Environmental chemical risk factors for Type 2 diabetes: an update

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Practice points
• Studies have suggested that exposure to several environmental chemicals may increase the risk of Type 2 diabetes.
• Moderate evidence, characterized by consistent findings from several well-designed prospective studies and meta-analyses, supports an association with diabetes for inorganic arsenic, organochlorine pesticides, dioxins and polychlorinated biphenyls.
• Limited evidence, including several well-designed prospective studies, has accumulated in support of effects of environmental tobacco smoke and ambient air pollution in the promotion of diabetes.
• Insufficient evidence is available to evaluate the role of bisphenol A, phthalates and organophosphate and pyrethroid insecticides, due to few studies and/or study designs inappropriate for assessing causal relationships (cross-sectional).
• Increased vulnerability to diabetes-promoting effects of environmental chemicals may result from exposure during the prenatal period or exposures to genetically susceptible individuals, although the mechanisms of such effects have not been definitively described.

SUMMARY Increasing evidence suggests a role for environmental chemicals in the promotion of Type 2 diabetes. This review summarizes epidemiologic studies of environmental chemical exposures reported to be associated with Type 2 diabetes and insulin resistance. Chemicals are classified as having moderate, limited and insufficient degrees of evidence in support of a diabetes-promoting effect. Moderate evidence exists for diabetogenic effects of inorganic arsenic and persistent organic pollutants, including organochlorines, dioxins and polychlorinated biphenyls. Limited evidence supports a role for environmental tobacco smoke and ambient air pollution. Insufficient evidence is available regarding the potential effects of bisphenol A, phthalates, organophosphates and pyrethroids; most studies of such short-lived pollutants have been cross-sectional and do not demonstrate causality.

Introduction

The global prevalence of diabetes has increased over the last three decades [1], accompanied by detrimental effects on life expectancy and quality of life [2]. Diabetes is a disease of abnormal glucose metabolism, characterized by impaired insulin production or secretion and, in the case of Type 2 diabetes (T2DM), reduced sensitivity to the effects of insulin. Obesity and sedentary lifestyle are widely cited contributors to the risk of T2DM, which represents up to 90% of prevalent cases of diabetes [3,4]. Numerous recent studies have suggested that environmental chemical exposures may also contribute to T2DM risk [5]. While more evidence is needed to establish causal associations,

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this review summarizes the current state of the human evidence linking common environmental pollutants to diabetes risk, and briefly considers how different underlying characteristics and timing of exposures may influence susceptibility. We include human epidemiological studies published prior to December 2014 using cohort, cross-sectional and case–control designs; studies without individual exposure estimates (ecological designs) are not included. Studies of diabetes-related outcomes (insulin resistance, metabolic syndrome) were not included unless the outcome of diabetes was also included in the study. In most studies, the term 'diabetes' was used to refer to a clinical diagnosis of diabetes of which the large majority were expected to be T2DM, although no antibody tests were reported.

A brief history of environmental chemical risks for diabetes

Early reports of potential links between diabetes and environmental chemicals arose from high-exposure occupational settings. Researchers in the 1970s observed that chronic exposure to carbon disulfide was correlated with decreased glucose tolerance ('latent diabetes') among workers [6,7]. Among Vietnam veterans who handled Agent Orange, a herbicide mix contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the IOM found 'limited/suggestive evidence' of an association between exposure and T2DM [8]. Some researchers still question whether this association is causal [9], although there is biological plausibility and mounting epidemiologic evidence for an association between persistent organic pollutants (POPs) and T2DM [10–13]. Excesses of T2DM have also been noted in nonoccupational cohorts with high exposures to environmental chemicals, such as inorganic arsenic contamination of drinking water [14]. Alarmingly, associations have also been reported between common, low-level chemical exposures in the general population and the incidence of T2DM. Studies of chemicals that are ubiquitous in daily life may hold the most promise for explaining a portion of the increasing global incidence of diabetes. However, currently there are challenges that hinder conclusive causal interpretations, as we discuss in some detail in this review. The chemical exposures discussed in this review, as well as their sources and the strength of existing evidence for an association with T2DM in humans, are presented in **Table 1.**

• Moderate evidence
Associations considered here to be supported by 'moderate' evidence are those for which several well-designed, prospective epidemiologic studies have been conducted with adequate control for known confounders, have produced relatively consistent results and meta-analyses of these studies have found positive associations with T2DM.

Inorganic arsenic
Sources of exposure
Inorganic arsenic is a naturally occurring contaminant in ground water and concentrations vary by geographic region. There is growing concern about the human health effects of inorganic arsenic due to widespread drinking water contamination around the world. Concentrations of inorganic arsenic in ground water exceeding 150 µg/l have been reported in areas of Taiwan, Argentina, Chile, Mexico, Bangladesh, India, Vietnam, Thailand and the USA [15]. The current US drinking water standard for inorganic arsenic is 10 µg/l. Humans become exposed by drinking contaminated water [16,17] and to a lesser extent by consuming contaminated foods [18].

Evidence for an association with T2DM
Chronic exposure to inorganic arsenic and the prevalence or incidence of diabetes has been examined in a number of populations around the globe. Exposure has been characterized by measuring concentrations present in drinking water and concentrations excreted in urine. Several cross-sectional [19–25] and longitudinal [26–30] studies have reported positive associations between arsenic exposure and diabetes, while some have reported no significant association [31–34]. A National Toxicology Program workshop review [35] found 'limited to sufficient support' for an association between inorganic arsenic and diabetes, but only at concentrations above 150 µg/l. A recent meta-analysis [14], which was not limited to high-exposure settings, reported a dose-response increase in the risk of T2DM of 13% for each 100 µg/l increase in inorganic arsenic in drinking water (95% CI: 1.00–1.27).

Proposed biological mechanisms
Laboratory studies indicate that inorganic arsenic exposure can impair the production and secretion of insulin from pancreatic β-cells *in vitro* [36]. A study in rats suggested that these

Table 1. Summary of chemicals, major sources of exposure and strength of evidence for association with Type 2 diabetes in humans.

Chemical	Major source of exposure	Strength of evidence
Arsenic – inorganic	Drinking water	Moderate
Dioxins, polychlorinated biphenyls and organochlorines	Contaminated foods	Moderate
Environmental tobacco smoke	Proximity to cigarette smokers	Limited
Ambient air pollution	Outdoor air	Limited
Organophosphate insecticides	Occupational, contaminated foods	Insufficient
Pyrethroid insecticides	Occupational, treated clothing and pets	Insufficient
Bisphenol A	Contaminated foods and household dust	Insufficient
Phthalates	Contaminated foods, dust, personal care products	Insufficient

effects may be related to the production of oxidative stress in the pancreas [37]. Moreover, arsenic exposure may alter the expression of genes known to be associated with insulin resistance and T2DM [38].

Limitations of current knowledge

While exposure to arsenic in drinking water at concentrations above 150 μg/l has been strongly associated with diabetes risk, findings in populations with lower levels of exposure have been more equivocal. Some studies examined excretion of total urinary arsenic which, while a measure of total dose, reflects only the past few days of exposure [39] and includes nontoxic arsenobetaine [40], which may have led to exposure misclassification. Urinary arsenic concentrations may also reflect genetic differences in metabolism and excretion of arsenic [41], which could contribute to arsenic toxicity. Moderate evidence, including recent prospective studies with strong methods of exposure assessment, suggests that chronic exposure to inorganic arsenic may increase the risk of T2DM in adults [5].

Dioxins, polychlorinated biphenyls & organochlorine pesticides
Sources of exposure

Dioxins are highly persistent organic chemicals that are by-products of a variety of industrial processes including the incineration of waste. Polychlorinated biphenyls (PCBs) are a class of chemicals that were widely used in the 20th century in industrial applications including transformers and hydraulic fluids [42]. This class includes compounds with dioxin-like properties, as well as nondioxin-like PCBs which act through separate pathways. Organochlorines are a class of pesticides widely used in agriculture and for public health purposes during the mid-20th century, which includes the insecticides

aldrin, dieldrin, chlordane, dichlorodiphenyltrichloroethane (DDT) and its breakdown product dichlorodiphenyldichloroethylene (DDE), heptachlor, mirex and the fungicide/biocide hexachlorobenzene. DDT was banned for agricultural use in the USA in 1972, but is still in limited use internationally for malaria vector control [42]. Some organochlorines remained in use for several decades after DDT was banned. Dioxins, PCBs and and organochlorines are all considered POPs; they are lipophilic (stored in fatty tissues) and are found in blood and adipose tissue [43]. Humans are exposed primarily by consuming contaminated high-fat foods, including dairy, eggs and animal fats [44–46]; infants may also be exposed by ingesting contaminated breast milk [43].

Evidence for an association with T2DM

Over 20 cross-sectional studies in highly exposed and background-exposed populations have reported positive associations of blood or adipose concentrations of dioxins [47–51], PCBs [46–49,51–60] and/or organochlorines [46,48,51–54,60–69] with diabetes, although some found associations attenuated after adjustment for other POPs [48,53] and a few reported nonsignificant associations following serum lipid adjustment [46,63,70]. Most of these studies included both genders and some were in Native American [46,53], predominantly African–American [57], Mexican–American [63] or Asian [49,55,66,71] populations.

Several longitudinal studies have also reported positive associations of PCB [71–73], dioxin [10,74] and/or organochlorine [12,72,75–78] concentrations with T2DM, while some studies reported no associations with certain POPs [78–80]. Among Vietnam War veterans who were involved in spraying Agent Orange, T2DM risk increased with serum TCDD concentrations [10,74]. In the Agricultural Health Study (AHS), farmers who

reported ever mixing or applying the organochlorine pesticides chlordane and heptachlor [75] and female spouses of farmers who ever personally applied the organochlorine dieldrin or herbicides historically contaminated with TCDD (2,4,5-T and 2,4,5-TP) [76] were at elevated risk of incident diabetes. In two prospective studies of serum PCBs, increased risk of incident diabetes was observed among women only [71,73]. The reasons for these gender-specific associations are unknown; however, women on average have higher proportions of body fat, and some researchers have suggested that adiposity and POPs may act synergistically to increase the risk of T2DM [51,56,60–61].

In a recent meta-analysis [13], the pooled odds ratio for T2DM associated with the highest category of serum PCB concentration versus the lowest was 2.14 (95% CI: 1.53–2.99), and the pooled OR associated with the highest serum concentrations of p,p'-DDE was 1.33 (95% CI: 1.15–1.54) [13]. Another recent meta-analysis restricted to prospective studies reported a positive association with incident T2DM for total PCBs (OR: 1.70; 95% CI: 1.28–2.27) and for the organochlorine hexachlorobenzene (OR: 2.00; 95% CI: 1.13–3.53), but a nonsignificant association with p,p'-DDE (OR: 1.25; 95% CI: 0.94–1.66) [12].

Proposed biological mechanisms
It is unclear whether dioxins and PCBs influence diabetes risk primarily by inducing insulin resistance or rather through toxicity to pancreatic β-cells, resulting in impaired insulin secretion. A study of adults living near a Superfund site found hyperinsulinemia associated with higher serum TCDD concentrations, suggesting reduced sensitivity to insulin [81], while a study of Danish children found an inverse association between serum PCBs and insulin concentrations, lending support to the mechanism of impaired β-cell function [82]. Animal studies provide support for both mechanisms: dioxin-like PCBs have been shown to impair glucose tolerance in mice [83], while sublethal doses of TCDD in the rat can reduce insulin production and secretion [84].

Derivatives of DDT may mimic the effects of endogenous estrogens in the body [85]. Estrogen receptor signaling is involved in many metabolic functions including glucose transport [86,87]. In a rat model, DDE was shown to activate nuclear receptors that influence metabolism by inducing hepatic enzymes [88]. Organochlorines may also influence diabetes risk by promoting adiposity and obesity [89,90]. DDT promotes adipocyte differentiation *in vitro* [91], lending some plausibility to the obesogenic hypothesis. However, the large majority of the studies listed above adjusted for BMI and still observed positive associations, suggesting an alternate mechanism of action. This relationship is further complicated by the results of a study in mice which suggested that adiposity may be protective against adverse effects of POPs, perhaps by sequestering toxins [83].

Limitations of current knowledge
While the majority of studies have reported positive associations between dioxin, PCB or organochlorine exposure and prevalent or incident T2DM, some questions remain as to whether these associations may be considered causal. For example, the positive dose-response relationship between TCDD and diabetes prevalence observed in the Vietnam veteran population could not be replicated in a separate, more highly exposed worker cohort [92]. The possibility of confounding due to other, correlated exposures cannot be excluded. In addition, the interpretation of cross-sectional studies of lipophilic chemicals in relation to diabetes are limited by the possibility that diabetes leads to higher concentrations of chemicals. However, this issue has been explored by prospective studies which examined changes in the elimination of POPs after diagnosis, and no evidence of reverse causality was detected for dioxins [93] or for DDE and PCBs [77]. Recent prospective studies have provided stronger evidence in support of a causal association between organochlorines and T2DM, particularly because both biological markers and questionnaire measures of exposure have resulted in the same finding. Questionnaire measures are unlikely to be influenced by biological changes in response to disease. Moderate evidence for TCDD, PCBs and organochlorine pesticides suggests that all three may contribute independently to diabetes risk. Because all three are highly lipophilic and bioaccumulate in human tissues, there may be common mechanisms that influence exposure, bioavailability and diabetes risk.

• Limited evidence
Associations considered here to be supported by 'limited' evidence are those for which several prospective epidemiologic studies have been conducted but have not produced consistent results, have not been examined systematically

by meta-analyses or for which some controversy still exists regarding the degree of bias or generalizability.

Environmental tobacco smoke

Sources of exposure

Nonsmokers are regularly exposed to environmental tobacco smoke (ETS), also known as secondhand smoke, in homes, workplaces and public places. In the USA in 2008, environmental smoke exposure affected approximately 88 million people [94]. Globally, the WHO estimates that a third of adults are exposed regularly to ETS and over 40% of children are exposed to tobacco smoke at home [95].

Evidence for an association with T2DM

Active smoking is associated with increased risk of T2DM [96]. Among nonsmokers, ETS exposure has also been associated with T2DM in two cross-sectional studies [97,98] and some, but not all, prospective studies. Among six prospective studies, five reported significant positive associations [99–103], and one study reported a nonsignificant association [104]. Two of the prospective studies [99,100] and one cross-sectional study [97] also reported positive dose-response associations between hours of ETS exposure and diabetes risk. A recent meta-analysis [105] of the six prospective studies reported a pooled relative risk of T2DM of 1.21 (95% CI: 1.07–1.38) associated with ETS exposure among never-smokers. However, three of the prospective studies followed participants for less than 10 years [100,101,103], one study for less than 5 years [103]. The relevant duration of exposure to ETS that may be associated with T2DM is unknown.

Proposed biological mechanisms

Tobacco smoke is complex mixture of chemicals, some of which promote inflammation and endothelial dysfunction [106]. Acute exposure to ETS caused impairment of flow-mediated vasodilation in healthy nonsmoking volunteers [107]. Previous human studies have noted that active smoking can impair insulin-stimulated glucose uptake after acute [108] and chronic [109] exposures.

Limitations of current knowledge

Active smoking and ETS exposure are strongly associated with increased risk of cardiovascular disease [106], and the causal pathways linking smoke exposure to T2DM may be complex. An association between ETS and T2DM is suggested based on the effects of active smoking, and the dose-response associations with ETS demonstrated in some prospective studies. However, the evidence is considered limited due to the relatively small number of existing prospective studies with greater than 10 years of follow-up for incident T2DM, and the fact that all ETS exposure data are self-reported, leading to possible measurement error.

Ambient air pollution

Sources of exposure

Nearly everyone is exposed to ambient air pollution. In high-income countries, urban outdoor air pollution is a leading risk factor for mortality, while in low-income and middle-income countries, indoor air pollution from solid fuel combustion is responsible for a larger proportion of deaths [110]. The composition of ambient air pollution may vary greatly between regions and between rural and urban areas. The most commonly studied components of ambient air pollution in relation to diabetes are fine and coarse particulate matter ($PM_{2.5}$ and PM_{10}, respectively), nitrogen dioxide (NO_2), nitrogen oxides (NOx) and overall traffic-related air pollution.

Evidence for an association with T2DM

Some recent studies have reported positive associations between constituents of ambient air pollution and diabetes [111–115], while others have reported no associations with specific pollutants [113,116–117] or associations among women only [118]. Many of these studies have involved very large sample sizes and some have estimated exposure over long periods of time. Long-term exposure to $PM_{2.5}$, PM_{10}, NO_2 or NOx and traffic density at the residential address have been associated, although not consistently, with prevalent [114,118] and incident [111–113,115,119] diabetes. Gestational diabetes prevalence was associated with NOx concentration and traffic density in one Swedish study [120], but no association was found with traffic density in a Dutch cohort [121]. In a US cohort, $PM_{2.5}$ concentrations during pregnancy were not associated with gestational diabetes; concentrations of NOx were not examined [122]. Two recent meta-analyses have been conducted to estimate associations of air pollutants with incident T2DM. One analysis [123] reported positive associations with incident T2DM for $PM_{2.5}$ (HR: 1.11 per 10 μg/m³, 95% CI: 1.03–1.20) and NO_2 exposure (HR: 1.13

per 10 µg/m³, 95% CI: 1.04–1.22), based on five prospective studies. Another meta-analysis [124], which included a greater number of studies, reported a higher estimate for $PM_{2.5}$, a similar estimate for NO_2 and a positive association between PM_{10} and incident T2DM (RR: 1.34 per 10 µg/m³, 95% CI: 1.22–1.47).

Proposed biological mechanisms

Animal exposure studies have demonstrated associations of ambient air pollution, particularly $PM_{2.5}$, with insulin resistance and impaired glucose tolerance in mice [125,126]. Short-term exposure to urban air pollution in healthy human volunteers acutely reduced insulin sensitivity [127]. Laboratory-based mechanistic studies suggest that $PM_{2.5}$ exposure influences hepatic and peripheral insulin resistance through modification of gene expression [128] and activation of inflammatory pathways [129]. Studies have primarily examined the metabolic effects of exposure to $PM_{2.5}$, and relatively little is known about the other constituents of ambient air pollution.

Limitations of current knowledge

The varying composition of ambient air pollution across geographic regions may account for some inconsistencies across studies. Associations with overall traffic density or distance to a major road may be confounded by other exposures such as noise [130], socioeconomic factors or by reduced physical activity related to high vehicle traffic and perceived safety issues. While several recent prospective studies have been conducted, and two meta-analyses have indicated positive associations between ambient air pollution constituents and incident T2DM, the evidence for a causal association is still considered 'limited' due to the lack of agreement regarding, which constituent or combination of constituents of air pollution may be responsible for observed associations. Advanced statistical treatment of exposure mixtures may be necessary to disentangle the effects of air pollution on T2DM.

• Insufficient evidence

Associations considered here to be supported by 'insufficient' evidence are those for which few or no prospective epidemiologic studies have been conducted, or only weak study designs have so far been employed. Some of these associations have biological plausibility but insufficient evidence exists to evaluate their potential role in T2DM in humans.

Organophosphate insecticides
Sources of exposure

Organophosphates are a class of insecticides used widely for agricultural purposes and, until recently, for residential uses. Two chemicals of this class, chlorpyrifos and malathion, are the most widely used insecticides in the USA [131]. Organophosphates are rapidly metabolized and excreted in urine [132]. Individuals may be exposed either through direct contact with pesticides applied in home or work environments, or through consumption of foods treated with pesticides [133].

Evidence for an association with T2DM

Recent studies have suggested that chronic occupational exposure to organophosphates may increase the risk of diabetes. In a prospective study of farmers and their spouses in the USA, self-reported ever-use of the organophosphates coumaphos, phorate, terbufos and trichlorfon were associated with increased risk of incident diabetes (adult-onset, unspecified type) in men [75], and fonofos, parathion and phorate ever-use were associated with incident diabetes in women [76]. Additionally, the organophosphates phorate and diazinon were associated with gestational diabetes among women in the AHS who reported any pesticide use during the first trimester of pregnancy [134].

Proposed biological mechanisms

Organophosphates exert neurotoxic effects by impairing acetylcholinesterase activity, and acute intoxication may cause cholinergic symptoms, including nausea, vomiting, weakness, paralysis and seizures [135]. Acute high-dose exposure to organophosphates also produces hyperglycemia in rats [136]. There is little known about possible mechanisms of long-term health effects of organophosphates, although laboratory studies provide some suggestive evidence. Rats exposed to organophosphates diazinon and parathion in the neonatal period demonstrated persistent changes in metabolism resembling prediabetes [137–139], and also exhibited greater weight gain on a high-fat diet compared with unexposed rats [139].

Limitations of current knowledge

The evaluation of organophosphate insecticides and diabetes is in its early phases, both

epidemiologic and laboratory investigations. Exposure characterization can be challenging due to the short biological half-lives of these chemicals; however, occupational cohorts with questionnaire-based measures of external exposure suggest that specific chemicals may be associated with adult-onset diabetes. The existing human evidence is considered insufficient to evaluate whether organophosphate exposure may increase the risk of T2DM, due to the small number of studies and lack of robust assessment of cumulative dose.

Pyrethroid insecticides
Sources of exposure
Pyrethroid insecticides are a class of current use pesticides that are synthetic analogs of a natural insecticide derived from chrysanthemums, pyrethrum [140]. Pyrethroid insecticides are widely used in agriculture, in flea and tick treatments for companion animals and to treat clothing and fabrics for insect repellence, with large use in military battle dress uniforms and bed nets in malaria-endemic regions [42,140].

Evidence for an association with T2DM
To date, only two human epidemiological studies have been conducted on pyrethroid exposure and T2DM risk. A study of factory workers in China found a higher prevalence of diabetes (type unspecified) among those with sustained occupational exposure to pyrethroids; however, there was no adjustment for BMI or control for other occupational exposures [141]. Among pesticide sprayers in Bolivia who exclusively sprayed pyrethroids, a positive trend was observed between the number of cumulative hours of exposure and the odds of abnormal glucose regulation, defined as glycated hemoglobin ≥5.6%, and a higher prevalence of prediabetes or diabetes among sprayers than among controls, although the unexposed controls may not have adequately represented the base population from which the exposed sprayers arose [142].

Proposed biological mechanisms
Pyrethroid toxicity in rats is associated with reduced rates of glucose utilization in the brain [143], and treatment of adipocytes with permethrin (a pyrethroid insecticide) resulted in reduced glucose uptake *in vitro* [144]. This is a nascent field of research and as yet there is no strong mechanistic evidence linking pyrethroid exposure to T2DM in humans.

Limitations of current knowledge
There is currently insufficient evidence regarding the extent of potential T2DM risk associated with pyrethroid use, based on few studies with significant limitations. However, given permethrin's widespread use for malaria control in developing countries, flea and tick control in developed countries and treatment of military uniforms, understanding any potential metabolic health impacts of permethrin is of critical importance.

Bisphenol A
Sources of exposure
Bisphenol A (BPA) is a man-made chemical that is used in a variety of consumer products, including certain plastics, thermal paper for receipts and amalgam dental fillings [145]. Humans may be exposed to BPA through contaminated food, inhalation of house dust and dermal absorption [146,147]. Infants may be exposed to BPA via breast milk and formula [148].

Evidence for an association with T2DM
Some, but not all, cross-sectional studies of urinary BPA in humans have found positive associations with T2DM. Among five studies conducted within the US NHANES study, four studies reported positive pooled associations of urinary BPA with diabetes [149–152] and one study reported no significant association [153]. There were, however, overlapping data used in these separate studies and some of the study authors noted that positive associations may have been driven by the results of one survey cycle (2003–2004) during which BPA concentrations were higher than in the two subsequent cycles [150,151]. A cross-sectional study in the Korean National Human Biomonitoring Survey found no association between urinary BPA and self-reported diabetes after covariate adjustment [154]; while a cross-sectional study in a Chinese cohort reported elevated risks of T2DM in the second and fourth quartiles of urinary BPA as compared with the first quartile, with no linear trend [155]. One prospective study was conducted in the US Nurses' Health Study, and positive associations were reported between BPA and incident T2DM among middle-aged women (ages 32–52 at enrollment) but not among older women (ages 53–79 at enrollment), after adjustment for BMI [156]. However, associations were based on measured BPA in a single urine sample collected prior to diagnosis, and the

reproducibility of BPA in urine over 1–3 years was low (intraclass correlation coefficient: 0.14).

Proposed biological mechanisms

The promotion of obesity may be one mechanism by which BPA exposure may increase the risk of T2DM, as suggested by several human epidemiologic studies [157–162]. Laboratory studies provide support for the concept that BPA can induce adipocyte differentiation *in vitro* [163]. Given that some cross-sectional associations between BPA and T2DM persisted after adjustment for BMI [149,152,156], there may also be effects of BPA that are independent of weight gain, such as the promotion of insulin resistance and inflammation of adipose tissue [164,165], or the activation of estrogen receptors to promote insulin secretion by pancreatic β-cells [166].

Limitations of current knowledge

Current evidence for an association between BPA and T2DM is considered insufficient because existing studies originate from few cohorts and lack strong study designs. It is possible that reverse causality could be responsible for observed cross-sectional associations between BPA and obesity or T2DM. Urine samples taken prior to diagnosis reduce this possibility, but BPA is quickly excreted from the body after ingestion [167] and therefore a urine measurement at a single point in time may not accurately represent chronic exposure over years [168]. Repeated measures of BPA ingestion or excretion in the context of longitudinal studies will be needed to examine whether T2DM may be associated with chronic, low-dose exposure.

Phthalates
Sources of exposure

Phthalates are man-made chemicals used as plasticizers and solvents in a wide variety of consumer and industrial applications. Humans may be exposed to phthalates by ingesting certain foods and medicines [169,170], through dermal absorption from certain personal care products [171,172], and by inhaling or ingesting household dust [173]. Phthalates are rapidly metabolized and excreted from the body, and phthalate metabolites measured in urine are a biomarker of recent exposure [42].

Evidence for an association with T2DM

Phthalate metabolites have been positively associated with diabetes in three cross-sectional studies [174–176] and in one prospective study [156]. A study among women in the USA (NHANES) found associations with mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-(3-carboxypropyl) phthalate and the sum of all di-(2-ethylhexyl) phthalate (DEHP) metabolites [174], although not all of these metabolites showed a linear dose-response. A study of women in Mexico reported positive associations with the sum of DEHP metabolites but an inverse association with MBzP; the significance of these associations was eliminated following covariate adjustment but the point estimates did not change meaningfully [176]. A study among elderly Swedes reported positive associations with T2DM for MiBP, monoethyl phthalate and monomethyl phthalate, but no association with mono-(2-ethylhexyl) phthalate, a DEHP metabolite [175]. In this study, ten metabolites were measured in serum (rather than urine) but only four could be detected in at least 70% of participants. In the only prospective analysis to date, from the Nurses' Health Study [156], a case–control design was used and phthalate metabolites were measured in a single urine sample collected when all participants were free of diabetes. The study found positive associations with incident diabetes for the sum of total phthalate metabolites as well as the sum of butyl phthalates (MnBP and MiBP) and the sum of DEHP metabolites, among middle-aged women (ages 32–52 at enrollment) but not among older women (ages 53–70 at enrollment). A recent systematic review [5] concluded that the evidence was insufficient to conclude whether or not an association between phthalates and T2DM was present.

Proposed biological mechanisms

There are plausible biological mechanisms which may link phthalates with diabetes and metabolic disruption. Certain phthalates have been shown to activate peroxisome-proliferator-activated receptors (PPARs), a family of nuclear receptors which regulate aspects of lipid and carbohydrate metabolism [177,178]. This modulation of PPAR activity has been suggested as one pathway by which phthalates, particularly DEHP, may promote adipogenesis and obesity [86]. Certain phthalates also have antiandrogenic activities [179]. Of importance for T2DM, DEHP may induce impaired insulin signaling in rat skeletal muscle, the primary site of peripheral glucose utilization [180].

Limitations of current knowledge

As with BPA, the short biological half-lives of the phthalates [181,182] present difficulties in assessing chronic exposures. The discrepancy between studies regarding the particular phthalate metabolites associated with diabetes is problematic and deserves further scrutiny using appropriate methods to examine complex mixtures of exposures. All of the studies described here were based on a single measurement of phthalate metabolites, which may not be sufficient to characterize typical exposure over time. The current evidence is therefore considered insufficient to draw conclusions regarding an association between phthalates and T2DM, due to the lack of studies with strong designs to assess chronic exposures.

Conclusions & future perspective

We have reviewed the state of the evidence to evaluate whether several environmental chemicals may promote T2DM in humans. While none of the associations described here can be conclusively described as causal, we found moderate evidence for inorganic arsenic, organochlorines, dioxins and PCBs, limited evidence for an effect of ETS and ambient air pollution, and insufficient evidence for the role of BPA, phthalates, organophosphate and pyrethroid insecticides. Prospective studies with both questionnaire-based and biomarker-based assessments of exposure will be needed to establish the effect of chemicals that are quickly eliminated following exposure. To date, most researchers have considered chemical exposures independently, but there may be interaction among chemical exposures in their contributions to diabetes risk, particularly among those sharing a common mechanism of action.

Identification of susceptible populations

Individual characteristics, such as genetic factors and BMI, may increase susceptibility to the diabetes-promoting effects of certain environmental chemicals. Genetic polymorphisms have been identified which modify associations between air pollutants PM_{10}, O_3, NO_2 and insulin resistance in a Korean population [183]. Other genetic polymorphisms have been identified which lead to differences in arsenic metabolism [41], and which may increase susceptibility to toxic effects of arsenic exposure [184–187].

Some researchers have suggested that individuals with obesity may be at greater risk of diabetes from exposure to environmental chemicals, particularly those chemicals that promote inflammation of adipose and other tissue, such as ambient air pollutants [188]. In support of this theory, certain studies have reported stronger associations between POPs and diabetes among overweight and obese study participants [51,56,61]; however, others have found no effect modification by BMI [77]. Interestingly, in a mouse model, adipose tissue appeared to sequester POPs such that mice with diet-induced obesity were less susceptible than lean mice to the adverse effects of PCB exposure on glucose homeostasis [83]. Studies in large cohorts will be needed to examine differential susceptibility to environmental chemicals by obesity or adiposity.

Prenatal environmental exposures & epigenetic influences on diabetes risk

Evidence from animal and human studies suggests that the prenatal period is a critical window during which exposures may influence lifelong disease risk. Obesity and diabetes risk in adulthood may therefore be related to *in utero* exposure to environmental chemicals, particularly endocrine-disrupting chemicals [189]. Certain studies in humans have found that the risk of diabetes or obesity in the offspring is increased with prenatal exposure to DDE, PCBs, BPA or maternal smoking [190–193], although others have found these associations to be nonsignificant [194] or, occasionally, inverse [195]. One possible mechanism by which prenatal environmental exposures may influence childhood or adult disease risk is through epigenetic modifications [189], mitotically heritable changes to DNA that affect subsequent gene expression. Another possible mechanism is through the promotion of adipocyte differentiation or proliferation at critical periods of development [196]. More research is needed to elucidate the role of *in utero* exposure to environmental chemicals in altering adult susceptibility to chronic disease.

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