CHEMTrust

Protecting humans and wildlife from harmful chemicals

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.

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This is the full report and further copies of this and a shorter summary version, which includes the Executive Summary (Section 1) and the Conclusions and Recommendations (Section 5), can be downloaded from www.chemtrust.org.uk

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Contents

Acknowledgements ..... **i**

Glossary of terms and list of abbreviations ..... **iii – iv**

1. Executive summary **1– 3**

2. Introduction ..... **4 – 7**

What are obesity and diabetes? 4

Trends in obesity and diabetes ..... 4 – 5

National initiatives and mounting concerns ..... 5 – 6

Human contamination 6

Endocrine disrupting properties of chemicals ..... 6 – 7

3. Environmental chemicals and obesity ..... **8 – 12**

Recent experimental evidence ..... 9 – 11

Human evidence for chemicals playing a role in obesity ..... 11 – 12

4. Environmental chemicals and diabetes ..... **13 – 18**

Arsenic and diabetes ..... 14 – 15

Bisphenol A (BPA) and diabetes 15

Persistent Organic Pollutants (POPs) and diabetes ..... 16 – 17

Other chemicals and diabetes 18

5. Conclusions and Recommendations ..... **19 – 21**

6. References ..... **22 – 25**

Glossary of terms and list of abbreviations

Adipocyte:
a cell specialised in storage of fat.

Adipogenic pathways:
biological and social mechanisms leading to storage of fat and obesity.

Cross-sectional study:
a study that measures the relationship between an exposure and a disease (or another health-related outcome) at one particular time.

Dioxins:
POPs formed during incomplete combustion of chlorinated chemicals; they are highly toxic.

Endocrine disruptors:
exogenous substances that mimic hormones in the endocrine system or disrupt in some way the normal physiological function of endogenous hormones.

Epigenetics:
the study of factors that influence gene expression without altering the genotype; heritable changes in gene expression that do not involve changes in DNA sequence.

Hexachlorobenzene:
a fungicide, formerly used to preserve wood and seeds and in the manufacture of other chemicals, now banned globally under the Stockholm Convention on POPs.

Homeostasis:
physiological processes that maintain the internal environment of the body in balance.

Hyperglycaemia:
abnormally high blood levels of sugar.

Hyperplasia:
enlargement of an organ or tissue from the increased production of cells.

Hypertrophy:
enlargement of an organ or tissue resulting from an increase in the size of its cells.

Insulin:
a hormone secreted by the β-cells of the islets of Langerhans in the pancreas, which controls the levels of glucose in blood by helping the uptake of glucose into cells and by causing the liver to convert glucose to glycogen; in the absence of insulin, glucose accumulates in the blood and urine, resulting in diabetes.

In utero:
a Latin term literally meaning "in the uterus", i.e., "in the womb". Used to describe an event occurring in the uterus of a mammal during pregnancy.

In vivo:
a Latin term literally meaning "within the living", i.e., experimentation using a whole, living organism.

Lipid:
sometimes used as a synonym for fats, a broad group of naturally occurring molecules which includes fats, waxes, fat-soluble vitamins or phospholipids; the main biological functions of lipids include energy storage, as structural components of cell membranes, and as signalling molecules.

Lipid homeostasis:
physiological processes that maintain body lipids in normal equilibrium.

Longitudinal study:
a study in which the factors hypothesised to influence the occurrence of a health outcome are measured at a different time (usually, before) from the outcome.

Nested case-control study:
an important type of case-control study in which cases and controls are drawn from a cohort. A set of controls is selected from subjects (i.e., non-cases) at risk of developing the outcome of interest at the time of occurrence of each case that arises in the cohort.

Odds ratio:
a measure of the risk of disease that a given factor contributes to cause or of the magnitude of some other type of association.

Organochlorine pesticides:
used against insects, the best known representative of this class of insecticides is DDT. Highly hydrophobic (repelled by water, nearly insoluble in water), with excellent solubility in organic solvents, fats and oils. They include atoms of chlorine in their molecular structure.

Persistent organic pollutants (POPs):
Persistent substances which are defined in international agreements, including the United Nations ECE POPs Protocol and the United Nations Environment Program (UNEP) Stockholm Convention on POPs. POPs are typically chemicals that are persistent (P), bioaccumulative (B) and toxic (T), and which can be transported long distances across national boundaries.

Polychlorinated biphenyls (PCBs):
organochlorine compounds and POPs of industrial origin; their production is now banned, but they remain present in many products whose use is permitted (e.g., electric transformers), and they still contaminate many animal and human food chains worldwide.

Pathogenesis:
the mechanism or process by which a disease is caused.

Phthalates:
synthetic chemicals used in formulations and as plasticisers, to make plastics flexible. They have had extensive use in building

materials, medical devices, toys, food packaging, personal care products and insecticides. The "phthalate syndrome", elucidated in laboratory studies, suggest some phthalates can cause decreased sperm count, undescended testes and reproductive tract malformations.

Prospective cohort study:
a study that follows over time groups of individuals (cohorts) with different characteristics and exposures to assess possible causes of health outcomes.

Reverse causality:
a colloquial expression used to refer to apparent but false cause-effect relationships in which the apparent cause is actually an effect and the apparent effect is actually a cause; a problem more common in cross-sectional than in longitudinal studies.

ROS signalling:
reactive oxygen species (ROS) are highly chemically-reactive molecules containing oxygen; they are toxic but also function as signalling molecules (i.e., they are part of the systems of communication that govern basic activities of cells). ROS increase during environmental stress (e.g., exposure to UV or ionising radiation).

Transnonachlor:
an organochlorine insecticide, it arises from the pesticide chlordane, which was used in agriculture in the United States from the 1950s until the 1980s, in homes and for termite control. People are usually exposed to these chemicals by eating food high in fat.

Xenobiotic:
a substance, typically a synthetic chemical, which is foreign to an ecological system or to the body.

Abbreviations

BFR	brominated flame retardant
BMI	body mass index
BPA	bisphenol A
CAS	Chemical Abstracts Service, a division of the American Chemical Society
***p,p'*-DDE**	1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (a major breakdown product of the insecticide DDT)
***p,p'*-DDT**	1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane
DES	diethylstilbesterol (a drug erroneously used to maintain pregnancy)
EACs	endocrine-active compounds
EDCs	endocrine disrupting chemicals
ECAs	environmental chemical agents
EWAS	environmental-wide association study
GWAS	genome-wide association study
HCB	hexachlorobenzene
HDL	high-density lipoprotein (e.g., high-density lipoprotein cholesterol)
HOMA-IR	homeostatic model assessment – insulin resistance
NHANES	National Health and Nutrition Examination Survey (United States)
NIEHS	National Institute of Environmental Health Sciences (United States)
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
OPs	organophosphate chemicals (usually pesticides)
OR	odds ratio (a measure of the magnitude of an association)
PBDEs	polybrominated diphenylethers (flame retardants)
PBT	persistent, bioaccumulative and toxic (characteristics of POPs)
PCBs	polychlorinated biphenyls
PAHs	polycyclic aromatic hydrocarbons
PFC	perfluorinated chemical
POPs	persistent organic pollutants
PPAR	peroxisome proliferator-activated receptors
TBT	tributyltin
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEFs	toxic equivalence factors
WHO	World Health Organisation
OCs	organochlorine compounds (a main type of POPs; e.g., dioxins, DDT, PCBs)

"The rise in the incidence in obesity matches the rise in the use and distribution of industrial chemicals that may be playing a role in generation of obesity, suggesting that endocrine disrupting chemicals may be linked to this epidemic."

The Endocrine Society, founded in 1916, is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. (2009)[1]

The commonly held causes of obesity – overeating and inactivity – do not explain the current obesity epidemic.

Because the obesity epidemic occurred relatively quickly, it has been suggested that environmental causes instead of genetic factors may be largely responsible.

What has, up to now, been overlooked is that the earth's environment has changed significantly during the last few decades because of the exponential production and usage of synthetic organic and inorganic chemicals. Many of these chemicals are better known for causing weight loss at high levels of exposure but much lower concentrations of these same chemicals have powerful weight-promoting actions."

Paula F. Baillie-Hamilton, a leading expert in the field of environmental medicine (2002)[2]

"We must learn to live with uncertainty and to make room for it in policy judgments. This will not be popular.

To seek to limit the hazards for high risk workers and critical population groups is admirable; but for the population as a whole it may have little relevance in circumstances where the dose response curve has no threshold and low-level exposure is widespread. In that case the only effective control is mass control. The problem then arises that an order of risk which might be important for the population is likely to be undetectable.

In that state of uncertainty we have to avoid both the panic of the professional protesters and the unfounded but seemingly unshakeable confidence of the professional experts."

Geoffrey Rose, an eminent epidemiologist whose ideas have been credited with transforming the approach to strategies for improving health (1987)[3]

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

1
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.

2 Introduction

What are obesity and diabetes?

Obesity is the presence of excessive body fat. Obesity has well-known deleterious effects on human health by increasing the risk of various chronic diseases including Type 2 diabetes, cardiovascular diseases, and some cancers. Failure to address the continued increase in obesity could result in an erosion of the health gains observed since the early 20th century.[4]

Diabetes mellitus, which is simply termed diabetes throughout this report, is a disease characterised by high glucose in the blood. Insulin is a natural hormone secreted by pancreatic β-cells to decrease blood glucose levels. It acts by communicating with the skeletal muscle and adipocytes to take up glucose, and with the liver to block glucose production.

Type 1 diabetes occurs when insulin is no longer produced in sufficient quantities due to an autoimmune attack against pancreatic β-cells, and therefore glucose homeostasis is highly disrupted. Type 2 diabetes occurs when cells fail to use insulin properly because of insulin resistance together with an inadequate response of the β-cells. In the early stage of Type 2 diabetes, the predominant abnormality is insulin resistance. At first, high blood glucose is not observed because β-cells can compensate for insulin resistance by increasing insulin secretion or β-cell mass, but insufficient compensation ultimately leads to the onset of Type 2 diabetes.

The major complications of both types of diabetes include cardiovascular disease – not least the high risk of heart attack, blindness and renal failure. While this report touches briefly on Type 1 diabetes, its focus is on Type 2, which is subsequently referred to as just diabetes in Sections 2-5 of this report. Although much more research is still needed on the role environmental chemicals may play in Type 2 diabetes, data relating to Type 1 diabetes are even more scant.

Trends in obesity and diabetes

The rising prevalence of obesity and diabetes is of great public health concern worldwide. Over the last several decades, the prevalence of obesity has risen dramatically, particularly in wealthy, industrialised countries, but also in poorer

developing countries. In the United States, more than 60% of adults are now either overweight or obese.[5] Similar statistics have been reported for many European countries, albeit with considerable geographic variation.[6] For example, in England, 61% of adults and 28% of children were overweight or obese in 2009.[7] It is particularly worrying that the number of children and adolescents who are overweight has risen in parallel with that reported for adults.[8]

Diabetes is a disease strongly related to obesity, and is fast becoming one of the most important worldwide epidemics of the 21st century.[9] For example, diabetes in England more than doubled between 1994 and 2009, to reach a figure of around 1 in 20 people affected.[10] Furthermore, it is also increasingly becoming more common in children, adolescents and young people.[10]

The increase in obesity in the population is usually attributed to excessive intake of calories and decreased physical activity, which are often assumed to be the major root causes. The role of genes in the increasing obesity rates has been the object of intense research.[11] However, the increase in obesity rates is so rapid that it cannot largely be explained by genes, as genetic changes at the population level occur extremely slowly. Although underlying genetic susceptibility can play a role in obesity development in some population subgroups and needs to be considered, the influence of genetic variants in the general population is likely to be small and cannot anyway be changed.

The increasing global prevalence of diabetes is conventionally said to be associated with rising rates of obesity, which are also a consequence of social trends towards higher energy intake and reduced energy expenditure. However, there is a discrepancy between the trends in obesity and diabetes. For example, the prevalence of obesity in the US is about 10 times higher than in Asian countries, but the prevalence of diabetes in the US is not substantially higher than in most Asian counties.[12] At present, rapid change of lifestyles, and a strong genetic susceptibility to diabetes in Asians, characterised by early β-cell failure and prominent central obesity, are hypothesised as main reasons for this discrepancy.[12] However, the changing human exposure to environmental chemicals is little considered.

The currently available knowledge indicates that chemical exposures may be involved in the development of diabetes. This may be secondary to increasing obesity or, as discussed below, chemical exposures themselves may be playing a role in the pathogenesis of diabetes by directly causing insulin resistance and/or pancreatic β-cell dysfunction.

National initiatives and mounting concerns

The US seems to be at the forefront of international activities to elucidate the role chemicals play in obesity and diabetes, although research is also under way in the EU and elsewhere.[13] For example, in January 2011 the US National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences (NIEHS), recognising that there was increasing interest in the concept that environmental chemicals may be contributing factors in the epidemics of obesity and diabetes, held a workshop for invited international experts to evaluate the science associating exposure to certain chemicals with the development of these disorders.[14] Participants evaluated the strengths, weaknesses, consistency and biological plausibility of findings reported by studies in humans and experimental animals for certain environmental chemicals, including arsenic, cadmium, POPs (including PCBs, DDT and DDE), nicotine, BPA, phthalates and organotins. As the workshop proceedings are in the public domain,[14] all its findings will not be repeated here.

Among the chemicals discussed at the workshop, it was concluded that there was sufficient evidence of an association in humans between contamination to POPs and risk of diabetes. The conclusion was based on a review of the evidence summarised in tables,[15] which include population-based cross-sectional and occupational studies as well as prospective studies. The review indicated that the strongest correlations with diabetes are for trans-nonachlor, DDE, dioxins and dioxin-like chemicals, including PCBs. In this report, we will briefly review recent evidence on this important issue.

Furthermore, mindful of the need to find methods to test chemicals for their ability to increase the risk of obesity and diabetes, the US NIEHS has also called for grant applications for the development of screens and tests to identify new environmental chemicals that alter weight gain, insulin sensitivity, glucose tolerance and lipid metabolism (alterations related or indicative of obesity, diabetes and/or metabolic syndrome). A forthcoming report on novel test methods for endocrine disruptors, to be produced under the auspices of the OECD, will also touch on the issue of test methods to identify chemicals which may play a role in obesity and diabetes.

Many countries have already set up task forces or committees to look at how to control the epidemics of obesity and diabetes, but in the EU remarkably little has yet been said on the potential need to control exposure to certain chemicals to reduce the incidence of these disorders. In 2010 in the US, however, the White House Task Force on Childhood Obesity published *Solving the Problem of Childhood Obesity Within a Generation,* its Report to the President which noted that developmental exposure to endocrine disrupting chemicals (EDCs) or

other chemicals possibly plays a role in the development of diabetes and childhood obesity. Furthermore, it recommended that Federal and State agencies conducting health research should prioritise research into the effects of possibly obesogenic chemicals. In addition, it stated that as knowledge accrues, reducing harmful exposures may require outreach to communities and medical providers, and could also entail regulatory action.

In the EU there are several policy initiatives relating to obesity and diabetes – but so far, apart from some research projects, these do not include due consideration of the potential role played by exposure to chemicals. Most notable EU policy initiatives relating to obesity include, but are not limited to, the following:

- In 2005, the launch of the EU Platform for Action on Diet, Physical Activity and Health.
- In 2007, the European Commission adoption of *A Strategy for Europe on Nutrition, Overweight and Obesity Related Health Issues,* a White Paper which is also termed the "Obesity" White Paper (COM(2007) 279 final).
- In 2007, the establishment of a High Level Group on nutrition and physical activity.
- In December 2010, the Commission's first review of the progress made in implementing the "Obesity" White Paper. This noted that the High Level Group on nutrition and the EU Platform for Action on Diet had become central structures for implementing the Strategy, but the negative trends in overweight and obesity were not improving.

Similarly, most notable EU policy initiatives relating to diabetes include, but are not limited to, the following:

- In 2002, MEPs created the EU Diabetes Working Group with the support of the former Health Commissioner, David Byrne. This Diabetes Working Group was officially re-launched in November 2009 on World Diabetes Day, when the urgent need for EU policy action on diabetes, particularly in the fields of research and public health, was highlighted.
- In April 2006, the European Parliament adopted a written declaration on diabetes.
- In June 2006, the EU Health Council in Vienna pledged to tackle the sharp rise in diabetes in the EU, noting that in half the EU countries, governments had no plan or special strategy to deal with the diabetes epidemic.

The need to tackle all possible causal factors in diabetes is underlined by estimates published in 2008 in the UK that some 10% of NHS spending goes on diabetes – which equates to £9 billion a year or £1 million an hour.[16] The proportion of the total healthcare budget estimated to be spent on diabetes in some other EU countries is as follows: Belgium 7%; Czech Republic 15%: Denmark 7%; Finland 11%; France 5%; Ireland 10%; Italy 6%; Lithuania 11%; Poland 8%; Spain 6%; The Netherlands 3%.[17]

Human contamination

In our daily lives, most of us are now exposed to dozens among tens of thousands of chemicals. In the EU, more than 100,000 chemical substances have been reported,[18] and approximately 12,000 new substances are added daily to the American Chemical Society's CAS registry.[19] Although only a proportion of these chemicals is introduced into the environment, comprehensive databases on the hazards posed by many such chemicals are lacking. Compared with high-dose exposure to a few selected chemicals in occupational settings, background exposure in the general population is characterised by low-dose and long-term (lifetime) exposure to a complex mixture of various chemical agents. Since all scientific studies on human chemical contamination focus on a limited set of compounds, it is not possible to state firmly how many chemicals we may accumulate during our lifetime; yet this is of relevance given the increasing health risks that arise with exposure to an increasing number of contaminants, and the interactions among a large variety of compounds. Some studies provide an illustration of the extent of the problem. For example, the *US Fourth National Report on Human Exposure to Environmental Chemicals* has documented a large number of compounds in a representative sample of the general population. [20] A significant number of the chemicals to which most of the population worldwide is exposed are transferred from mother to fetus through the placenta during pregnancy, and subsequently to the baby through breast feeding. This is a particularly vulnerable time of exposure.

Endocrine disrupting properties of chemicals

Many chemicals have endocrine disrupting properties. EDCs are exogenous substances that mimic or disrupt, in some way, the normal physiological function of endogenous hormones.[21] They encompass a wide variety of chemicals, including some used in plastics, cosmetics and other consumer products, pesticides, and other industrial by-products and pollutants. Although some natural products such as phytoestrogens found in plants are also EDCs, this report focuses on man-made chemicals whose presence in human society became generalised after World War II. In most people, exposure occurs largely through dietary intake as EDCs contaminate the food chain,[22] although exposure also occurs directly from several common consumer products.[21]

EDCs can act via a variety of molecular and physiological mechanisms, including binding to receptors, acting either as agonists

or antagonists, or altering hormone synthesis and metabolism. For example, many chemicals to which humans are exposed have now been found to have the ability to disrupt the normal functioning of the sex hormones estrogen and androgen, and the thyroid hormones.[21] Lists of EDCs and information about some screening and testing initiatives to identify chemicals with such properties can be found on the following websites:

http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm

http://www.epa.gov/scipoly/oscpendo/index.htm

http://www.endocrinedisruption.com/endocrine.TEDXList.overview.php

Exposure levels deemed safe are typically based on traditional toxicological assessment methods being applied to the results of relatively short-term toxicity tests in rodents. The assessment of disruption of endocrine regulatory systems requires a different approach.[23] For example, traditional toxicological approaches are inappropriate for revealing outcomes such as "reprogramming" of the molecular systems in cells as a result of exposure to very low doses, particularly during critical periods in development. Changes in cell signalling and gene expression do not always require exposure during fetal development; low-dose exposure for a long time after birth also can lead to changes in cell signalling and gene expression.

One assumption of traditional toxicology is that the dose-response relationship is linear. Results from animal studies which use high doses of chemicals are extrapolated to humans with very low levels of exposure. However, the assumptions that dose–response curves are monotonic and that there are threshold levels (and, hence, safe levels) are often not valid for chemicals with hormonal activity.[23]

Hormones act through binding to specific receptors. In many biological systems relevant to human health, a linearity of dose and receptor occupancy occurs only up to a dose that occupies about 10% of receptors. At higher doses, the effect of higher occupancy rate does not linearly increase as – in the case of estrogens – the dose of hormone increases.[24,25] Furthermore, a linear biological response is observed at a much lower dose than that showing linearity with receptor occupancy.[24,25] However, when exposure to high concentrations occurs (within the typical toxicological range of chemical testing), down-regulation of receptors has been reported through changes of gene expression.[26,27] Thus, high doses of chemicals can exert inhibitory effects on processes that are stimulated at much lower doses, resulting in inverted U dose-response curves. A frequently reported characteristic of EDCs is that they have strong effects at concentrations below the previously identified NOAEL (No Observed Adverse Effect Level).[23] Therefore, there is a misplaced belief that monotonic or linear dose-response relationships are the norm and can be used to predict low-dose effects of environmental pollutants.[23]

The misleading idea that a dose-response relationship must be linear when a causal relationship exists is also sometimes seen in epidemiological research. But chemicals that act as EDCs may show various shapes in their dose-response curves when true causal effects are observed in humans. While experimental studies in animals can intentionally include a broad range of chemical doses in one experiment, in human studies the distribution of each chemical in the study population tends to be restricted. Under the assumption of inverted U dose-response curves, the only situation in which we could observe a kind of dose-response relationship would be in populations with very low levels of the chemical closer to the former part of inverted U. If a population had a distribution of the exposure higher than the former part of the inverted U, we could not observe a dose-response relationship any more. Therefore, human studies on the clinical effects of EDCs can be more valid when performed in populations with low concentrations.

The characteristics of EDCs may therefore contribute to an apparent lack of consistency of results in human studies even though "consistency" of results across human studies is often rightly considered a criterion supporting causality.

In addition, there can be other reasons for an apparent lack of consistency when, in fact, real and relevant causal relationships exist, due to the character and mechanisms of action of EDCs.

First, the most common human exposure scenario is the simultaneous exposure to a substantial number of chemicals, most of them at relatively low concentrations, with the likelihood that these chemicals exhibit complex interactions, such as additivity or multiplicity of some effects. When one specific EDC is studied in humans, findings from two human populations can vary depending on the distribution of other EDCs, even though both exposure level and exposure duration of the specific EDC considered in the two studies are the same. Another important issue is that health effects of EDCs are likely to be dependent on the status of endogenous hormones. Naturally, levels of endogenous hormones and receptor sensitivity are different, depending on the stage of development (e.g., infancy, puberty, age and gender).[28]

3 Environmental chemicals and obesity

In 2002, Paula Baillie-Hamilton proposed a hypothesis linking exposure to chemicals with obesity,[2] and this is now gaining credence. Exposure to low concentrations of some chemicals leads to weight gain in adult animals, while exposure to high concentrations causes weight loss.[2] Historically, the main purpose of measuring the weight of experimental animals was to gather basic information on their general health, and toxicologists were mainly concerned about weight loss as a sign of toxicity; as a result, a significant amount of evidence showing chemicals to cause weight gain has been ignored.[2]

Weight gain effects have been reported in animal studies after exposure at low concentrations to a variety of chemicals, including diethylstilboestrol (DES), organochlorine pesticides (such as DDT, endrin, lindane, and hexachlorobenzene), organophosphates, carbamates, polychlorinated biphenyls (PCBs), polybrominated diphenylethers (PBDEs), chemicals used in plastics such as phthalates and BPA, heavy metals such as cadmium and lead, and solvents.[2] and see Table 1

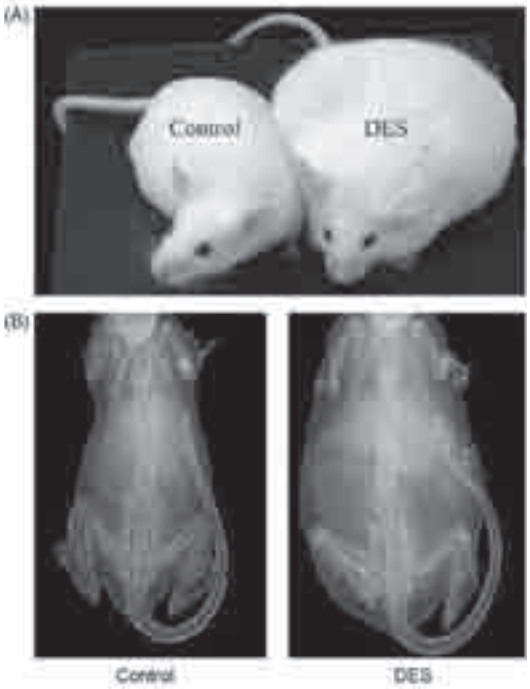

Fig. 1. Control and DES-treated mice. (A) The difference in body size of the two groups at ~6months of age. The mouse on the right had been exposed to 1ug/kg DES. (B) Densitometry images of control and DES treated mice. DES mouse is much larger than the control at 6 months of age. (Photo generously provided by Retha Newbold, National Institute of Environmental Sciences/NIH, Research Triangle Park, NC)

Recent experimental evidence

In 2006, the weight gain effects of chemicals were reformulated under the "obesogen hypothesis", a term coined by Bruce Blumberg.[29] There are numerous recent scientific papers providing experimental evidence of the mechanisms of obesity of various potential obesogenic chemicals.[29-34] As a detailed analysis of biological mechanisms is outside the scope of this report, we will only briefly summarise some findings from recent cell and animal studies.

The obesogen hypothesis essentially proposes that exposure to chemicals foreign to the body disrupts adipogenesis and the homeostasis and metabolism of lipids (i.e., their normal regulation), ultimately resulting in obesity. Obesogens can be functionally defined as chemicals that alter homeostatic metabolic set-points, disrupt appetite controls, perturb lipid homeostasis to promote adipocyte hypertrophy, stimulate adipogenic pathways that enhance adipocyte hyperplasia or otherwise alter adipocyte differentiation during development. [29-34] These proposed pathways include inappropriate modulation of nuclear receptor function; therefore, the chemicals can be termed EDCs.

Embryonic, fetal and infantile stages are especially vulnerable to disruption from relatively low doses of EDCs. Over the last few decades, evidence has been accumulating to show that the risk of developing chronic diseases in adulthood is highly influenced by environmental factors, acting early in life (this is called the foetal origins of adult disease). For example, maternal protein deficiency or under-nutrition, which limits foetal growth leading to a low birth weight, predisposes to obesity and insulin resistance at adulthood.[35] However, in our modern society, poor food availability during pregnancy is not a widespread limiting factor for fetal development. Exposure to chemicals may be more relevant to today's way of life in the developed world. It is plausible that environmental chemicals influence epigenetic processes that play a role in the fetal origins of obesity and insulin resistance. In addition to fetal exposure, the risk of obesity due to exposure to obesogenic chemicals can increase even during adolescence and adulthood. Weight gain effects after chronic treatment with atrazine (a herbicide) or POPs at low doses were also observed in experimental studies on adult animals.[36, 37]

Possible candidate obesogens are displayed in Table 1. As always, extrapolations of *in vitro* and animal findings to humans should be made with caution, because the toxicokinetics and toxicodynamics of the substance in humans may lead to a different outcome from that in animals. Nevertheless, chemical agents do typically behave similarly in different species.[38] Furthermore, in the absence of firm data to the contrary, evidence for adverse effects in animals should be considered as relevant for humans, particularly given the ethical and logistic limitations of studies in human populations. Therefore, regulation may need to proceed on the basis of animal tests.

Possible candidate obesogens encompass a wide range of compounds with different chemical and physical properties. Therefore, it is likely that there are other chemicals in the environment that increase the risk of obesity, which have yet to be recognised. In future it could be useful to develop a methodology to assess the obesogenic potential of a given chemical, similar to the process followed by the International Agency for Research on Cancer (IARC) to assess potential human carcinogens.[39]

Rather than focusing on a specific chemical, it is more reasonable to discuss several common molecular mechanisms which many chemicals share. First, some chemicals that bind to peroxisome proliferator-activated receptor (PPAR) γ can be obesogens as activation of PPARγ has been shown to stimulate adipogenesis *in vitro* and *in vivo*.[68] Examples of PPARγ agonists with confirmed obesogenic effects are tributyltin chloride (TBT),[34] certain phthalates[69] and thiazolidinediones (anti-diabetic drugs).[70] However, not all chemicals that activate PPARγ are adipogenic or correlated with obesity in humans, suggesting multiple mechanisms through which obesogens can target PPARγ that may not involve direct activation of the receptor.[71] Ligand-independent mechanisms could act through obesogen-mediated post-translational modification of PPARγ which cause receptor de-repression or activation.[71]

Second, chemicals with inappropriate activation of estrogen receptors (ER) can be obesogens. At a cellular level, preadipocytes express ERα and ERβ, and during development, estrogens contribute to an increase in adipocyte number, with subsequent effects on adipocyte function.[72] Studies using 3T3-L1 cells suggested that early exposure to chemicals binding to ER may enhance adipocyte differentiation and may permanently disrupt adipocyte-specific gene expression and leptin synthesis.[73] Substantial evidence therefore exists to consider EDCs with estrogenic activity as a risk factor in the etiology of obesity and obesity-related metabolic dysfunction. Some examples of obesogens with estrogen-like activity are DES,[33] BPA,[74,75] and alkylphenols.[76]

Third, EDCs can also induce obesity through modulating the pregnane X receptor (PXR) and constitutive androstane receptor (CAR). PXR and CAR were originally defined as xenosensors involved in regulating the metabolism of xenobiotics and their contribution to fatty acid, lipid and glucose metabolism has only recently been appreciated.[77] In fact, the combined activities of PXR and CAR modify and eliminate nearly all chemicals encountered by the living organism and a variety of EDCs activate PXR and/or CAR. [78] On the other hand, the aryl hydrocarbon receptor (AhR) is also a xenosensor

Table 1: Possible candidate environmental obesogens

Category of chemicals	Examples of chemicals	Usage or exposure route	Evidence suggesting possible obesogenic effects *		
			In vitro studies	Rodent studies	Epidemiological studies†
Persistent Organic Pollutants	Dioxins	They are by-products of incomplete combustion, found as food contaminants at generally low concentrations.			41
	PCBs	Now banned but still a legacy from past use. Common in fatty foods at generally low concentrations.	42	42	41,43
	Organochlorine pesticides (DDT, hexachlorobenzene etc.	DDT now banned in agriculture, but metabolites are still found in EU, US and other populations. DDT is currently used for malaria control in tropical areas. Hexachlorobenzene was used as a fungicide but is now banned.		2	41, 43, 44
	Atrazine	Banned in EU, but still one of most widely used herbicides in the world.		36	
	Perfluorinated Chemicals (PFCs)	Used for water-proofing and for stain resistant properties. Some are now highly regulated, but very persistent in humans, so widespread exposure exists. PFOA has been measured in carpeting, textiles, food contact paper, dental floss and at very low levels in non stick cookware.		45, 46	47
	Polybrominated diphenyl ethers (PBDEs)	Were used as flame retardants in some consumer products, including electronic equipment. Penta-BDE was used in foam found in car seats.		48	
Short-lived, but ubiquitous chemicals	Bisphenol A	Can leach from food can liners and from polycarbonate plastic into food. Used for thermal paper till receipts and lottery tickets.	32	32	
	Phthalates	Plasticisers in plastics such as PVC. Used in bathroom flooring, shower curtains, garden hoses etc. Also found as contaminants in food.	49		50, 51
	Polyphenols	Surfactants widely used in detergents, emulsifiers, antistatic agents, demulsifiers, and solubilisers and are found commonly in wastewater.	52		
	Organophosphate pesticides (parathion, malathion, chlorpyrifos, diazinon, dichlorvos)	Pesticides with short half lives.		55	
Metals	Organotins, e.g. TBT	TBT has been used extensively in antifouling paints. It is an impurity in tetrabutyl tin used in the synthesis of organotin stabilisers, and an impurity in dibutyl tin used mainly as a PVC stabiliser. Triphenyltin (TPT) has been used as a pesticide.	32	32	
	Lead	Typical levels have decreased since its use in petrol and paints was banned. Still found in some drinking water, where it originates from lead pipes or solder.		56	57
Pharmaceuticals	Diethylstilbestrol (DES)	Now banned. Was erroneously used to maintain pregnancy.		58	
	Some antipsychotics	Used in mental health conditions.		59	60
	Thiazolidinediones	Used to treat diabetes.		61	61, 62
Air pollution	Pre-natal maternal smoking, pre-natal nicotine exposure			63	64, 65, 66
	Diesel exhaust	Heavy vehicles and cars running on diesel fuel.		67	

*Whenever there are comprehensive review articles, we referred to them, rather than list all individual articles.
†As there was a wide range of quality in evidence from epidemiological studies, and those studies have not shown consistent results, each individual study should be carefully evaluated.
Where a family of chemicals is referred to, the evidence may relate to one or more of the chemicals in that family group.

binding to a wide range of chemicals, in particular those that are dioxin-like. AhR agonists can be obesogens by cross-talk with ER[79] or PPARγ.[40]

Finally, there can be other mechanisms, such as inappropriate activation of the thyroid hormone receptor (TR). Thyroid hormone levels accelerate metabolism, increase lipolysis and provoke weight loss, while the opposite results are observed in decreased thyroid hormone levels. Therefore, EDCs that interact with TR can be obesogens. For example, BPA may act as an antagonist of the TR pathway.[80]

Human evidence for chemicals playing a role in obesity

While substantial laboratory evidence shows chemicals can affect weight gain in animals and therefore supports the hypothesis that EDCs promote or otherwise influence obesity (see Table 1 above), the evidence in humans is still limited.[51] When human studies are classified into *in utero* vs. adult exposures, the former studies were prospective and mainly focused on persistent chemicals while the latter studies were cross-sectional or prospective and dealt with persistent or non-persistent chemicals.

Findings from epidemiological studies on the effects of *in utero* exposure to environmental pollutants on body weight and size varied from negative to positive associations, depending on the chemical.[51] Some studies have reported positive associations with inadvertent exposure to chemicals. For example, *in utero* exposure to organochlorine pesticides such as DDE or hexachlorobenzene has been associated with future obesity,[44,81-84] but other studies did not replicate these findings.[85-87] Also, positive associations tended to be different in subgroups, particularly by gender.[51] Mixed results have also been reported for PCB exposure in relation to body mass index (BMI).[44,81,84,88] Smoking in pregnancy has been associated with giving birth to offspring more likely to put on excess weight as they grow up.[65,66] To the best of our knowledge, as yet there has been no study in humans on the effects of *in utero* exposure to non-persistent chemicals, such as BPA or phthalates. Given the ubiquitous exposure of pregnant women to these chemicals, such studies are now warranted.

The epidemiological literature on exposures during adulthood has recently increased. Positive cross-sectional associations of serum concentrations of some POPs (such as DDT or dioxins) with adiposity were reported in the US general population,[89,90] but again they differed by gender. As mentioned before, differences and inconsistencies in results by gender or other characteristics are to be expected when different risk factors are measured in the studies under comparison, and when different measured and unmeasured interactions influence the outcome of interest.

The interpretation of cross-sectional studies showing associations between serum concentrations of persistent chemicals such as POPs and adiposity is problematic because adiposity itself delays the metabolism of these chemicals and prolongs their half-lives.[91] However, there are data which strongly support cross-sectional findings of a relationship between POPs and obesity. For example, one prospective study of 90 subjects who were diabetes-free during 18 years of follow-up observed that some POPs (including *p,p'*-DDE and PCBs) predicted the future risk of obesity.[43] It is important to note that the dose-response curves between serum concentrations of some POPs and BMI were exactly inverted U-shaped: as serum concentrations of POPs at the baseline increased, BMI increased until a critical low dose; above this dose, BMI did not increase, and it even started to decrease as serum concentration of POPs increased. This shape of the association confirms what had been expected from experimental studies on EDCs in animals. Another prospective study among the elderly reported positive associations between levels of the less chlorinated PCBs, p,p-DDE or dioxins and abdominal obesity, while the highly chlorinated PCBs inversely predicted future risk of abdominal obesity.[41]

Concerning non-persistent but ubiquitous compounds, some metabolites of phthalates were positively associated with adiposity, even though the associations were also different depending on gender and age.[50,51] However, the concentrations of phthalates in serum or urine primarily reflect recent exposure, making the interpretation of cross-sectional findings more difficult.

Even though population-based studies in humans are essential to confirm the relevance of environmental obesogens, testing hypotheses on the relationships between chemical exposures and obesity in humans is particularly difficult because of the major roles that both diet and physical activity play in obesity. Even when sophisticated statistical adjustments are applied, the strong effects of diet and physical activity on obesity may not be completely eliminated because of measurement errors in estimating calorie intake and physical activity in human beings. An additional difficulty stems from the fact that humans are exposed to many chemicals *through* the diet. Thus, higher food consumption can lead to both obesity and increased body levels of chemicals. Furthermore, as humans are exposed to a mixture of many chemicals, some of which are suspected to be obesogens, a human study focusing on one or several chemicals (depending on feasibility and researchers' interests) may not provide a sufficiently valid, comprehensive or relevant answer. Even when the results are positive, we cannot be fully sure whether the measured chemicals are really the culprits, or whether unmeasured but

highly related other chemicals are to blame: body levels of POPs and other environmental pollutants are often highly correlated. In epidemiological studies it may be difficult or impossible to disentangle the specific contribution of each of many factors; yet epidemiological studies are the only option to study human beings living under real-life conditions.

As previously mentioned, experimental studies in animals showed weight gain effects of chemicals at low doses, and it is also well-known that exposure to high doses of some of the same chemicals lead to weight loss. In spite of this, previous epidemiological studies did not consider these relationships in data analyses and interpretation. As previously highlighted (see Section 2.5), even when non-linear relationships are carefully considered, various plausible scenarios may exist in which the low dose effects of chemicals in humans would be apparent, depending on the distribution of the concentrations of the chemical. Thus, in some circumstances, human studies on the clinical consequences of EDC exposure may be more validly performed among populations with low concentrations of compounds.

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.

4 Environmental chemicals and diabetes

A causal role of obesity in diabetes is well-established by the fact that weight reduction is associated with a decreased incidence of diabetes in many studies.[105] For example, weight loss following bariatric surgery (e.g., gastric band surgery) in morbidly obese patients with diabetes may lead to a reversal of the pathophysiology, and to the subsequent resolution of diabetes.[106] Nevertheless, there is evidence that chemical exposures also play a role.

Evidence suggesting a relationship between human contamination with environmental chemicals and the risk of diabetes has existed for over 15 years, with the volume and strength of the evidence becoming particularly persuasive since 2006, as shown below. Some of the most interesting studies with mechanistic and animal data suggesting that environmental chemicals play a role in the etiology of diabetes are summarised in Table 2.

When interpreting the table it is important to keep in mind that diabetogenic agents can be defined in several ways. For example, chemicals causing obesity and insulin resistance could be termed diabetogenic. This type of chemical was already discussed in the previous Section on chemicals and obesity. Other diabetogenic agents are chemicals which can cause pancreatic β-cell dysfunction. A recent review article summarised the known effects of several chemicals on β-cell function with reference to mechanistic studies that have elucidated how these compounds interfere with the insulin-secreting capacity of β-cells.[92] Based on available evidence, some chemicals may belong to all of these categories while others may belong to one of them. Furthermore, as always, it is essential to assess whether those used in experiments are relevant to actual levels of contaminations in humans. In the case of epidemiological studies, there is a wide range in the quality of the evidence. In future it could be useful to develop a methodology to assess the diabetogenic potential of a given chemical agent similar to the process followed by IARC to assess potential human carcinogens.[39]

Table 2: Possible candidate environmental diabetogenic agents

Category of chemicals	Examples of chemicals	Evidence suggesting effects on risk of Type 2 diabetes		
		In vitro studies	Rodent studies	Epidemiological studies†
Persistent organic pollutants (POPs)	Dioxins	92-94	92, 94, 95	92, 94, 96
	PCBs	37, 92, 94	37, 94	92, 94
	Organochlorine pesticides (DDT, Chlordane, etc)	37, 94	37, 94	92, 94
	Polybrominated diphenyl ethers		97	92
	Atrazine		36	98
Short-lived, but ubiquitous chemicals	Bisphenol A	1, 94	1, 94	1, 94
	Phthalates		99	50, 92
	Organophosphate and carbamate pesticides	92, 94, 100	92, 100	98, 101
Metals, elements	Arsenic	92, 102	92, 102	92, 102
	Cadmium	92, 103	92, 103	
	Mercury	92, 103	92, 103	
	Nickel	92, 103	92, 103	
	Organotins, e.g. TBT		104	
Cigarette smoking	Pre-natal maternal smoking, pre-natal nicotine exposure		63	

*Whenever there are comprehensive review articles, we referred to them, rather than list all individual articles.
†As there was a wide range of quality in evidence from epidemiological studies, and those studies have not shown consistent results, each individual study should be carefully evaluated.
Where a family of chemicals is referred to, the evidence may relate to one or more of the chemicals in that family group

Among the chemicals listed in the Table 2, we will discuss POPs, BPA and arsenic in detail because they had substantial evidence from both experimental and human data. However, before discussing these chemicals, it is worthwhile to discuss some common mechanisms which many chemicals share.

Many chemicals act as EDCs, disrupting estrogen, and therefore they can generate a pregnancy-like metabolic state characterised by insulin resistance and hyperinsulinemia through acting on insulin-sensitive tissues and on β-cells.[94] Adult exposure in mice produces insulin resistance and other metabolic alterations; in addition, during pregnancy, EDCs alter glucose metabolism in mothers, as well as glucose homeostasis and endocrine pancreatic function in offspring.[94]

Even though EDCs with estrogenic activity have been most widely studied in experimental studies, there are numerous possible other mechanisms, and certain chemicals may be simultaneously active on several biochemical pathways. Laboratory studies suggest that many hormone disrupting chemicals, and the sites they bind to in the body, may be involved in metabolic disruption, not just sex hormone disruptors. Other receptors that are coming to the forefront in research include PXR (pregnane X receptors), CAR (constitutive androstane receptors), AhR (aryl hydrocarbon receptors), GR (glucocorticoid receptors) and PPAR (peroxisome proliferator-activated receptors). For example, PXR, CAR and the AhR act as sensors that regulate the metabolism of pollutants, which is one way by which an organism protects itself from toxic chemicals; in addition, chemicals that bind to these receptors (including many hormone disruptors) can alter lipid and glucose metabolism.[78]

Given that several lipophilic EDCs with properties that induce insulin resistance have accumulated in adipose tissue, their release from adipocytes must be considered a potential factor linking obesity and insulin resistance.[94] Furthermore, these lipophilic EDCs might explain why not all obese individuals have insulin resistance (the "metabolically healthy obese"), and why some individuals with normal weight have insulin resistance, diabetes and other metabolic problems (the "metabolically obese with normal weight").

Arsenic and diabetes

Arsenic is abundant in the Earth's crust and can be released into groundwater under certain conditions. People can be exposed to arsenic from food and water as well as via inhalation; for example, from breathing sawdust or smoke from arsenic-treated wood, or from the burning of arsenic-rich coal. In pregnancy, arsenic readily crosses the placental barrier. Human biomonitoring studies tend to report

total arsenic, but it is important to identify how much intake is from inorganic arsenic because the organic form, mostly found in seafood, is not considered to be of toxicological significance.

Arsenic was first significantly linked to diabetes in Taiwan and Bangladesh, where high levels are present in the drinking water. An increased prevalence of diabetes has consistently been observed among residents in the high arsenic exposure areas in Taiwan and Bangladesh, showing a dose-response relationship with arsenic levels in drinking water.[107,108] However, inconsistent findings have been reported from community-based studies in low arsenic exposure areas, including the US general population.[109-113] Systematic reviews of the literature suggest a possible role of high arsenic exposure (>500 ug/L) in diabetes.[102]

In vitro and animal studies highlight the fact that arsenic exposure can potentially increase the risk of diabetes through its effects on the inhibition of insulin-dependent glucose uptake[114] and insulin signalling,[115] impairment of insulin secretion and transcription in pancreatic β-cells,[116] and modification of the expression of genes involved in insulin resistance.[117] However, the concentrations used in most mechanistic experiments are much higher than concentrations seen in humans, and the observed effects may not be applicable to populations chronically exposed to arsenic via the environment.[102,109] One recent experimental study using very low levels of arsenic reported that these low levels provoke a cellular adaptive oxidative stress response that increases antioxidant levels, dampens ROS (reactive oxygen species) signalling involved in glucose-stimulated insulin secretion, and thus disturbs β-cell function.[118] Cellular adaptive oxidative stress response is a natural human response to xenobiotics, not confined to arsenic; thus, if this mechanism is true, similar β-cell dysfunction may be observed with other xenobiotics, not only arsenic.

When thinking about diabetogenic effects of environmental chemicals, it is relevant to keep in mind that arsenic can act as a potent EDC that can affect the function of five steroid hormone receptors (namely the receptors for glucocorticoid, androgen, progesterone, mineralocorticoid and estrogen hormones), as well as the function of related nuclear receptors for thyroid hormone and retinoic acid. These effects were observed at levels of 0.01 to 2.0 (micromolars/pbb) in cell culture, and at or below 10 ppb in several animal models.[119]

Bisphenol A (BPA) and diabetes

BPA is a man-made compound that has endocrine disrupting properties.[120] Generalised and continuous human exposure to BPA occurs through drinking water, the use of polycarbonate plastic in babies' feeding bottles, dental sealants, some toys, dermal exposure and inhalation of household dust. BPA is one of the world's highest production volume compounds.[120]

In rodents it has been demonstrated that small doses of BPA have profound effects on glucose metabolism, and this altered blood glucose homeostasis may enhance the development of diabetes.[120] BPA is believed to exert its biological effects by modulating the estrogen receptor, although it also has other endocrine disrupting properties.[120] Animal experiments indicate that four days' exposure to a dose of BPA twice the dose considered safe every day by the EU Food Safety Authority (50ug/kg/day) led to deleterious effects on energy balance and glucose homeostasis.[121,122] A recent rodent experimental study observed that BPA exposure of 10~100 ug/kg/day during days 9~16 of gestation contributed to the development of gestational diabetes, obesity and a pre-diabetic state in the mother later in life.[123] Also, *in utero* exposure to BPA at 10ug/kg/day was associated with decreased glucose tolerance and increased insulin resistance in male offspring at six months of age compared with controls.[123] However, in the same study, animals exposed *in utero* to a higher dose of BPA (100ug/kg/day) showed different metabolic effects, compared with those exposed to 10ug/kg/day of BPA: although glucose intolerance was present, it was mild; insulin sensitivity was the same as among the control animals, and pancreatic β-cells had a tendency to decrease glucose stimulated insulin secretion.[123] On the other hand, another experimental study in mice, which looked at perinatal exposure to a much lower dose of BPA (0.025ug/kg/day), did not support this hypothesis.[74]

Despite strong evidence from some experimental studies, evidence in humans is limited. In a cross-sectional analysis of the US general adult population (using data from the 2003-04 NHANES study), subjects reporting diabetes had higher concentrations of BPA in urine.[124] However, in a subsequent study using more recent 2005-06 NHANES data, the researchers failed to find statistically significant associations with diabetes, although pooled estimates remained significant.[125]

A good example of the methodological challenges that studies in humans need to solve is that a single urine sample from an individual is unlikely to be a valid measurement of a subject's exposure history. Once ingested, BPA is metabolised to form a highly water-soluble metabolite, and in adults the half-life is estimated to be about 5-6 hours.[126] Therefore, a single measurement of the concentration of BPA mainly reflects recent exposure; the causal significance of such studies is thus unclear, since an effect of BPA on diabetes risk is likely only after chronic exposure. No prospective human study of BPA has yet been reported.

Persistent Organic Pollutants (POPs) and diabetes

Human exposure to POPs includes a large variety of chemicals that are resistant to environmental degradation and which bioaccumulate in human and animal tissues, biomagnify in food chains, and have impacts on human health and the environment.[127] Thus, POPs are defined by international institutions as chemicals that are persistent (P), bioaccumulative (B) and toxic (T) (i.e., PBT), and which can be transported long distances across national boundaries. Many POPs were used as pesticides, and these include aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, hexachlorobenzene, mirex and toxaphene. Other POPs are industrial chemicals or by-products and these include PCBs, dioxins, furans, polycyclic aromatic hydrocarbons (PAHs), and some fluorinated compounds and brominated flame retardants. Organometallic compounds such as TBT and triphenyltin also have PBT characteristics.

The most problematic chlorinated POPs were banned several decades ago in most developed countries. However, exposure to banned POPs in the general population still occurs because they still widely contaminate animal and human food chains (usually at low levels, but with occasional episodes of massive contamination); in most people the main route of exposure is the diet. Once present in human body fat (and organs rich in lipids, such as the nervous system), POPs are slowly but continuously released from adipose tissue into the circulation. Therefore, POPs stored in the body are a source of continuous internal exposure. One of the main consequences of the fact that many POPs are highly lipophilic (soluble in lipids) is that they can diffuse readily across cell membranes and hence gain access to nuclear receptors and DNA.

The earliest evidence linking exposure to POPs with diabetes came from studies on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). There is a consistent finding of a slight increase in diabetes incidence among subjects with elevated serum TCDD concentrations, as well as abnormal glucose and/or insulin levels among subjects who were exposed to TCDD.[130] Notably, a series of epidemiological studies on US Air Force veterans involved in spraying defoliants during the Vietnam War led to a report by a committee of the National Academy of Sciences' Institute of Medicine, which concluded that there was suggestive evidence of an association between dioxin exposure and diabetes.[131]

Interestingly, in early epidemiological studies on TCDD, dose-response relationships tended to be more clearly observed among US Air Force veterans with relatively low concentrations of TCDD than among workers occupationally exposed to high doses of TCDD.[130] A molecular epidemiological study among US Air Force veterans of the Vietnam War observed that the GLUT4:NFkB ratio, a marker for the diabetogenic action of dioxin, showed significant correlations with serum dioxin residues and with fasting glucose among veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam. Surprisingly, the associations were also observed among members of the comparison group, who had low levels of dioxin (comparable to those of the general public).[132] Such an association in the comparison group was particularly significant among individuals with known risk factors, such as obesity and family history of diabetes.[132] This fact strongly suggests the need for epidemiological studies in the general population, and the importance of accounting for known risk factors for diabetes.

In the past few years, there have been numerous cross-sectional studies and a few prospective studies on serum concentrations of several POPs and diabetes in the general population of different countries (notably in the US, with few studies from Europe). The most compelling evidence was observed in a series of cross-sectional studies in the US using National Health and Examination Survey (NHANES) data. For example, when a summary measure of six POPs (which were most commonly detected in this general population) was used, the adjusted odds ratios (the common estimate of the relative risk) for diabetes across quartiles of the summary measure were 1.0, 14, 14.7, and 38.3.[133] Strikingly, in this study obesity was not associated with diabetes among people with very low levels of POPs; and diabetes itself was very rare even among people with BMI>=30kg/m^2 (Figure 2).[133] These findings suggest that the POPs that have accumulated in the adipose tissue, rather than the adiposity itself, play a critical role in the pathogenesis of diabetes.[134,135] In subsequent studies among non-diabetics using the same NHANES dataset,[90,136] serum concentrations of some POPs were associated with insulin resistance and metabolic syndrome, which are commonly regarded as clinically significant components of a pre-diabetic status.

Using the NHANES data sets, different researchers have analysed the risk of diabetes and specific environmental chemicals (e.g., arsenic, BPA or POPs), focusing on one or a few chemicals at a time. By contrast, one recent study performed multiple cross-sectional analyses associating 266 unique environmental factors with diabetes; it is an innovative Environmental-Wide Association Study (EWAS), analogous to a Genome-Wide Association Study (GWAS).[137] The most significant associations were with organochlorine pesticides and PCBs.

Recent prospective studies[138-141] mostly confirmed the findings from cross-xal studies, although the specific kinds of POPs predicting diabetes and the shapes of the dose-response curves varied across studies. For example, a prospective study in a cohort of Great Lakes sport fish consumers in Michigan demonstrated a strong

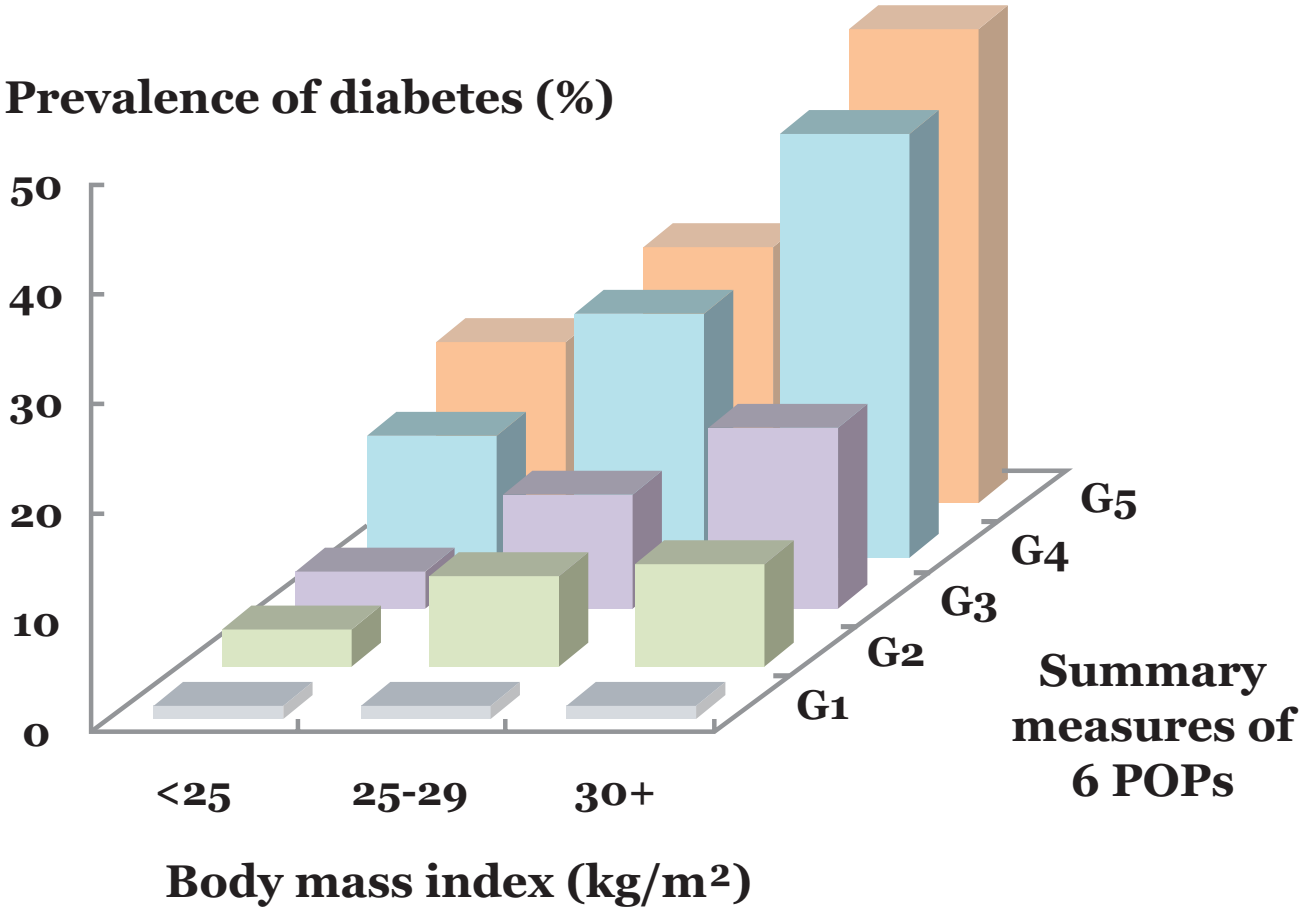

Figure 2. Interaction between obesity and persistent organic pollutants (POPs) on the prevalence of Type 2 diabetes in the US general population.[133] The height of each column reflects the prevalence of diabetes in each population group. The summary measure of six POPs (1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin; 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin; PCB153; p,p'-DDE; oxychlordane; and trans-nonachlor) was calculated by summing their individual ranks. The summary measure was classified into five quintiles, from G1 (the lowest) to G5 (the highest). Among people with lower concentrations of the summary POPs (G1 row), the frequency of diabetes did not increase with increasing BMI, and diabetes was very rare (even among people with BMI>=30kg/m²). Furthermore, the frequency of diabetes increased with rising concentrations of POPs, even among people with low BMI (<25).

association of incident diabetes with p,p'-DDE, but not PCBs.[141] Similarly, in a nested case control study among a cohort of Swedish women, p,p'-DDE was also a risk factor for developing diabetes later in life, but not PCB153.[140] However, in a nested case-control study performed in young adults within the Coronary Artery Risk Development in Young Adults (CARDIA) cohort, trans-nonachlor and highly chlorinated PCBs predicted diabetes while p,p'-DDE did not.[139] In a prospective study among the elderly in Sweden,[138] both moderately and highly chlorinated PCBs and trans-nonachlor strongly predicted future risk of diabetes, but the association between p,p'-DDE and diabetes was not as strong as seen in the Michigan study.

One recent experimental study confirmed a causal relationship between POPs and obesity-related metabolic dysfunction such as insulin resistance in rats.[37] Exposure to POP mixtures through contaminated fish oil induced severe impairment of whole-body insulin action (e.g., significant inhibition of insulin-dependent glucose uptake); and it contributed to the development of abdominal obesity and hepatosteatosis (fat in the liver). In particular, when adipocytes were incubated with different POP mixtures, the insulin action was dramatically reduced with both the mixture of organochlorine pesticides and DDTs. POPs also changed the functioning of genes that are important regulators of lipid homeostasis. Interestingly, impaired insulin action was observed with one nanomolar of mixed POPs, and there were no clear further effects on insulin action with ten or hundred times higher concentrations of mixed POPs, suggesting low dose effects.

Other chemicals and diabetes

Besides organochlorine pesticides, there is also substantial evidence linking the effects of pesticides such as organophosphates and carbamates on glucose and lipid metabolism through various mechanisms.[100] Organophosphates and carbamates exhibit this effect through inhibition of acetyl cholinesterase or by affecting target organs directly. Also, these pesticides induce cellular oxidative stress via an effect on mitochondrial function and therefore disrupt glucose and lipid metabolism.[100] Even though human evidence is scarce, two epidemiological studies among agricultural farmers have reported positive associations between use of some herbicides or insecticides and gestational diabetes or diabetes.[98,101]

Passive cigarette smoking is also linked to disturbance of glucose metabolism. Animal studies suggest maternal nicotine exposure may cause impaired glucose homeostasis in offspring as a result of both defective insulin secretion (caused by impaired pancreatic β-cell mass and function) and reduced peripheral insulin sensitivity.[63] However there is currently no information on the risk of diabetes due to developmental nicotine exposure in humans.

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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