CHEMTrust

Protecting humans and wildlife from harmful chemicals

Summary & Conclusions

REVIEW OF THE SCIENCE LINKING CHEMICAL EXPOSURES TO THE HUMAN RISK OF OBESITY AND DIABETES

A CHEM Trust report by Miquel Porta and Duk-Hee Lee

CHEM (Chemicals, Health and Environment Monitoring) Trust's aim is to protect humans and wildlife from harmful chemicals. CHEM Trust's particular concerns relate to chemicals with hormone disrupting properties, persistent chemicals that accumulate in organisms, the cocktail effect and the detrimental role of chemical exposures during development in the womb and in early life.

Both wildlife and humans are at risk from pollutants in the environment, and from contamination of the food chain. CHEM Trust is working towards a time when chemicals play no part in causing impaired reproduction, deformities, disease, deficits in brain function, or other adverse health effects.

CHEM Trust is committed to engaging with all parties, including regulatory authorities, scientists, medical professionals and industry to increase informed dialogue on the harmful role of some chemicals. By so doing, CHEM Trust aims to secure agreement on the need for better controls over chemicals, including certain pesticides, and thereby to prevent disease and protect both humans and wildlife.

A CHEM Trust report by

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This is the summary version of CHEM Trust's report, *Review of the science linking chemical exposures to the human risk of obesity and diabetes*. It includes Section 1, which is the Executive Summary, and Section 5, the Conclusions and Recommendations, of that report. The full report is referenced and also includes an Introduction (Section 2) and Sections 3 and 4 on environmental chemicals and obesity, and diabetes, respectively.

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Cover photos clockwise from top left, include pinching side of tummy [Credit: iStockphoto], supermarket + trolley [Credit: iStockphoto], chimney pollution [Credit: dreamstime], fat child [Credit: iStockphoto], 'doabetes' word [Credit: iStockphoto], fat and thin person back to back [Credit: iStockphoto], fat oldies walking away [Credit: iStockphoto], tape measure around fat belly [Credit: iStockphoto].

REVIEW OF THE SCIENCE LINKING CHEMICAL EXPOSURES TO THE HUMAN RISK OF OBESITY AND DIABETES

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Executive summary

It is a commonly held view that obesity is all to do with too many calories taken in and too few expended in exercise, with a genetic predisposition in some individuals. However, a new line of research suggests that exposure to certain man-made chemicals in our environment can play an important role in the development of obesity. While obesity is a known risk factor for diabetes, evidence is growing that chemical exposures are also implicated in diabetes. The epidemiological evidence for a link between chemical exposures and diabetes is stronger than that linking chemicals with obesity.

This review summarises the recent science which suggests that exposure to certain common chemicals is linked with the increasing incidence of obesity and diabetes. The human population is exposed to these suspect chemicals on a daily basis, mostly via food and consumer products.

With diabetes care accounting for around 10% of the total health spending in many EU countries, there is urgent need for action to address the damage to metabolic health caused by exposure to chemicals. Action to reduce chemical exposures is warranted alongside further research, particularly as diabetes incidence

is now increasing alarmingly in the young population.

The role of chemical exposures in obesity

The concern that man-made chemical exposures may be contributing to obesity is based on both laboratory and epidemiological studies. Some scientific studies that support the link between exposure to certain chemicals and obesity are referenced in Table 1, along with indications of how exposure to these chemicals may occur.

Laboratory studies suggesting exposure to certain chemicals impacts on obesity

The evidence that chemical exposures can affect weight gain in animals is compelling. The term "environmental obesogens" refers to man-made chemicals that can disrupt normal controls over adipogenesis and energy balance. Chemicals implicated in causing weight gain have been identified in *in vitro* and/or *in vivo* experiments, and include a variety of chemicals with diverse physical and chemical properties such as persistent organic pollutants (POPs – e.g., dioxins, polychlorinated biphenyls (PCBs) and certain organochlorine pesticides (OCPs), perfluorinated chemicals (PFCs) and brominated flame retardants (BFRs)), bisphenol A (BPA), organotins, diethylstilbestrol (DES), phthalates, organophosphate pesticides, lead, pre-natal nicotine exposure, diesel exhaust and some antipsychotic drugs. Therefore, it is likely that there are other chemicals in the environment that increase the risk of obesity, which have yet to be recognised.

A number of mechanisms have been suggested by which chemicals might contribute to the development of obesity, such as altering homeostatic metabolic set-points, disrupting appetite controls and perturbing lipid homeostasis during development. Even though the fetal period is critical for reprogramming gene expression through epigenetic changes leading to the development of future obesity, exposure to certain chemicals during adulthood can also lead to obesity.

Many of the chemicals that can cause weight gain and related metabolic effects in animals have been noted to have several endocrine disrupting properties. In fact, "environmental obesogens" can be called endocrine disrupting chemicals (EDCs), as they appear to exert their biological effects through binding to various nuclear receptors.

It is very important to recognise that EDCs can have different effects at low doses and at high doses, and can show non-linear dose response relationships. Weight gain due to chemical exposure has been observed with low doses of certain chemicals, while it is well-known that at high doses the same chemicals induce weight loss due to cellular toxicity. For example, *in utero* exposure of female mice to low doses of DES can cause offspring to be obese in adulthood, whereas mice exposed *in utero* to higher doses show weight loss at the same age. A similar pattern is observed with other chemicals.

Epidemiological studies suggesting exposure to chemicals impacts on obesity

There are some data to support the hypothesis that chemicals promote obesity in humans. Human studies have dealt with *in utero* exposure or adult exposure depending on study design. Some human studies suggest that *in utero* exposure to persistent chemicals such as POPs (organochlorine pesticides such as DDE or hexachlorobenzene and PCBs) or passive smoking is linked with future obesity, even though other studies did not replicate these findings. Adult or childhood exposure to some chemicals such as POPs, some phthalates and some pharmaceuticals are linked to obesity. Recent prospective studies have noted that low-dose exposure to persistent chemicals such as dioxins, some PCBs, and organochlorine pesticides during adulthood predicted future obesity.

In conclusion, the concern that chemicals in the environment may be partly responsible for the increasing occurrence of obesity in human populations is based on a significant and growing number of mechanistic studies and animal experiments, as well as on some clinical and epidemiological studies. The weight of evidence is compelling, although ethical and logistic factors have so far made it difficult to prove such associations in human studies.

The role of chemical exposures in diabetes

Type 2 diabetes is characterised by the body becoming more resistant to the action of the hormone insulin (which is secreted by the pancreas and works to balance the body's glucose levels) and pancreatic β-cell insufficiency. It is particularly alarming that the incidence of Type 2 diabetes is increasing in young people as well as in the older generations. Type 1 diabetes is due to an immune attack on insulin-producing cells in the pancreas; it is characterised by low or absent endogenous insulin and has a peak age of onset during childhood. While some researchers have tentatively suggested that both Type 1 and Type 2 may represent a spectrum of disease, this review focuses on the role of environmental chemicals in Type 2 diabetes (referred to as just diabetes in Sections 2 to 5 of this report). This is because little information is available on the relationship between human contamination with chemicals and the risk of Type 1 diabetes.

Laboratory studies suggesting exposure to chemicals impacts on diabetes

Diabetogenic chemicals can be defined in several ways. For example, chemicals causing obesity and insulin resistance could be termed diabetogenic. This type of chemical is discussed in Section 3, which relates to chemicals and obesity. Other diabetogenic agents are chemicals which can cause pancreatic β-cell dysfunction. Based on the available evidence, some chemicals may belong to all these categories while others may belong to just one.

Possible candidate environmental diabetogenic agents include POPs (such as dioxins, PCBs, some organochlorine pesticides and some brominated flame retardants), arsenic, BPA, phthalates, organotins and organophosphate and carbamate pesticides. Table 2 summarises this evidence. It should be noted that diabetes itself has not been caused in animals exposed to these chemicals in laboratory studies, but metabolic disruption closely related to the pathogenesis of Type 2 diabetes has been reported for many chemicals.

For arsenic, *in vitro* and animal studies show that exposure can potentially increase the risk of diabetes through its effects on the inhibition of insulin-dependent mechanisms. Mechanisms of action have yet to be fully elucidated for many other chemicals – but exposure to BPA can, for example, have profound effects on glucose metabolism in rodents. Researchers have shown that in rodents, BPA exposure during pregnancy contributes to insulin resistance (seen in gestational diabetes), obesity in the mothers four months after giving birth, and a pre-diabetic state in offspring later in life. Another recent experimental study in rodents reported that exposure to mixtures of POPs, through contaminated fish oil, induced severe impairment of whole-body insulin action.

Epidemiological studies suggesting exposure to chemicals impact on diabetes

Evidence suggesting a relationship between human contamination with environmental chemicals and the risk of Type 2 diabetes has existed for over 15 years, with the volume and strength of the evidence becoming particularly persuasive since 2006. Chemicals linked to Type 2 diabetes in human studies are POPs (including dioxins, PCBs, and some organochlorine pesticides and brominated flame retardants), arsenic, BPA, organophosphate and carbamate pesticides, and certain phthalates even though not all of them have shown consistent results.

Among them, the most consistent and strong association has been observed with chlorinated POPs. Even though most of these were banned several decades ago in developed countries, the general population is still exposed because they persist in the body and are also still widely found as contaminants in the food chain. The earliest evidence linking exposure to POPs with diabetes came from a series of studies on TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among US Air Force veterans involved in spraying defoliants during the Vietnam War. However, in the general population, organochlorine pesticides or PCBs have shown much stronger associations in many cross-sectional studies. Recent prospective studies mostly confirmed cross-sectional findings although the specific kinds of POPs predicting Type 2 diabetes and the shapes of the dose-response curves varied across studies. Interestingly, in at least one cross-sectional study, obesity was not associated with Type 2 diabetes among people with very low levels of POPs – suggesting that the POPs that have accumulated in adipose tissue, rather than the adiposity itself, play a critical role in the pathogenesis of Type 2 diabetes.

In the case of arsenic, even though studies suggest a possible role for high arsenic exposure in diabetes, inconsistent findings have been reported from community-based studies in low arsenic exposure areas. Human evidence on BPA is limited and inconsistent despite strong evidence from experimental laboratory studies. However, epidemiological studies are often beset with the difficulties of controlling multiple exposures and other lifestyle factors, as well as dealing with issues such as timing and extent of exposure, and ethical issues.

Aim of this report

The aim of this report is to analyse the compelling weight of scientific evidence indicating that chemicals may play a role in causing obesity and diabetes. We hope this review will stimulate informed debate leading to better targeted action and research to prevent both diabetes and obesity; the latter being particularly difficult to treat successfully, while the former can result in increased risks of other serious diseases such as coronary heart disease and blindness.

Conclusions and recommendations

Our conclusions and recommendations are outlined in full in Section 5 of this report, but the overriding conclusion is that given the current epidemics of obesity and diabetes, action to reduce exposures to many chemicals possibly implicated in obesity and, more certainly, in diabetes, is warranted on a precautionary basis.

5 Conclusions and Recommendations

conclusions

Overall conclusions concerning chemicals implicated in obesity and diabetes

- Laboratory and animal research, as well as some epidemiological studies, suggest that human exposure to certain man-made chemicals present in our environment (which includes food) can play an important role in the development of obesity.
- Similarly, evidence is now growing that certain chemicals are also implicated in diabetes, and moreover, the epidemiological evidence of a link between chemical exposures and diabetes is stronger than that linking chemicals with obesity. The chemicals implicated include some to which the general population are typically exposed on a daily basis. Pregnant women, children and adults are exposed mostly via the food chain and consumer products.

Evidence concerning chemicals implicated in obesity

- The evidence that chemical exposures can affect weight gain in animals is compelling. The term "environmental obesogens" refers to man-made chemicals that can disrupt normal physiological controls over adipogenesis and energy balance. Chemicals implicated in causing weight gain have been identified in *in vitro* and/or *in vivo* experiments, and include a variety of chemicals with diverse physical and chemical properties such as POPs (e.g., dioxins, PCBs and certain OCPs, PFCs and BFRs), BPA, organotins, DES, phthalates, organophosphate pesticides, lead, pre-natal nicotine exposure, diesel exhaust and some antipsychotic drugs.
- Substantial evidence exists to consider exposure to EDCs with estrogenic activity as a risk factor in the etiology of obesity and obesity-related metabolic dysfunction.
- There is some evidence to support the hypothesis that chemicals promote obesity in humans. However, the available epidemiological studies do not always report consistent findings and are hampered with the difficulties of controlling for exposure to multiple chemicals and getting good data on exposure, particularly during sensitive time windows. Nevertheless, human studies suggest that *in utero* exposure to certain

POPs (including organochlorine pesticides (e.g., DDE and hexachlorobenzene) and PCBs) or passive smoking are linked with future obesity.

- Adult or childhood exposure to some chemicals such as POPs, phthalates and some pharmaceuticals have also been linked to obesity. The weight of evidence is compelling, although ethical and logistic factors have so far made it difficult to prove such associations in human studies.

Evidence concerning chemicals implicated in diabetes

- Evidence suggesting a relationship between human contamination with environmental chemicals and the risk of diabetes has existed for more than 15 years, with the volume and strength of the evidence becoming particularly persuasive since 2006.
- Chemicals linked to diabetes in human studies are POPs (including dioxins, PCBs, some organochlorine pesticides and some BFRs), arsenic, BPA, organophosphate and carbamate pesticides, and certain phthalates.

The obesity-diabetes link and the role that chemicals in body fat may play

- Obesity is a known risk factor for diabetes, and chemical contaminants accumulated in body fat may play a role in the causal relationship between obesity and diabetes. There is compelling evidence of an association between serum concentrations of some POPs (organochlorine pesticides and PCBs) and diabetes in the general population. Recent studies mostly confirmed this conclusion, although the specific kinds of POPs increasing the risk of diabetes and the shapes of the dose-response curves varied across studies. In at least one study, obesity was not associated with diabetes among people with very low levels of POPs, suggesting that the POPs that had accumulated in adipose tissue, rather than the adiposity itself, play a critical role in the pathogenesis of diabetes.

The suspect chemicals are EDCs

- Many of the chemicals that can cause weight gain and related metabolic effects in animals have been noted to have endocrine disrupting properties. Environmental obesogens are considered to be EDCs, as they have been suggested to exert their biological effects through binding to various nuclear receptors.

The unique properties of EDCs

- EDCs can have different effects at low and high doses, and can show non-linear dose response relationships. Weight gain due to chemical exposure has been observed with low doses of certain chemicals, while it is well-known that at high doses the same chemicals induce weight loss due to cellular toxicity. Embryonic, fetal and infantile stages may be especially vulnerable to obesity from relatively low doses of EDCs. Nonetheless, the risk of obesity due to obesogenic pollutants can also increase during adolescence and adulthood. Most humans are exposed to a mixture of several EDCs and other environmental compounds with toxic properties throughout their entire life, including the critical fetal period.

recommendations

Precautionary exposure reduction to chemicals linked to diabetes and obesity

- Given the current epidemics of obesity and diabetes, and the emergence of this new line of science linking chemicals to obesity and diabetes, action to reduce exposures to such chemicals is warranted on a precautionary basis.

Acting quickly is likely to be cost-effective

- Action to reduce exposures to chemicals suspected of playing a role in obesity and/or diabetes is likely to be cost-effective as these disorders represent an enormous burden in terms of overall health spending and quality of life.

Political action is needed

- National governments and the EU need to urgently put forward mechanisms to identify EDCs to ensure that currently used chemicals suspected of playing a role in obesity and diabetes are substituted with safer alternatives. EU legislation will need to be reviewed with this in mind.

Action is needed at all levels to tackle EDC exposure

- Health professionals, citizens' organisations, companies, authorities and society at large need to be better informed of the role that chemical exposures may play in causing diabetes and obesity. National governments and the EU need to take a lead in providing this education.

- Individuals, industry, the agricultural sector, dieticians and the medical professions all have roles to play in reducing exposures both in the home and in occupational settings.
- Personal changes in lifestyle (e.g., increasing physical activity, lowering caloric intake) are certainly important for the prevention of obesity and diabetes, but this should not obscure the need for government policies within and outside the health sector to decrease human exposure to obesogenic and diabetogenic environmental compounds. Furthermore, as many of the chemicals implicated widely contaminate the animal and human food chains and some are also released from some food containers, dietary interventions ignoring the presence of contaminants in food may hamper the expected beneficial effects of dietary recommendations.
- In order to protect fetuses and newborn babies, specific advice is needed for pregnant women and midwives regarding EDCs in the diet and in consumer products used by pregnant women and/or babies.

Prevention is better than treatment

- Public health policies, including those seeking to reduce exposure to suspect chemicals, need to be implemented swiftly because once diabetes and obesity are established they are almost irreversible. To preserve quality of life, prevention in both cases is vastly preferable to treatment.
- Evidence for the association between exposure to EDCs and obesity should lead to a paradigm shift in how to tackle obesity. The focus should be broadened from one based on individual lifestyle, diagnosis and treatment to one that includes population prevention measures, such as POPs-free food and the elimination of exposure to chemicals implicated in obesity and diabetes.

Exposure data, sufficient funding and international coordination is needed

- Population-based biomonitoring must be strengthened in all EU countries to provide a better understanding of the extent of human contamination by environmental obesogens and diabetogens in the general population.
- Progress is also needed in identifying the sources of exposure (e.g., which food products, which consumer products). Further research is particularly warranted on the role that food additives, contaminants in animal feed and human food, and packaging may play in obesity and diabetes.
- The EU should ensure adequate funding is available for coordinated research to elucidate the role that chemical exposures play in obesity and diabetes, and also to ensure international coordination on this important topic.
- Screens and tests to identify chemicals that can impact on obesity and diabetes should be developed, and certain chemicals should be required to undergo such testing.

Consideration of the developing world

- More attention should be given to protecting populations in the developing world from exposure to environmental pollutants, including that arising from electronic waste, food contamination, air pollution and the erroneous use of certain pesticides.

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