gender, and race group (group norm) or toward normal or healthy body mass index values. Empirical estimation methods suggest that eating behavior is significantly influenced by group norms but not healthy goals,<sup>87</sup> underlining the importance of social influence as a dynamic pathway. One recent computational systems science model focused on this pathway linked purposive diet behavior to coevolving social norms of body image, and included realistic constraints imposed by physiology.<sup>55</sup>

Dynamic modeling of the hedonic reward system and the process of reward learning in the specific context of food has also been limited, although there are strong conceptual models of these processes supported by extensive empirical evidence. Mathematical and computational models of the process of reward learning often

center around the well-validated algorithm of temporal difference learning,<sup>88-90</sup> including some recent application to the food context,<sup>38,91</sup> and the use of systems science modeling to capture the potential role of environmental effects in shaping reward learning about food.<sup>38</sup>

## POTENTIAL APPLICATIONS FOR INTEGRATED MODELS

Despite some progress in developing models of the homeostatic, hedonic, and cognitive factors that individually influence food-intake behavior, there is a need for more integrated and quantitative modeling that can account for dynamic feedback among these processes. Very few modeling efforts have adopted this level of analysis, potentially because the interrelated mechanisms cross different levels of aggregation, draw on diverse data sources, and require the interaction of many stakeholders across disciplines. Here we provide a roadmap with examples on how integrated systems models can inform research and policy applications at different levels of analysis.

At the individual level, systems models can take on 2 distinct roles. First, they can contribute to a more nuanced understanding of how multiple biological processes lead to the behaviors and outcomes of interest. Empirically validated mechanistic models are needed to assess the relative contribution of different mechanisms within and among homeostatic, hedonic, and cognitive domains to the risk of obesity, as well as the interaction of these mechanisms with broader environmental determinants.<sup>38</sup> Systems models also test the integrity of our theoretical understanding and flag the need for new data or for quantifying

specific mechanisms. Just as simple statistical models are used for power calculations in experimental design, more complex systems models can identify the need for, and inform the design of experimental studies.<sup>92</sup> Individual-level models can also have broad practical applications. By providing more reliable projections of outcomes, integrated models can help design diets and other individual interventions consistent with individual biological and motivational mechanisms, thus increasing adherence and effectiveness. Individual-level models with social dynamics are indispensable in the design of interventions that leverage social influence (e.g., between parents and children or among peers) to maximize the intervention impact and understanding coevolving social norms and individual behavior.<sup>54,55,93</sup> Such interventions are a promising avenue in light of their relative effectiveness in changing individual behavior.<sup>94</sup>

Systems models can also be used at the organizational and societal levels to improve our understanding and analyze policy. Integrated systems models are needed to quantify the contribution of candidate obesity drivers within the multitude of economic and environmental factors to individual-level homeostatic, hedonic, and cognitive mechanisms for energy intake and expenditure. From emergence of industry standards and social norms for eating and physical activity to changes in pricing and menu availability, systems models will be needed to understand the coevolution of food supply chains with consumer taste, in which hedonic and cognitive feedbacks are closely interlinked. On the other hand, reliable projections of obesity trends, based on biologically sound

systems models, are needed in diverse applications, such as projecting health care costs or capacity planning for specific health services. Cost–benefit analysis for policy design and evaluation, from school and workplace interventions, to assessing the impact of taxes on high-caloric food, regulations (e.g., restaurant menus, size of sugar-sweetened beverage bottles), and urban planning and transportation system design would all benefit from systems models. These models will provide a reliable link between intervention and its impact on obesity by accounting for both direct (e.g., change in energy intake) and indirect (e.g., intake substitution effects in presence of taxes and changes in movement patterns with new transportation options) influence channels in settings where controlled experiments are infeasible.

## REVIEW

In the same way that a thermostat attempts to control the temperature of a home through operation of heating and air-conditioning systems, body weight has often been thought of as being controlled through operation of a homeostatic feedback control system. However, a heating and air-conditioning system that is sufficiently powered for the year-round climate of Northern California is unlikely to be sufficient to maintain the indoor temperature of the same home in Minnesota or Florida. There is nothing “wrong” with the system; it is merely overwhelmed by its environment.

The majority of human obesity is likely the result of underpowered homeostatic control of food intake in the context of a dramatically changed food environment that is unique in our evolutionary history. Just in the past several

decades, food has progressively become cheaper,<sup>95</sup> fewer people prepare meals at home,<sup>96</sup> and more food is consumed in restaurants.<sup>97</sup> Since the late 1970s, US per capita food availability has increased by approximately 750 kilocalories per day.<sup>95</sup> Interestingly, the current US obesity epidemic can be attributed to each person eating an extra 250 kilocalories per day above the late 1970s levels, which implies that an additional 500 kilocalories per day of the increased food available was wasted.<sup>6</sup>

Because two thirds of the per capita increase in cheap, palatable, and readily available food was not eaten, this may suggest that people’s homeostatic feedback circuits partially resisted the opportunity for overconsumption. Of course, some individuals were more susceptible to the changing food environment than others. Although we cannot definitively rule out the role of deficient homeostatic control of food intake in such individuals, we believe that a more likely explanation lies in their responsiveness to environmental food cues and subsequent eating in the absence of physiological hunger because of the activation of hedonic circuits and an increasingly acceptable and facilitating social context for overconsumption.

A reversal in obesity trends will not be easy or fast. It will require a significant change in many of the inertial environmental drivers. Moreover, the social and environmental balancing feedback mechanisms may slow down such a change. On the other hand, large-scale changes can be accelerated through social contagion feedbacks and transformation of norms facilitated through change agents. Therefore, projecting the future of obesity and developing more effective policies and

interventions can benefit from models that integrate homeostatic, hedonic, and cognitive feedback mechanisms in obesity. Given the relative scarcity of dynamic models of hedonic and cognitive mechanisms, and the multiple interactions among all 3 hierarchical feedback systems, we have argued that developing richer dynamic models to inform science and policy should be a priority in the study of obesity. Despite challenges in its application, systems science modeling has begun to address this need and offers the potential for further insight. ■

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## Proposed Actions for the US Food and Drug Administration to Implement to Minimize Adverse Effects Associated With Energy Drink Consumption

Energy drink sales are expected to reach \$52 billion by 2016. These products, often sold as dietary supplements, typically contain stimulants. The Dietary Supplement Protection Act claims an exemplary public health safety record. However, in 2011 the number of emergency department visits related to consumption of energy drinks exceeded 20 000. Nearly half of these visits involved adverse effects occurring from product misuse.

Political, social, economic, practical, and legal factors

shape the landscape surrounding this issue. In this policy analysis, we examine 3 options: capping energy drink caffeine levels, creating a public education campaign, and increasing regulatory scrutiny regarding the manufacture and labeling of energy drinks.

Increased regulatory scrutiny may be in order, especially in light of wrongful death lawsuits related to caffeine toxicity resulting from energy drink consumption. (*Am J Public Health.* 2014;104:1175–1180. doi:10.2105/AJPH.2014.301967)

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**ENERGY DRINKS THAT ARE** marketed to enhance weight loss and physical and mental performance are sold not as beverages but as dietary supplements. Energy drink consumption is increasingly popular among all age groups, resulting in rising public health concern related to harmful health consequences associated with excess caffeine intake.<sup>1</sup> An upward trend has been noted in the number of emergency department visits related to consumption of energy drinks, which doubled between 2007 and 2011 to reach more than 20 000 such visits.<sup>2</sup> Nearly half of these visits involved adverse side effects occurring from product misuse or abuse, such as combining drinks with prescription

medications, alcohol, or illicit drugs. Up to 50% of children, adolescents, and young adults consume energy drinks, and about half of the caffeine overdoses reported in 2007 occurred among those younger than 19 years.<sup>3</sup>

Energy drink sales account for a large part of the \$7 billion US sports, energy, and weight loss supplement industry, with the global energy drink market expected to reach \$52 billion by 2016.<sup>4,5</sup> These popular products typically contain large doses of taurine, caffeine, and stimulant-rich extracts from guarana and yerba mate.<sup>3</sup> When labeled as dietary supplements, these products can legally circumvent the US Food and Drug Administration (FDA)