The rise of obesogens: could synthetic chemicals be the hidden catalysts of the obesity epidemic?

Abstract

Obesity is a huge problem in both the developed and developing world. Rapidly rising levels of obesity mean that every year, a greater proportion of the population is at risk from diseases such as type II diabetes and various cardiovascular disorders. My ILA aims to explore the role of obesogens, endocrine-disrupting chemicals that contribute to obesity, by examining their impact on factors such as adipocyte differentiation and appetite control which lead to weight gain. Understanding obesogens is crucial for effective policy-making and prevention strategies, although it is evident that factors such as diet and exercise are ultimately more significant, and that tackling the obesity epidemic is an incredibly complex issue which requires the consideration of a broad variety of contributing factors.

1. Introduction: an overview of the obesity epidemic

In 1997, the World Health Organization (WHO) declared obesity to be a global epidemic (1). Since then, numbers have only continued to rise increasingly rapidly. The largest observed increase has been in the US; National Health and Nutrition Examination Surveys (NHANES) have found that the proportion of obese adults in the age range 20-74 has increased from around 14.5% of the population in the period 1976-1980 (2) to 30.5% in the period 1999-2000 (3) – an increase of approximately 110% in only around 20 years. As of 2018, the figure sits at around 42.8%, and by 2030, just under half of all US adults are expected to be of obese weight status (4).

The commonly proposed reason for this astronomic increase, and a fixture of the health and wellness industries, is the concept of 'calories in, calories out'. On the surface, this model of weight gain has its merits – as diets and, more broadly, lifestyles, have shifted in the developed world to favour energy consumption over expenditure, so too has the incidence of obesity dramatically increased (5). At the same time, this concept is insufficient as it massively simplifies a problem rooted within a complex spectrum of socioeconomic factors, belying a huge range of confounding variables such as the quality of those calories consumed as well as a demographic's access (or lack thereof) to good quality food.

It would also be wrong to assume that this problem is limited to developed countries. Whilst the prevalence of obesity is generally lower across African and South East Asian countries, more recent trends show that the mean body mass index (BMI) in many of these developing countries is on a sharp rise, and with it, the proportion of adults and children that are obese (6,7). A case study in The Gambia published in 2020 found that obesity rates in Gambians aged 16 years and over had increased from an estimated 2% in 1996, to a prevalence of 8% in men and 17% in women in recent years, particularly in urban areas (8).

This global rise is of huge concern as there are well-established links between obesity and a huge range of further health complications. Obese individuals are more likely to suffer from a wide range of health complications including (but not limited to): type 2 diabetes; coronary heart disease, heart failure and strokes; respiratory problems such as asthma; weakened immune systems; cancer; and kidney disease (9). This comes not only at a great personal cost for the sufferer, but also as an extreme burden on health services globally – as of 2014, the estimated annual cost of obesity sits at around two trillion dollars, due to the direct costs of healthcare as well as the indirect costs of lost economic productivity (10,11).

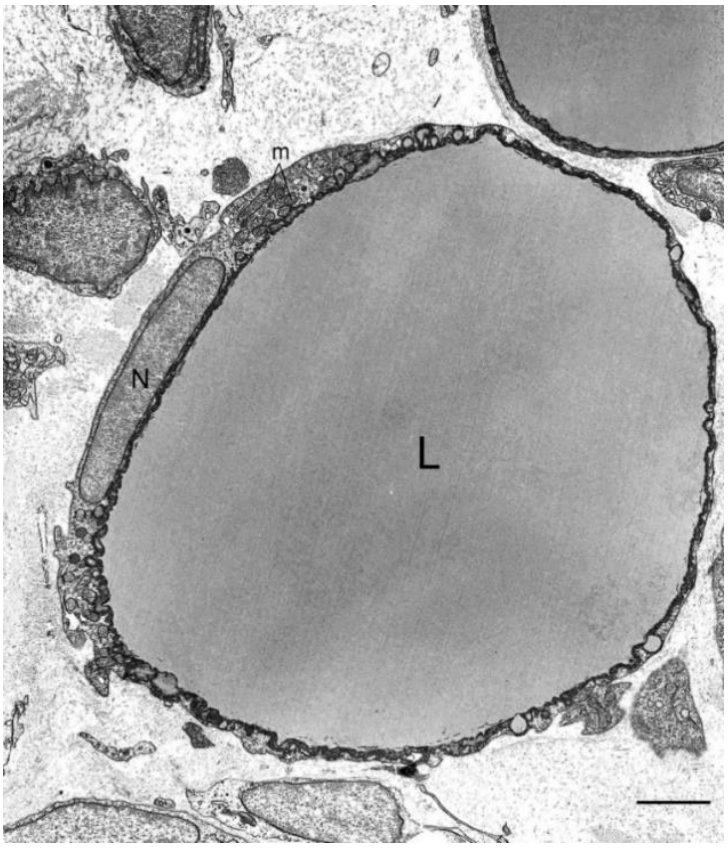
It seems clear that as we have transitioned to an increasingly automatised and sedentary lifestyle, and as the volume of readily available, high-calorie food has increased, the prevalence of obesity has followed suit. However, the question remains; within the complex web of factors and variables responsible for the expansion of this epidemic, could one comparatively inconspicuous factor be driving the increase at an ever faster rate?

2. Introduction to Obesogens

An endocrine-disrupting chemical (EDC), also called an endocrine disruptor, is any chemical, natural or artificial, that can interfere with the endocrine system, usually by mimicking or blocking the action of the body's own hormones (12,13). Just under 1500 potential EDCs have been classified (14), and these come from a wide variety of sources, including pesticides, flame retardants, cosmetics, and compounds used to produce plastics.

The possibility that EDCs may be able to promote obesity in humans was first hypothesised in 2002 by Dr Paula Baillie-Hamilton (15,16), and in 2006 the term 'obesogen' was coined in a paper published by Felix Grün and Bruce Blumberg to describe such a molecule. In the paper, Grün and Blumberg define obesogens as "molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity" (17). In other words, they are substances that promote the differentiation and proliferation of white adipose tissue responsible for the characteristic weight gain seen in obesity.

White adipose tissue (WAT) is made up of white adipocytes, cells responsible for the storage of energy as triglycerides. When the body's energy expenditure requirements outweigh its energy intake, the adipocytes break down the triglyceride store via lipolysis, releasing free fatty acids which can be oxidised readily for the production of large amounts of ATP (18).



(19) *TEM micrograph of a white adipocyte: N is the nucleus, M the mitochondria, and L the lipid droplet*

Much of the WAT is subcutaneous, meaning it is stored under the skin. This allows it to act not only as an energy store but also as heat insulation and a protective buffer against impact. WAT is also present as visceral adipose tissue, which is packed around the intraabdominal organs such as the stomach, intestines, and kidneys (20). However, problems can arise when these cells proliferate too expansively, either through an increase in adipocyte number, called hyperplasia, or an increase in the size of individual adipocytes, hypertrophy (21). The storage capacity of the subcutaneous WAT, the largest depot of adipose tissue, is limited. This means that excess adipose tissue accumulation increases the load of the visceral adipose tissue, and can also lead to fat accumulation in abnormal areas, such as in excessive quantities around the liver and heart (21). A potential consequence of this is the accumulation of toxic lipid compounds in non-adipose tissue which can lead to cellular dysfunction and in some cases cell death, a condition known as lipotoxicity (22).

Furthermore, it has been observed that the proliferation of WAT induces a dangerous inflammatory response (23). In 1994, the discovery of leptin, a hormone secreted by adipose tissue (24) revealed that WAT functions not only as a storage tissue, but also as an active endocrine organ, and in addition to the wide variety of cytokines, hormones, and other products secreted by WAT (jointly referred to as 'adipokines'), when under stress - as they are in the case of obesity - adipocytes secrete inflammatory mediators and chemoattractants such as monocyte chemoattractant protein-1 (MCP-1) (25). These attract and recruit macrophages to the tissue, which themselves secrete, among other things, tumour necrosis factor (TNF-α), a cytokine (also secreted in smaller quantities by stressed WAT) that promotes an inflammatory response, perpetuating the process (26,27). However TNF-α also promotes the phosphorylation of serine, an amino acid, in the protein 'insulin receptor substrate 1' (IRS-1), which inactivates it and hence impairs the insulin signalling pathway (28–30). The culmination of this series of events is that the cells eventually become insulin resistant. As insulin promotes the maturation and proliferation of adipocytes by stimulating triglyceride synthesis and preventing lipolysis (28), the desired effect of inducing insulin resistance may be, in the case of obesity, to try and prevent further accumulation of adipose tissue. However, as discussed earlier, the amount of visceral and ectopic (abnormal) adipose tissue is greatly increased in obese individuals, meaning that important insulin-sensitive tissues, such as muscle tissue, and organs, such as the liver, are exposed to the effects of this insulin resistance as well (29). As a consequence, obese individuals are at a much higher risk of developing type 2 diabetes; in the period 1999-2002, 54.8% of US type 2 diabetics were also obese, and if you include those in the overweight weight category (a BMI greater than 25 (31)), the number rises to 85.2% (32).

From this it can be seen that obesity is characterised by an increase in adipose tissue mass and volume, and that the risk factors associated with obesity stem from this proliferation. Obesogens function by promoting the differentiation and growth of the adipocytes that make up these tissues through a number of different mechanisms, so it is clear why they should be a matter of concern.

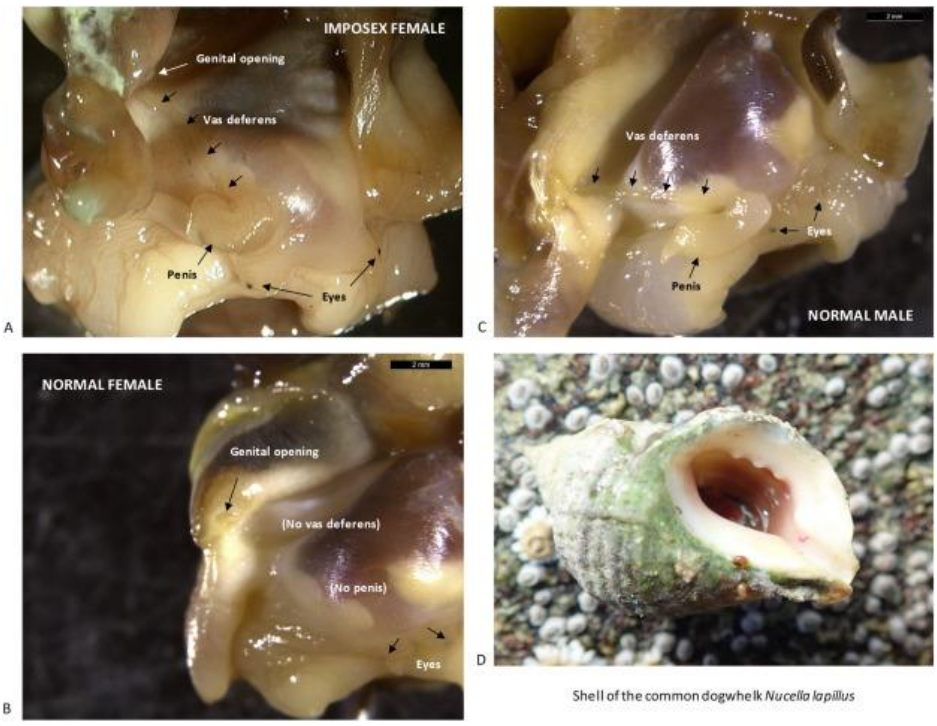
3. Biological mechanisms of obesogens

How exactly do obesogens, generally simple molecules, cause the body to produce abnormal numbers of adipocytes? As a loose definition, the term obesogen encompasses a huge class of different molecules which can function in a multitude of different ways. This sections aims to discuss a few of the most common/well-researched biological mechanisms by which an obesogen may work.

3a. Nanomolar ligand affinity for 'master regulator' nuclear receptors

In the late 1960s, tributyltin (TBT), a toxic biocide, was mixed into paints to function as an effective antifouling agent for ship hulls (33). Discovered in 1954 by a research group from the Netherlands (34), TBT was extremely effective at preventing barnacles and other marine organisms from infesting the bottom of wooden and steel plated boats. However, the TBT slowly leached from the paint into the surrounding marine environments. Due to its relatively long half-life, particularly in anoxic marine sediments, TBT is able to accumulate in ocean floor sediments, only to be released back into the seawater, re-contaminating the area (33). (To be precise, TBT is an umbrella term given to a closely related family of organotin compounds with similar characteristics – the organotin commonly used in hull paints was primarily bis(tributyltin) oxide, TBTO)

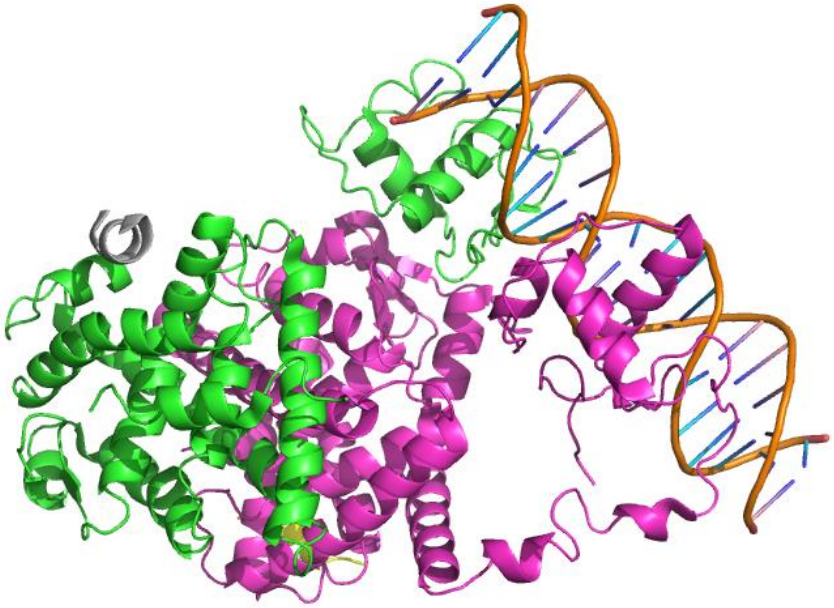
Scientists first began to notice the effects of this TBT contamination in the 1970s, when numerous marine species were observed to have developed abnormal disorders. In particular, scientists noticed a severe decline in populations of the rocky shore sea snail, *Nucella Lapillus,* commonly known as the dog whelk. They found that this decline was due to the masculinisation of female dog whelks, a condition known as 'imposex', which was induced by TBT (35). Imposex females are characterised by the growth of a penis and vas deferens (sperm duct) which, at high enough concentrations of TBT, grew large enough to block the vulva and prevent the release of egg capsules, hence rendering the female sterile (36).



(37) *Photographs showing the development of a penis and vas deferens in imposex female dog whelks*

Further research was carried out on TBT to try and deduce the mechanism by which this could happen, and in the early 2000s Bruce Blumberg (mentioned earlier), whilst in a meeting in Japan, heard about a research group which had found that TBT also caused masculinization in fish (38,39). Hypothesising that the TBT functioned by activating a sex steroid receptor, he conducted his own research, testing to see if TBT activated any known nuclear receptors. Instead, he found that it activated the nuclear receptor 'peroxisome proliferator-activated receptor gamma' (PPAR-γ) (40). Further study showed that TBT is also an agonist to retinoid X receptors, which is theorised to be the mechanism by which imposex is induced in gastropods such as the dog whelk (41,42).

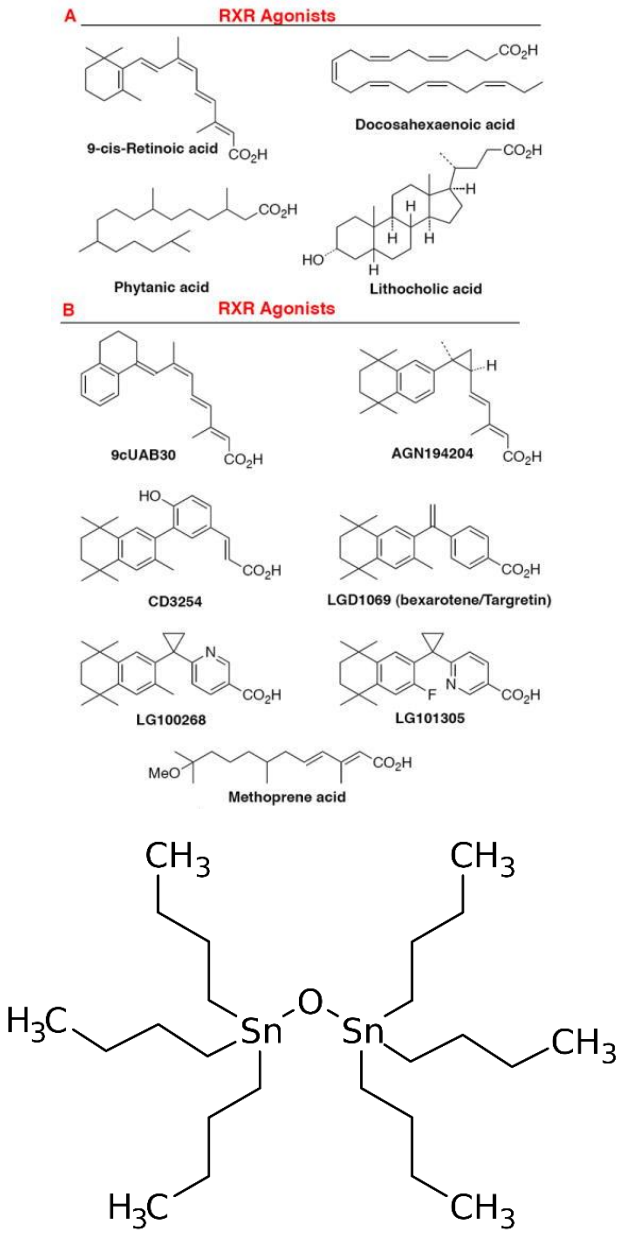
PPAR-γ is a nuclear receptor that is highly expressed in adipose tissue, and has been named the 'master regulator' – in other words, the apex, or most important, factor in a biological regulatory hierarchy – of adipogenesis, the process by which adipocytes mature from stem cells (41,43). It forms a heterodimer with RXR, which when subsequently bound to a ligand, regulates the transcription of target genes. Through an increase in the mRNA expression of genes which promote fatty acid uptake and storage, and a decrease in the expression of genes that induce lipolysis in WAT, the heterodimer stimulates the differentiation of multipotent stem cells and preadipocytes into adipocytes, in addition to increasing the size of existing adipocytes (41,44,45).



(46) *Structure of the PPAR-γ receptor bound to DNA*

Therefore, obesogens such as TBT, which have a high ligand affinity for these particular nuclear receptors may be inducing obesity by acting as agonists to indirectly promote the expression of genes responsible for the differentiation and proliferation of white adipocytes. Animal studies have demonstrated that TBT induces adipogenesis in mice and frogs and that prenatal exposure has a particularly significant effect on adipose tissue accumulation, regardless of normal postpartum diet and exercise (47).

Perhaps the most troubling fact to consider is that, as ligands, organotins such as TBT do not bind in a typical manner, particularly so in RXR activation. Typical RXR ligands have a carboxylic acid functional group, and mimic the structure of 9-cis-retinoic acid. TBT and its associated organotins, put simply, do not follow this trend in the slightest, but nonetheless are potent agonists to both the PPAR-γ and RXR receptors (47). This strongly hints at the possibility that there are a wide range of substances and molecular structures that could have the potential to induce obesogenic effects through similar mechanisms to TBT and so, although TBT may have been the first obesogen to have been identified by Blumberg et al. in their seminal paper from 2006, it is certainly not the only one.



TOP: (48) *chemical structures of several typical RXR agonists;* ***A*** *– natural agonists;* ***B*** *– synthetic agonists. Note the carboxylic acid functional groups, CO_2H, and broad structural similarity to 9-cis-retinoic acid (top left)*

BOTTOM: *the structure of bis(tributyltin) oxide, TBTO, also an RXR agonist, but atypical in terms of functional group and 3D structure*

3b. Appetite and satiety dysregulation

The craving for a sugary snack in the middle of the night, or hunger after a long run, and conversely the feeling of fullness attained after a hefty meal stem from the same area of the brain: the arcuate nucleus (ARC). The ARC is a region of the brain responsible for appetite and satiety (49), and hence controls and maintains energy homeostasis. Neurons that stimulate appetite, such as those that produce neuropeptide Y (NPY) and agouti-related peptide (AgRP) are said to be orexigenic; and those that inhibit satiety (i.e induce an appetite), such as the neurons that produce pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), are anorexigenic (50). These

neurons develop prenatally in a process referred to as neurogenesis (although the occurrence of neurogenesis in adult human brains is hotly contested and is the subject of much research) (51).

Bisphenol A (BPA) is a synthetic compound widely used in plastic manufacturing, predominantly for the production of polycarbonate plastics and epoxy resins used to line food and beverage packaging, and has been in use since the 1960s (52). Many may be familiar with it, as many household appliances and plastic products around today proudly declare themselves to be 'BPA free'. This is due to various health concerns linked to BPA, although the presence of 'BPA free' products may be of little comfort – in a representative sample of the US population, BPA was detected in the urine of over 92% of the participants (53). Despite this, based on the current levels of BPA occurring in foods, the FDA considers BPA to be safe (54) – regardless, a strong case is being made as to the endocrine-disrupting potential of BPA, and it is a strong contender on a growing list of potential obesogens.

Different studies have postulated that BPA may be obesogenic through a variety of mechanisms, but one particular mechanism is through its interaction with neural progenitor cells (NPC), the precursors to neuronal cells, such as the NPY/AgRP orexigenic neurons. Studies conducted on mice suggest that prenatal BPA exposure leads to an increase in unregulated neurogenesis, altering brain structure and function (55–57), and potentially disrupting the balance between appetite stimulators and inhibitors, leading to, later in life, increased food intake and hence weight gain.

BPA is not the only compound theorised to have an impact on appetite. For example, monosodium glutamate, or MSG for short, is a flavour enhancer that is particularly popular in Asia; recently studies have proposed that it may disrupt the secretion of glucagon-like peptide-1 (GLP-1), a hormone that, among other functions, acts in the hypothalamus to promote satiety (58–60). Considering the socio-economic context of the obesity epidemic itself, in the majority of cases, decreased satiety and increased appetite will lead to an increased consumption of cheap and readily available food, sacrificing the quality of the calories consumed for the volume of calories provided; and whilst this mode of action, an indirect exacerbation of the existing factors that have been driving the obesity epidemic, is much less well-researched than the mechanism discussed previously, it seems just as, if not more, worrying.

3c. The search for new mechanisms

The obesogen field is still a relatively novel area of research and study; around 50 obesogens have been identified so far, and the mechanisms for most of them are yet to be determined (61). One growing field of interest is in a transgenerational approach to studying obesogens, as evidence suggests that certain obesogens, like TBT and BPA, can cause effects that are inherited across multiple generations (62). However, gaining a better understanding of factors like the role of epigenetics – a relatively new field itself – in hereditary obesity is essential for further exploring the potential consequences of obesogens.

It is therefore important to keep in mind that, whilst much more is understood now about obesogens than when they were first discovered, there is still much to learn and so at this time, determining the relative impact of such chemicals on a global scale is, to put it mildly, difficult.

4. Epidemiological evidence for obesogens

Some of the mechanisms by which an obesogen may function have been discussed; however, is there sufficient epidemiological evidence to suggest they could be a leading factor in the expansion of the obesity epidemic? The global transition to a much more urbanised lifestyle for most of the developed and developing world, and the accompanying changes in diet and exercise that have followed clearly

correlate with the rising trend in obesity, and so it would be perfectly reasonable to assume that, in comparison to such a huge societal shift, the effect of obesogenic chemicals would be minimal.

Unfortunately, even for TBT, the most well-researched obesogen, epidemiological studies of human TBT exposure are few and far between. This may be due to the difficulty of accurately determining gross exposure to any given chemical: the exposure may occur through multiple routes; the detected concentrations of chemicals with short half-lives will vary significantly over time; and sample contamination during the collection of data can ruin an epidemiological study – in the case of TBT, it was recently shown that plastic containers, widely used in studies on the prevalence of TBT in human specimens, strongly bind organotins themselves, meaning that the estimated organotin levels in the specimens from these studies was most likely significantly underestimated (59,61).

It may be unsurprising, therefore, that perhaps the strongest epidemiological evidence for the impact of obesogens itself predates the obesogen field. Numerous studies have found that, whilst nicotine is an appetite suppressor, there is a strong causal relationship between pregnant smokers and an abnormal rate of weight gain in their corresponding children once born, highlighting the consequences an EDC such as nicotine can have for the development of obesity (16,63).

On the topic of childhood weight gain, trends in the prevalence of childhood overweight and obesity cannot be ignored. In the period 1980-2005, across the school-age population of 25 countries and pre-school populations of 42 countries, an increase in the prevalence of childhood overweight could be observed in almost all countries, with the only exceptions being among school-age children in Russia and Poland in the 1980s (64). This is particularly significant, as the factors typically associated with the obesity crisis, particularly in the west, such as diet and a sedentary lifestyle, are not as predominant for children and infants. Generally, the extent to which one child may be more or less active than another is much less pronounced than between adults, and so this hints that there are external factors at play, especially when accounting for as sharp a rise in childhood obesity as has been observed in the past few years – in 2010, 43 million children under the age of 5 were estimated to be overweight or obese, an increase of 60% in only 20 years (65,66).

Finally, although studies on obesogens in human populations are challenging to effectively carry out, model studies on animals can give researchers indicative and reliable results. Exposing mice, rats and zebrafish to obesogens such as TBT have shown clear evidence of induced weight gain across multiple studies (41,47). Whilst these animals are not perfect models, they are much closer to humans than, say, the molluscs claimed as victims by TBT. All three animals mentioned share roughly 70% of their DNA with humans (67,68), and the mechanisms of adipogenesis and weight gain between these animals and humans are largely evolutionarily conserved (69).

Overall, it does not seem like a stretch to imply that obesogens could likely be playing a role in the accelerated epidemic of obesity.

Conclusion

The field of obesogens, and indeed that of EDCs in general, is still a novel area of research. Whilst it may not currently be possible to arrive at a definitive conclusion as to the magnitude of their impact, the evidence available indicates that they should be a serious cause for concern, and if we want to slow the current acceleration of the obesity epidemic, we need to carefully consider how, going forwards, the potential negative effects of such compounds can be mitigated.

Policy-making plays a crucial role in addressing the obesity epidemic and mitigating the impact of obesogens, and so governments and regulatory bodies need to prioritize the regulation and monitoring of potential obesogens in consumer products, although long-term human studies and further

epidemiological research will be necessary to comprehensively assess the effects of these chemicals on human health and inform evidence-based policies.

Having said that, it also seems apparent that, if a world were to exist where all demographics had access to high quality food, frequent exercise and generally healthy lifestyles, the introduction of obesogenic chemicals at the levels present in our environment would not singlehandedly fuel a global obesity epidemic. I do not believe that the evidence presented denotes that obesogens are the core drivers of the epidemic; rather, obesogens may exacerbate existing problems within urban societies, accelerating an epidemic that has its roots in a much less tangible web of factors.

For this reason, in addition to policy interventions, preventive measures should focus on promoting healthier lifestyles, including balanced diets and regular physical activity. Education and awareness campaigns can help individuals make informed choices and adopt healthier behaviours, and collaborative efforts among healthcare professionals, policymakers, food industries, and communities are essential for effective prevention and management of obesity.

In conclusion, it is clear that no single factor can be held solely culpable for the rapid global rise of obesity. Addressing the obesity epidemic requires a multi-faceted approach that considers the complex interplay of factors influencing weight gain. Understanding the role of obesogens and their mechanisms of action is pivotal in order to develop effective prevention strategies, and as more research becomes available, implementing evidence-based policies, in addition to promoting healthier lifestyles, will be crucial in order to secure a future with reduced obesity rates and improved public health.

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