

Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function

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Abstract The prevalence of diabetes mellitus is currently at epidemic proportions and it is estimated that it will increase even further over the next decades. Although genetic predisposition and lifestyle choices are commonly accepted reasons for the occurrence of type 2 diabetes, it has recently been suggested that environmental pollutants are additional risk factors for diabetes development and this review aims to give an overview of the current evidence for this. More specifically, because of the crucial role of pancreatic beta cells in the development and progression of type 2 diabetes, the present work summarises the known effects of several compounds on beta cell function with reference to mechanistic studies that have elucidated how these compounds interfere with the insulin secreting capacity of beta cells. Oestrogenic

compounds, organophosphorus compounds, persistent organic pollutants and heavy metals are discussed, and a critical reflection on the relevance of the concentrations used in mechanistic studies relative to the levels found in the human population is given. It is clear that some environmental pollutants affect pancreatic beta cell function, as both epidemiological and experimental research is accumulating. This supports the need to develop a solid and structured platform to fully explore the diabetes-inducing potential of pollutants.

Keywords Diabetes mellitus type 2 · Environmental pollutants · Endocrine disruptors · Insulin-secreting cells · Review

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Abbreviations

[Ca ²⁺] _i	Intracellular free calcium concentration
CREB	cAMP response element-binding protein
E ₂	17β-Oestradiol
EDC	Endocrine-disrupting compound
EPA	Environmental Protection Agency
ER	Oestrogen receptor
ERE	Oestrogen responsive element
FAO	Food and Agriculture Organization
GSIS	Glucose-stimulated insulin secretion
JMPR	Joint FAO/WHO Meeting of Pesticide Residues
K _{ATP} ⁺ channel	ADP/ATP-sensitive potassium channel
LOAEL	Lowest observed adverse effect level
ncmER	Non-classical membrane oestrogen receptor
NOAEL	No observed adverse effect level
NOS	Nitric oxide synthase
OPC	Organophosphorus compound
PCB	Polychlorinated biphenyl
PI3K	Phosphatidylinositol 3-kinase
POP	Persistent organic pollutant
RfD	Reference dose
ROS	Reactive oxygen species
TCDD	2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin

Introduction

Changes in human lifestyle and behaviour (e.g. poor diet, lack of exercise), in addition to genetic predisposition and environmental influences, have resulted in a dramatic increase in the incidence of diabetes mellitus worldwide [1]. This global diabetes epidemic is chiefly due to type 2 diabetes as it makes up more than 90% of all diabetes cases [1].

Type 2 diabetes results from interactions between genetic susceptibility, environmental factors and lifestyle choices. Our understanding of the causes of diabetes, besides genetics, has remained rudimentary, for the most part being limited to the impact of physical inactivity or unhealthy dietary choices [2]. For obesity, which is closely associated with diabetes, a relationship with environmental endocrine-disrupting compounds (EDCs) has been hypothesised based on epidemiological data and *in vivo* rodent studies. In this scenario the chemicals that disrupt lipid regulation and adipogenesis are defined as obesogens [3]. Although evidence that environmental pollutants might be an additional risk factor for diabetes development is accumulating, a systematic investigation of the possibility that environmental pollutants could be key players in the aetiology of type 2 diabetes [4] has not yet been

performed. However, there are strong experimental indications that some pollutants, such as bisphenol A [5] and certain persistent organic pollutants (POPs) [6], affect processes that are related to diabetes development.

While reduced insulin sensitivity and beta cell function are the core pathophysiological defects in type 2 diabetes [7], the relative importance of these abnormalities is still under debate [8]. However, it has recently been acknowledged that beta cell failure is the triggering factor [9] for the progression of pre-diabetic states (impaired glucose tolerance or impaired fasting glucose or both) to full-blown type 2 diabetes. Obviously, investigation of the effects and mechanisms of action of compounds should focus on their roles in both the development and progression of insulin resistance and beta cell dysfunction. To date, with regard to research on environmental causes, insulin resistance has received more attention than beta cell function. However, considering the critical role of pancreatic beta cells in the progression of type 2 diabetes, there is a great need to focus on the impact of chemicals on the function of these cells. This could provide crucial information on normal beta cell function and physiology as well as on compound-specific toxicity.

This review aims to give an overview of the interference of normal beta cell function by environmental pollutants, specifically focusing on proposed mechanisms of disruption of insulin secretion. Furthermore, a critical discussion on the discrepancy between experimental and environmentally relevant exposure concentrations is given, followed by comments on the value of mechanistic studies in human risk assessment.

Insulin secretion

The role of the pancreatic beta cell is to sense an increase in the concentration of nutrients (notably glucose) in the blood and to deliver an appropriate quantity of insulin into the systemic circulation. This ensures that the sugar is efficiently taken up and stored as glycogen or triglycerides by peripheral tissues (liver, muscle and adipose tissue) [10]. Figure 1 summarises the mechanism of glucose-stimulated insulin secretion (GSIS) as currently understood. After the initial, rapid triggering phase mediated by ADP/ATP-sensitive potassium channels (K_{ATP}⁺ channels; Fig. 1, see label A), additional signals are necessary to produce the sustained secretion elicited by glucose [11] via a K_{ATP}⁺ channel-independent pathway (reviewed in [10–12]). Furthermore, to sustain the insulin secretion capacity and the glucose responsiveness of beta cells, glucose also elicits effects at the translational (Fig. 1, see label D) [13] and transcriptional level (Fig. 1, see label C) [14, 15].

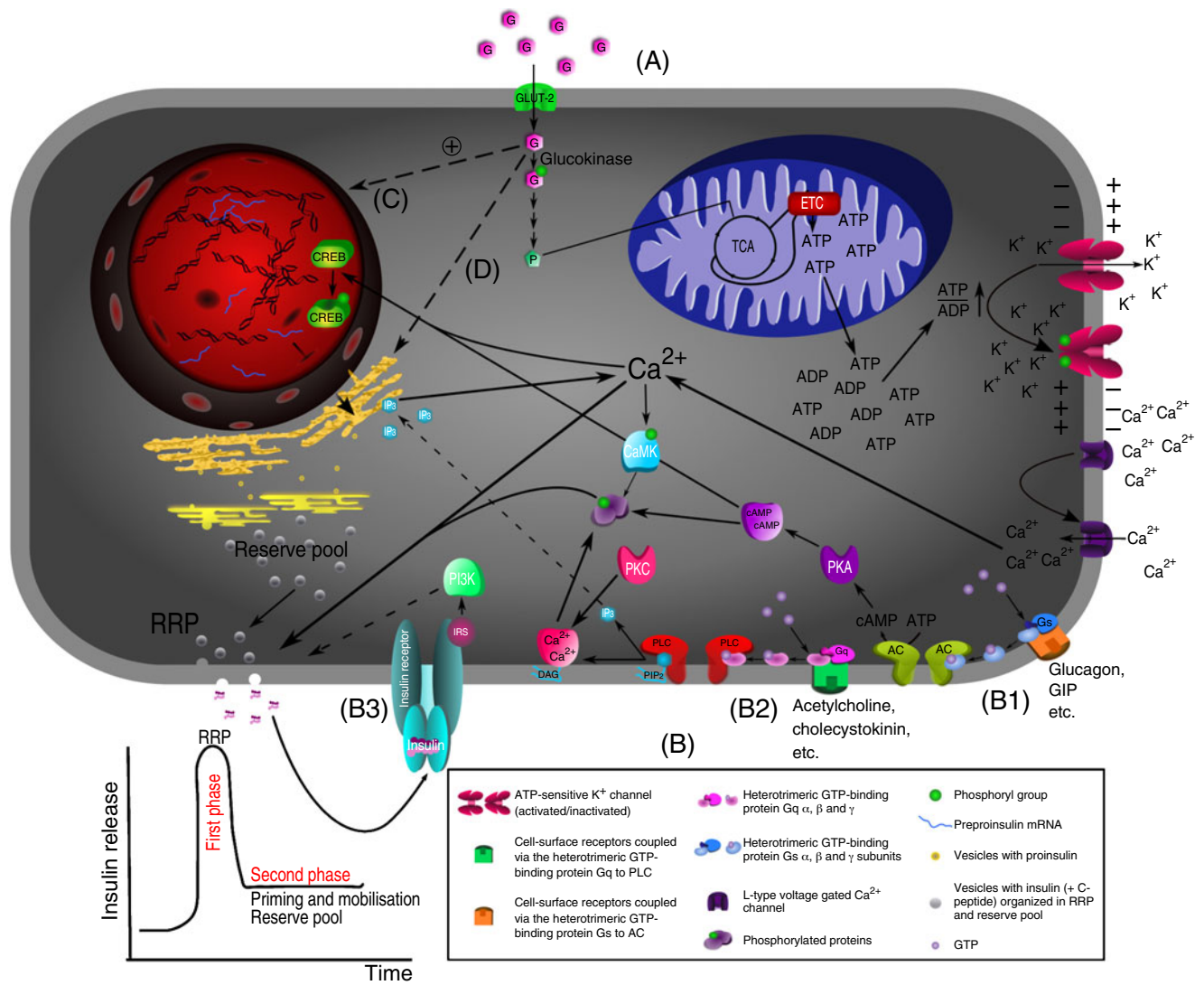


Fig. 1 Mechanism of insulin secretion. (A) The classical pathway of GSI. Once glucose is taken up via GLUT-2, it is phosphorylated to glucose 6-phosphate by the high K_m glucokinase, followed by entry into the glycolytic pathway and mitochondrial oxidation. Mitochondrial ATP production promotes the closure of K_{ATP}^+ channels, and as a consequence the depolarisation of the plasma membrane. In turn, the decrease in voltage leads to the opening of voltage-sensitive Ca^{2+} channels and an influx of Ca^{2+} ions, increasing $[Ca^{2+}]_i$. High $[Ca^{2+}]_i$ induces activation of CaMK, resulting in phosphorylation of enzymes and proteins important in insulin secretion. The combination of high $[Ca^{2+}]_i$ and activation of potentiating proteins triggers exocytosis. After this initial, rapid triggering phase (first phase), the amplification or K_{ATP}^+ channel-independent pathway (second phase) sustains secretion elicited by glucose. To sustain insulin secretion and adequate nutrient sensing, glucose also directly influences transcription (C) and translation (D). (B) Possible pathways of both nutrient and non-nutrient secretagogues that are thought to be involved in insulin secretion. (B1) Glucagon, GIP, etc. bind to cell surface receptors that are coupled to AC via the heterotrimeric GTP-binding protein G_s . Receptor binding activates AC, which produces cAMP from ATP. cAMP binds to PKA, resulting in phosphorylation and activation of

insulin secretion promoting proteins. Additionally, PKA, together with Ca^{2+} , activates the CREB transcription factor which induces, amongst others, insulin gene transcription. (B2) The neurotransmitter acetylcholine and the gastrointestinal hormone cholecystikinin affect insulin secretion by binding to receptors associated with the heterotrimeric GTP-binding protein G_q coupled to PLC. Activation of PLC leads to hydrolysis of PIP_2 with concordant production of IP_3 and DAG. IP_3 stimulates release of Ca^{2+} from the endoplasmic reticulum, activates CaMK and thereby stimulates insulin secretion. The plasma membrane-bound DAG activates PKC, which translocates from the plasma membrane to the cytosol and phosphorylates a number of proteins that facilitate insulin secretion. (B3) The autocrine effect of insulin on insulin secretion. Although debate is ongoing as to whether insulin secretion is negatively or positively affected by insulin, it is thought to be mediated by PI3K. AC, adenylate cyclase; CaMK, Ca^{2+} /Calmodulin-dependent protein kinase II; DAG, diacylglycerol; ETC, electron transport chain; G, glucose; GIP, glucose-dependent insulinotropic polypeptide; IP_3 , inositol triphosphate; P, pyruvate; PIP_2 , phosphatidylinositol bisphosphate; PK, protein kinase; PLC, phospholipase C; RRP, ready releasable pool; TCA, tricarboxylic acid cycle

Besides glucose, other nutrient and non-nutrient secretagogues actively regulate beta cell function, presumably by binding to their respective membrane-bound receptors followed by activation of intracellular signal transduction pathways (Fig. 1, see labels B1, B2 and B3) [12].

At the whole body level, insulin secretory capacity depends not only on the adequate functioning of the individual beta cells, but also on the total number of beta cells, which is physiologically regulated [15]. A multitude of potential hormonal regulators of beta cell growth and proliferation have been described, e.g. gastrin, epidermal growth factor, incretins, growth hormone and insulin(-like) molecules [15]. The G-protein/cAMP/cAMP response element-binding protein (CREB) and insulin/Akt systems are key signalling axes for beta cell survival and proliferation. In turn, glucose also potentiates signalling and regulates gene expression through the latter systems, thereby preserving the ability of beta cells to respond to growth stimulation (reviewed in [14]).

Clearly, normal insulin production depends on a multitude of signal transduction pathways in which many key regulators are present. Adequate glucose sensing not only rapidly regulates insulin synthesis and secretion, but, chronically, is also critical for the maintenance of the glucose-responsive state and the number of beta cells. The large number of regulating factors that can be manipulated relatively easily makes beta cell function a sensitive target for environmental pollutants.

Environmental pollutants and diabetes

Epidemiological evidence

The most convincing evidence for a relationship between diabetes and environmental pollutants comes from accidental or occupational exposures to high levels of these compounds [6]. One of the most striking examples is dioxin exposure, which has been positively linked to the elevated prevalence of type 2 diabetes in several populations, e.g. US Air Force veterans from the Vietnam war [6, 16], dioxin-exposed individuals following the Seveso accident [17], and populations living nearby [18] or working at [19] industrial plants producing dioxin-containing pesticides or herbicides. Apart from dioxin, other environmental pollutants have been epidemiologically associated with type 2 diabetes, as summarised in Table 1 [20–39] (reviewed in [6]).

Associations, however, do not necessarily imply a causal link. It is possible that diabetic individuals have a reduced capacity to excrete or metabolise pollutants, or that compounds might actively contribute to disease development and progression. In-depth investigation of the effect of

chemicals on the processes leading to the development of diabetes is thus required. As deterioration of beta cell function has a key role in diabetes development, it is unsurprising that the first indication of the possible involvement of environmental pollutants in diabetes onset or progression came from experimental studies investigating mechanisms and effects on insulin secretion.

Experimental evidence: effects on beta cell function

Oestrogens and xenoestrogens

Although long considered a plain sex hormone, it is now acknowledged that 17β -oestradiol (E_2) plays an important role in the function of the cardiovascular, musculoskeletal, immune and central nervous systems [40]. Moreover, E_2 has recently been linked to alterations in whole body glucose homeostasis [41]. The most powerful evidence comes from situations where oestrogen levels are outside the physiological range, such as in menopause or pregnancy. Both are considered to be risk factors for diabetes development [42].

With regard to the underlying mechanisms, Alonso-Magdalena et al. [43] showed that oestrogens have direct acute and chronic effects on beta cell function and that different receptors mediate oestrogen action. They demonstrated that chronic E_2 treatment increases the insulin content of beta cells, thereby enabling the cells to secrete more insulin without altering pancreatic beta cell mass or viability. Experiments using oestrogen receptor (ER) knockout mice (both $ER\alpha$ and $ER\beta$, $Esr1^{-/-}$ and $Esr2^{-/-}$) established that direct activation of $ER\alpha$ in vivo and in vitro regulates pancreatic insulin levels [43, 44]. Furthermore, oestrogen-mediated protection of beta cells from injury-stimulated apoptosis also depends on binding to $ER\alpha$ [45].

Administration of physiological E_2 concentrations in vivo and in vitro acutely stimulates GSIS [46, 47]. This rapid response is characterised by increased cGMP levels, activating protein kinase G, which closes K_{ATP}^+ channels. This, in turn, causes membrane depolarisation, and the resulting increase in the intracellular free calcium concentration ($[Ca^{2+}]_i$) enhances glucose-induced signals [46] and insulin secretion. Additionally, the E_2 -stimulated increase in $[Ca^{2+}]_i$ rapidly activates the CREB transcription factor, which plays a key function in beta cell survival and division [48]. In this manner, E_2 initiates a signalling pathway at the plasma membrane that rapidly modifies nuclear function [49]. Initially, Nadal et al. [46] suggested that the rapid responses of beta cells to E_2 are mediated by a non-classical membrane ER (ncmER), but recently they indicated that acute oestrogen effects are probably the result of binding to an extra-nuclear $ER\beta$ [50]. Although two membrane

Table 1 Overview of studies showing epidemiological evidence of the association between the exposure to environmental pollutants and diabetes

Reference	Location	Population/ setting	Age (years)	Diabetes definition	Considered adjusted variables	n	Compounds measured	Compounds with a statistically significant association			
								PCBs	Dioxins	OC pesticides	Others
Philibert et al. [20]	Canada	First Nation community	15–86	Self-reported physician-diagnosed diabetes	Age, sex, place of birth, current smoking status, total serum lipids	101	PCBs (8), <i>p,p'</i> -DDE	PCB-74, PCB-153		<i>p,p'</i> -DDE	
Krämer et al. [21]	Germany	SALIA cohort study (1985–1994, follow-up 2006, 2008–2009) Different polluted areas (7)	54–55	Self-reported physician-diagnosed diabetes	Age, BMI, socioeconomic status, smoking, exposure to environmental tobacco smoke, occupation exposure to temperature and dust, heating with fossil fuels	1,775	NO ₂ and traffic-related PM exposure				NO ₂ , PM
Uemura et al. [22]	Japan	Survey (2002–2006)	15–73	Self-reported physician-diagnosed diabetes Non-diagnosed participants with plasma HbA _{1c} >6.1%	Age, sex, BMI, smoking, regional block, residential area, survey year	1,374	PCDDs (7), PCDFs (10), dioxin-like PCBs (12)	Dioxin-like PCBs	PCDDs, PCDFs, total dioxins		
Ukropec et al. [23]	Slovakia	Recruitment by primary care physicians from heavily polluted Slovakian district of Michalovec and two reference districts (Svidnik and Stropkov)	21–75	FFG >7.0 mmol/l (all participants) and 2 h glucose >11.1 mmol/l (OGTT, 60% of participants)	Age, sex, BMI	2,047	PCBs (15), <i>p,p'</i> -DDE, <i>p,p'</i> -DDT, HCB, β-HCH	Total PCB		<i>p,p'</i> -DDE, <i>p,p'</i> -DDT	
Glynn et al. [24]	Sweden	Women, study on organochlorines and endometrial cancer risk	54–75	Self-reported physician-diagnosed diabetes	Age, BMI, body weight change during the preceding 3 months, place of residence, serum lipids, smoking, duration of breast- feeding, intake of fatty fish, total intake of fish	1,004	<i>p,p'</i> -DDE, HCB, β-HCH, <i>trans</i> -nonachlor, oxychlorane, PCBs (7)			HCB	
Rignell-Hydrom et al. [25]	Sweden	WHIA cohort (1995–2000)	50–59	Baseline OGTT test Women with previously confirmed diabetes were excluded	Age, calendar year, BMI, heredity, country of birth, education, smoking, alcohol intake, hormone replacement therapy, physical activity	742	PCB-153, <i>p,p'</i> -DDE	PCB-153		<i>p,p'</i> -DDE	
Rylander et al. [26]	Sweden	Fishermen and their wives from the Swedish east coast	49–84	Self-reported physician-diagnosed diabetes	Age, sex, BMI	380	PCB-153, <i>p,p'</i> -DDE	PCB-153		<i>p,p'</i> -DDE	

Table 1 (continued)

Reference	Location	Population/ setting	Age (years)	Diabetes definition	Considered adjusted variables	n	Compounds measured	Compounds with a statistically significant association			
								PCBs	Dioxins	OC pesticides	Others
Wang et al. [27]	Taiwan	Yu Cheng cohort (1993–2003)	≥30	Self-reported physician-diagnosed diabetes		748	Total PCB	Total PCB (in women)			
Codru et al. [28]	USA	Mohawk adults (one adult/ household)	≥30	FPG >125 mg/dl Taking prescribed glucose-lowering medication	Age, sex, BMI, serum lipid levels, smoking history	352	Total PCB, PCB-153, PCB-74, DDE, HCB, mirex	Total PCB, PCB-153, PCB-74	DDE, HCB		
Cox et al. [29]	USA	HHANES (1982–1984), Hispanic Americans	20–74	Self-reported physician- diagnosed diabetes	Age, sex, BMI, place of birth, education, poverty index	1,303	<i>p,p'</i> -DDT, <i>p,p'</i> -DDE, dieldrin, oxychlordan, β-HCH, HCB, <i>trans</i> -nonachlor	<i>p,p'</i> -DDT, <i>p,p'</i> -DDE, β-HCH, oxychlordan, <i>trans</i> -nonachlor			
Everett et al. [30]	USA	NHANES (1999–2002)	≥20	Self-reported physician-diagnosed diabetes Non-diagnosed participants with HbA _{1c} >6.1%	Age, sex, BMI, race, country of birth, education, poverty income ratio, waist circumference, physical activity	1,830	PCB-126, HxCDD, <i>p,p'</i> -DDT	PCB-126	<i>p,p'</i> -DDT		
Lang et al. [31]	USA	NHANES (2003–2004)	18–74	Self-reported physician-diagnosed diabetes	Race/ethnicity, BMI, education, annual household income, smoking, waist circumference, urinary creatinine concentration in mg/dl	1,455	BPA				BPA
Lee et al. [32]	USA	NHANES (1999–2002)	≥20	FPG ≥126 mg/dl Non-fasting glucose ≥200 mg/dl Self-reported physician-diagnosed diabetes	Age, sex, BMI, race/ethnicity, poverty income ratio, waist circumference	2,016	PCB-153, HpCDD, OCDD, oxychlordan, DDE, <i>trans</i> -nonachlor	PCB-153	HpCDD, OCDD	Oxychlordan, DDE, <i>trans</i> - nonachlor	
Lee et al. [33]	USA	NHANES (1999–2002)	≥20	FPG ≥126 mg/dl Non-fasting glucose ≥200 mg/dl Self-reported physician-diagnosed diabetes	Age, sex, BMI, race, poverty income ratio, waist circumference	1,721	PCDDs (3), PCDFs (3), dioxin-like PCBs (4), nondioxin-like PCBs (5), OC pesticides (4)	Dioxin-like PCBs		Oxychlordan, <i>trans</i> -nonachlor, β-HCH, DDT	

Lee et al. [34]	USA	CARDIA cohort study (1985–1986; follow up: 1987–2006)	18–30	Newly diagnosed (start 1987) based on: glucose-lowering medications FPG ≥ 126 mg/dl at two or more examinations	Age, sex, BMI, race	180	OC pesticides (9), PCBs (35), PBDEs (1), PBB (1)	Highly chlorinated PCBs	<i>trans</i> -Nonachlor	PBB-153
Lim et al. [35]	USA	NHANES (2003–2004)	≥ 20	FPG ≥ 126 mg/dl Non-fasting plasma glucose ≥ 200 mg/dl Taking insulin or an oral agent	Age, sex, BMI, race/ethnicity, poverty income ratio	1,367	PBDEs (5), PBB-153			PBB-153, PBDE-153
Montgomery et al. [36]	USA	Agricultural Health Study (1993–1997; follow up 1999–2003).		Self-reported physician-diagnosed diabetes	Age, sex, BMI, state, summer exercise, education, smoking	31,787	Exposure assessment based on questionnaire, taking pesticide type, duration and frequency of use in account. 50 pesticides. Cadmium	Dioxins	Chlordane, heptachlor, alachlor, aldrin, cyanazide	Dichlorvos trichlorfon
Schwartz et al. [37]	USA	NHANES (1988–1994)	≥ 40	FPG ≥ 126 mg/dl Taking insulin or an oral agent	Age, sex, BMI, race	8,722	Cadmium			Cadmium
Turyk et al. [38]	USA	Cross-section of Great Lakes sport fish consumers (1992, follow-up 2004–2005)		Self-reported physician-diagnosed diabetes Non-diagnosed participants with HbA _{1c} $> 6.1\%$ (or $> 6.3\%$) (blood measurements)	Age, sex, BMI, triacylglycerols, cholesterol, sport fish meals, smoking, alcohol use, hypothyroid disease, medication use	503	Total PCB (13), Total dioxin-like PCBs (2), total PBDE (8), BDE 47, BDE 153, <i>p</i> , <i>p'</i> -DDE	Dioxin-like PCBs	<i>p,p'</i> -DDE	
Navas-Acien et al. [39]		Review of epidemiological studies					Arsenic			Arsenic

Although not all studies made a clear distinction between type 1 and type 2 diabetes, almost all authors assumed an association with type 2 diabetes, referring to the age of the participants or physician diagnosis

Glucose concentrations should be multiplied by 0.055 or divided by 18 for conversion of milligrams per decilitre to millimoles per litre

For the IUPAC names of chemicals mentioned in this table, please see ESM Table 1

Abbreviations: β -HCH, β -hexachlorocyclohexane; BDE, brominated diphenyl ether; BPA, bisphenol A; CARDIA, Coronary Artery Risk Development in Young Adults; FPG, fasting plasma glucose; HCB, hexachlorobenzene; HHANES, Hispanic Health and Nutrition Examination Survey; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; HxCDD, 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin; *n*, number of participants included in study to estimate association of measured pollutants with type 2 diabetes; NHANES, National Health and Nutrition Examination Survey; NO₂, nitrogen dioxide; OC, organochlorine; OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; PBB, polybrominated biphenyl; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PM, particulate matter; *p,p'*-DDE, 2,2'-bis(4-chlorophenyl)-1,1-dichloroethylene; *p,p'*-DDT, 2,2'-bis(4-chlorophenyl)-1,1,1-trichloro-ethane; SALIA, Study on the Influence of Air Pollution, on Lung, Inflammation and Aging; WHILIA, Women's Health In the Lund Area

molecules behaving as ncmERs were identified in beta cells, namely the sulfonylurea receptor and the G-protein-coupled oestrogen receptor (also known as GPER or GPR30) [51], they only seem to trigger actions at pharmacological rather than physiological E_2 concentrations [44, 52, 53]. Thus, the specific contribution of each of these receptors ($ER\alpha$, $ER\beta$, ncmER) in oestrogen-mediated effects on insulin storage and secretion is still not fully known.

Based on these findings, Alonso-Magdalena et al. [43] suggested that environmental oestrogens or xenoestrogens might have a role in the aetiology of type 2 diabetes. They hypothesised that if the positive effect of E_2 on beta cell function and insulin secretion is taken a step further, prolonged exposure to high oestrogen levels could hyperactivate beta cells. At the whole body level, the ensuing sustained hyperinsulinaemia would be able to induce peripheral insulin resistance and glucose intolerance. This chain of events, commonly referred to as the metabolic syndrome, can explain discrepancies in epidemiological data regarding the beneficial or detrimental effects of oestrogens on glucose homeostasis: a direct stimulatory and protective effect on the beta cell, which, when inappropriately activated, results in insulin secretion not justified by the prevailing glucose concentration. Therefore, the presence of compounds that mimic the actions of E_2 , so-called xenoestrogens, could profoundly affect normal insulin metabolism and beta cell function. Experiments with bisphenol A provide supporting evidence that environmental oestrogens are strong candidates for the exacerbation and acceleration of the development of type 2 diabetes [47].

Bisphenol A has been shown in multiple independent studies, both in vitro (reviewed in [54]) and in vivo (reviewed in [55]), to act as a xenoestrogen and is registered as an EDC [42] in, among other places, the European Union [56]. Although EDCs were initially linked to effects on the reproductive system and thyroid, nowadays it is recognised that other hormonal and physiological systems may also be fundamentally affected. Supporting evidence comes from the association between EDCs and the metabolic syndrome [42].

Until recently, bisphenol A was considered to be a weak oestrogen because in some bioassays (e.g. uterotrophic assays, in vitro receptor binding assays), it can be up to 100,000-fold less potent than E_2 [57]. However, bisphenol A is as potent as E_2 in its effects on beta cell function [47]. In terms of rapid effects on insulin secretion, it has been shown that the dose bisphenol A needed to increase insulin secretion is the same as the dose of E_2 . As for E_2 , both changes in $[Ca^{2+}]_i$ [51] and CREB phosphorylation and activation [48] are reported. An in vivo experiment showed that bisphenol A rapidly increases plasma insulin and decreases blood glucose values [47]. Because this rapid

response is unaffected by the administration of an anti-oestrogen that blocks the classical ERs, the authors suggested that it is mediated by ncmER [47], although they later declared that these receptors are more likely to trigger their actions at pharmacological E_2 concentrations and that $ER\beta$ might be the responsible receptor [50].

Long-term treatment with bisphenol A causes the pancreatic insulin content to increase, and this increase is completely abolished when anti-oestrogens are administered [47]. Furthermore, although both $ER\alpha$ and $ER\beta$ are present in mouse pancreatic beta cells, $ER\alpha$ is the receptor responsible for the regulation of insulin content by both bisphenol A and E_2 [42]. Since the mouse insulin gene does not contain an oestrogen response element (ERE), the equally effective upregulation of the insulin content by bisphenol A relative to E_2 cannot be explained by the classic pathway of ER–ERE binding [42]. One possible explanation is that bisphenol A could act via $ER\alpha$ through other mechanisms, such as activation of other transcription factors or activation of protein kinases through extra-nuclear $ER\alpha$.

The findings on the equal potency of bisphenol A and E_2 with respect to effects on pancreatic beta cells are in line with recent developments on the controversial oestrogenicity of bisphenol A [47]. Current opinion holds that bisphenol A is a selective oestrogen receptor modulator and thus its potency and mode of action can vary between different tissues and even between different cell types in the same tissue (reviewed in [57]).

Strengthened by the demonstration of an association between bisphenol A concentrations and diabetes prevalence (Table 1) [31], the above-mentioned studies show that some xenoestrogens are able to alter beta cell function at environmentally relevant doses and thus might be an additional risk factor for diabetes development or progression. However, the modus operandi of other xenoestrogens (e.g. diethylstilbestrol, nonylphenol) remains to be elucidated.

Although our knowledge of how oestrogenic compounds such as bisphenol A, nonylphenol and diethylstilbestrol interfere with insulin homeostasis is far from complete, the disruptive effect of other classes of compounds is much less known. Figure 2 gives an overview of the chemicals for which a mechanism has been proposed and how they might affect insulin secretion.

Organophosphorus compounds

Organophosphorus compounds (OPCs) are cholinesterase-inhibiting chemicals that are mainly used as pesticides. Inhibition of acetylcholinesterase and the subsequent accumulation of the neurotransmitter acetylcholine at nerve synapses is also the suggested mechanism for OPC toxicity in non-target species [58, 59]. Many OPCs and their

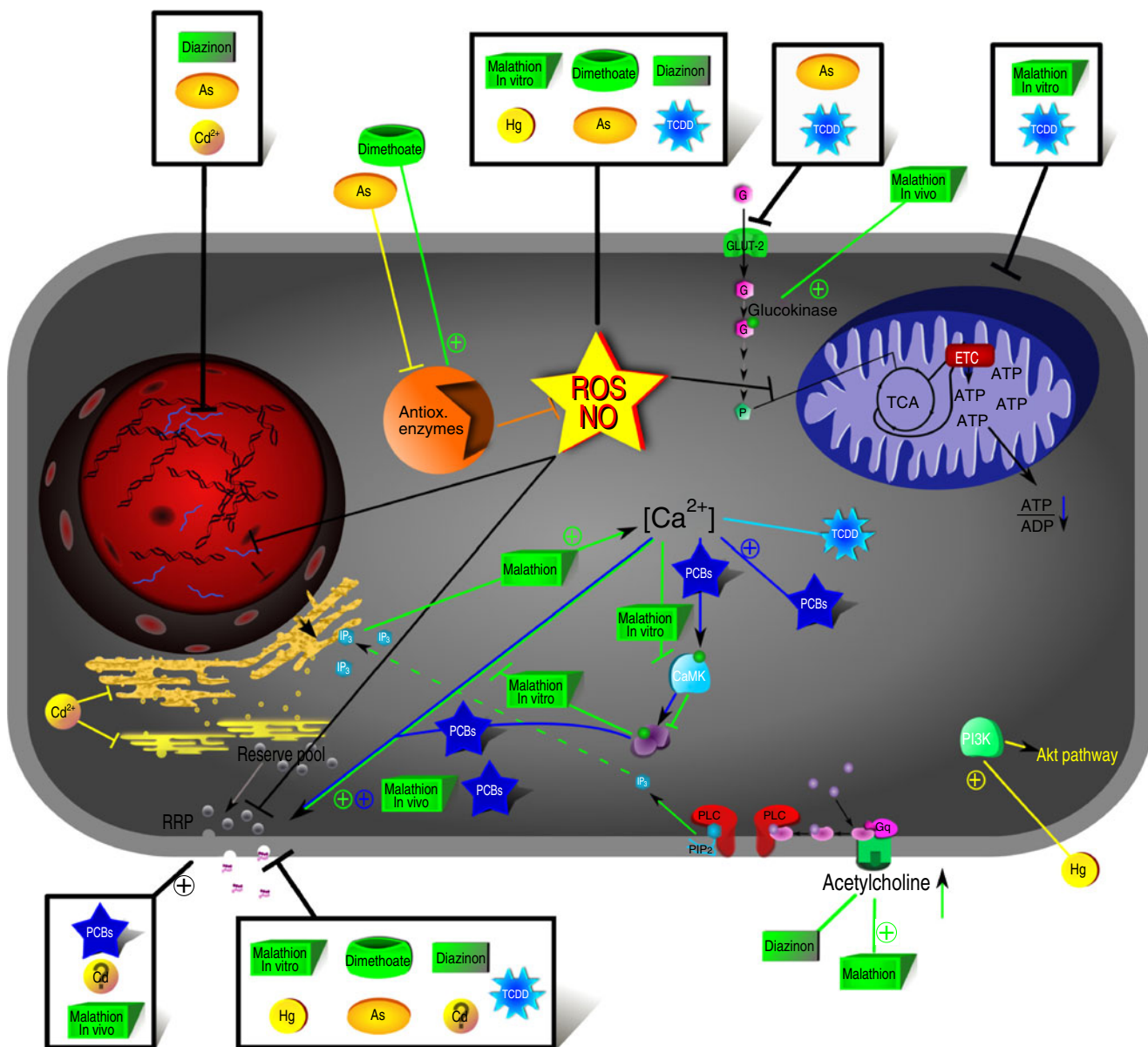


Fig. 2 Disruption of insulin metabolism by environmental pollutants. Current information on the possible mode of action of these chemicals is represented. For key to unlabelled molecules, please see Fig. 1. OPCs are labelled green; POPs, blue; and metals, yellow

metabolites have been shown to be carcinogenic EDCs. They interfere with oestrogen action and thyroid hormones by specifically increasing the expression of oestrogen-responsive genes [60] and preventing thyroid hormone-receptor binding, respectively [61]. The induction of pancreatitis after OPC exposure indicates that OPCs might be able to specifically target pancreatic tissue [62, 63]. That hyperglycaemia is frequently reported and is considered to be one of the main adverse effects of OPC poisoning in humans and animals is suggestive of specific targeting of the endocrine pancreas by these compounds. The unbalanced glucose homeostasis is probably due to inhibition of

acetylcholinesterase at central and peripheral synapses that act in the endocrine regulation of glucose metabolism [64]. Although OPC exposure could possibly be linked to insulin resistance [65], little is known about the impact of OPCs on pancreatic beta cells and the molecular mechanisms supporting this disruption. Malathion is currently one of the most studied OPCs with respect to the mechanisms underlying hyperglycaemia. Remarkably, in vitro and in vivo studies on the effect of malathion on pancreatic beta cells provide contradictory results. In vitro data report a higher insulin content but lower insulin secretion by islets isolated from malathion-treated rats [65, 66], whilst reports

of subchronic exposures to malathion *in vivo* show a significant increase in plasma insulin and glucose levels [59, 65–67].

In an attempt to disentangle the molecular mechanisms that underlie the malathion-induced increase in insulin secretion *in vivo*, Pournourmohammadi et al. [65] proposed a role for acetylcholine itself. Through interaction with muscarinic M₃ receptors, accumulating acetylcholine is thought to increase GSIS, either through a rise in [Ca²⁺]_i or through affecting the efficacy of Ca²⁺ in stimulating exocytosis [68], as frequently observed in other tissues [65]. Additionally, the activation of key enzymes involved in insulin secretion, namely glutamate dehydrogenase and glucokinase, has been suggested to explain the malathion-induced increase in insulin secretion (Fig. 2) [67].

Vosough-Ghanbari et al. [66] made further progress in defining the role of Ca²⁺ in pancreatic malathion toxicity. The authors proposed that a malathion-stimulated increase in Ca²⁺ levels could cause a functional loss of Ca²⁺/calmodulin-dependent protein kinase, a protein associated with insulin secretory granules that is probably involved in exocytosis or insulin granule transport, thereby decreasing Ca²⁺-induced insulin secretion. However, malathion exerts its cytotoxic effects by induction of apoptosis via a direct effect on the islet's mitochondrial function [65], [Ca²⁺]_i elevation, generation of reactive oxygen species (ROS), and depletion of ATP [66] (Fig. 2). Therefore, the observed [Ca²⁺]_i increase is not a direct indication of insulin secretion, since it is also increased during apoptosis, another known action of malathion in pancreatic cells.

Apart from malathion, diazinon and dimethoate are commonly used OPCs that have been shown to elevate plasma glucose levels while decreasing plasma insulin levels [58, 64]. Both compounds induced oxidative/nitrosative stress in islets of Langerhans, and diazinon produced insulin insufficiency [58]. Diazinon-mediated changes in the cholinergic system could also influence insulin secretion (in a similar manner to malathion; Fig. 2). Other OPCs, including dichlorvos [69] (Table 1) and formothion [70], have previously been reported to have hyperglycaemic effects, but molecular and mechanistic evidence is still missing.

The literature cited above clearly indicates that OPCs have the capacity to disrupt beta cell function and warns of their diabetes-inducing potential, since both hyperinsulinaemia and hyperglycaemia were reported. However, caution should be exercised when seeking to implicate OPCs as one of the main mechanisms of diabetes development because OPC poisoning has also been related to pancreatitis, which is a risk factor for diabetes development.

POPs

POPs are organic chemicals that are persistent and widely distributed in the environment, have bioaccumulative properties and are toxic to humans and wildlife [71]. Studies have linked POPs to a large spectrum of adverse effects on wildlife species and humans, such as reproductive, developmental, behavioural, neurological, endocrine and immunological alterations. Several POPs have been suggested to be potential EDCs, as they affect fertility, reproduction [72] and thyroid hormone signalling [73] in both wildlife and humans. POPs have also recently been linked to the development of pathologies associated with the metabolic syndrome, including type 2 diabetes, liver and cardiovascular disease (Table 1). In spite of numerous links with disruption of glucose homeostasis (e.g. hyperglycaemia, hyperinsulinaemia, diabetes), these studies are suggestive, though inconclusive, with regard to environmental contaminants as aetiological agents for diabetes and other metabolic diseases.

One of the most investigated POPs related to adverse effects on glucose and lipid metabolism is the extremely toxic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Several hormone systems in different cell types and tissues and at different developmental stages are being altered by dioxin [74], leading to a complex disruption of multiple endocrine systems. One of the most common symptoms seen in animal species after TCDD exposure is loss of body weight or reduced weight gain [75], commonly referred to as wasting syndrome [76]. Since hypophagia, hyperlipidaemia and hypertriglyceridaemia are observed in TCDD-induced alterations in body weight, the assumption is made that affected animals are unable to utilise the energy-rich nutritional compounds available in their blood. Metabolic derangements related to glucose metabolism have been considered to play a crucial role in the induction of this wasting syndrome [75]. The most important reported effects of TCDD on glucose homeostasis are the reduction of glucose uptake by adipose tissue, liver and pancreas (in vivo as well as in vitro) [77, 78], accompanied by decreased insulin production and secretion by the pancreatic beta cells [79]. The biological basis of this decline is still unclear, but TCDD probably affects GSIS by different mechanisms (Fig. 2). First, glucose transport is thought to be reduced as a consequence of TCDD binding to the aryl hydrocarbon receptor [75]. This causes changes in translational and transcriptional mechanisms resulting in diminished GLUT expression, amongst other effects [77, 78, 80]. Furthermore, abolishment of glucose-induced Ca²⁺ influx and mitochondrial alterations are assumed to be important factors in dioxin-reduced GSIS [81].

Another suggestion concerning beta cell dysfunction is that TCDD exposure could affect the activity of pancreatic

nitric oxide synthase (NOS) [82]. Although the exact function of NOS in pancreatic beta cells is still unknown, multiple studies [83] point to an important negative control of the enzyme on pancreatic beta cell function [84], although paradoxically low nitric oxide levels are noted to have positive effects [83]. As such, environmental toxicants capable of affecting NOS activity need to be tested for their potential to disrupt insulin secretion and metabolism.

Compared with TCDD, the effects of polychlorinated biphenyls (PCBs) on insulin secretion are less thoroughly studied and mechanistic information is sparser. To investigate PCB toxicity, Fischer et al. [85] exposed rat insulinoma RINm5F cells to a commercial mixture of PCBs (Aroclor 1254; Monsanto, St Louis, MO, USA) and three specific PCB congeners (two non-coplanar congeners [PCB-153, PCB-47] and one coplanar congener [PCB-77]). The observed concentration-dependent increase in insulin secreted in cell culture medium for both Aroclor 1254 and the non-coplanar congeners suggest a secretagogue-like effect. This stimulation probably results from a mechanism that includes an increase in $[Ca^{2+}]_i$; followed by activation of a Ca^{2+} /calmodulin-dependent protein kinase [86] (Fig. 2).

In summary, the studies described above provide the first evidence of a possible mechanistic link between glucose metabolism disorders and low-level POP exposure. This information on the effects of PCBs and TCDD on insulin secretion clearly indicates that a more detailed and comprehensive investigation of the targeted effects of these environmental pollutants on beta cells and their involvement in type 2 diabetes development and progression is needed.

Metals

Several metals, such as cadmium, mercury and the metalloid arsenic, have been epidemiologically linked to the incidence of type 2 diabetes (reviewed in [87, 88]). The ability of metals to disrupt insulin secretion was first reported in the 1970s [89]. In this study, cadmium was suggested to have an inhibitory effect on the secretory activity of pancreatic beta cells, mediated by interference with calcium uptake. A decade later, it was suggested that at low concentrations cadmium stimulates insulin secretion, while high levels result in a significantly diminished rate of insulin release [90]. Moreover, in the Third National Health and Nutrition Examination Survey, cadmium was related with both impaired fasting glucose and diabetes [37]. In rats, chronic and subchronic cadmium exposure resulted in an accumulation of cadmium in the pancreas and reduced serum insulin levels, suggesting a possible direct toxic effect of cadmium on the pancreas [88, 91]. In an attempt to

unveil the underlying mechanism, Lei et al. [91] proposed that cadmium affects insulin transcription and translation (Fig. 2). However, a clear outline of its mode of action has not yet been published.

Arsenic seems to affect pancreatic beta cells by the induction of oxidative stress [92] and the reduction of insulin transcription and secretion [93]. The latter was deduced from altered expression of the following genes: (1) *Pdx1* (previously known as *Irf1*) [93–95], a transcription factor that is essential for pancreas development, insulin production and glucose homeostasis [96]; and (2) the insulin gene [97]. Other studies reported effects on glucose uptake, induction of ROS production, interference with the activity of key antioxidant enzymes [98], apoptosis, necrosis and inflammation reactions [39, 93] (Fig. 2).

Mercury, as mercuric chloride ($HgCl_2$), has also been shown to target the pancreas by altering intracellular Ca^{2+} homeostasis in beta cells and decreasing insulin secretion from toadfish islets [99]. The association between type 2 diabetes and the Minamata disease (methylmercury [MeHg] poisoning) in Japan has further underlined the idea of the existence of mercury-induced beta cell damage [100]. The mechanism of action of mercury on pancreatic beta cells is still largely unknown. However, Chen et al. [100] examined the role of the phosphatidylinositol 3-kinase (PI3K)–Akt signalling pathway in mercury-exposed mice (in vitro and in vivo) and showed that insulin secretion is inhibited whereas oxidative stress and PI3K activation are induced. Both, PI3K and ROS are implicated in Akt signalling pathway-dependent pancreatic beta cell dysfunction.

Humans at risk?

Although the studies described above clearly indicate that some environmental pollutants are able to alter beta cell function, it has yet to be determined whether the prevailing environmental concentrations of pollutants can be a risk factor for diabetes. A first hint that the general population is exposed to concentrations that may increase diabetes prevalence is derived from epidemiological studies (Table 1). However, clear causality between human exposure to pollutants and diabetes is so far lacking. An important problem is the fact that the majority of mechanistic studies employ exposure concentrations far above the concentrations found in the human population. To allow profound risk assessment, however, more experimental data at environmentally relevant concentrations are needed. Current risk assessments predominantly use no or lowest observed adverse effect levels (NOAEL/LOAEL), preferably derived from chronic animal studies or, if available, human exposure data to calculate acceptable daily intake doses or reference doses (RfD). Both are

expressed in grams per kilogram per day. To extrapolate data from animal studies, uncertainty factors are used to account for, for example, species differences, length of exposure, LOAEL or NOAEL.

An overview of compound concentrations used in the cited mechanistic studies and compound RfD, if available, is presented in Table 2. At first sight the concentrations used in mechanistic (in vivo) studies are notably higher than the RfD determined by the US Environmental Protection Agency (EPA). However, low doses of bisphenol A ($10\text{--}100\ \mu\text{g kg}^{-1}\ \text{day}^{-1}$) administered to mice significantly altered glucose and insulin homeostasis. These doses are in the range of the RfD of $50\ \mu\text{g kg}^{-1}\ \text{day}^{-1}$ defined by the US EPA [101], based on a LOAEL of $50\ \text{mg kg}^{-1}\ \text{day}^{-1}$ derived from studies performed in the 1980s [46]. Considering the uncertainty factors used for extrapolation of animal data to humans, doses as low as $10\ \mu\text{g kg}^{-1}\ \text{day}^{-1}$ affecting rodents are strong indications of human relevance. This fact, amongst others, has led to discussions about the RfD determined by the US EPA [46, 102].

Malathion also evoked effects on insulin secretion at concentrations ($5, 10$ or $20\ \text{mg kg}^{-1}\ \text{day}^{-1}$) close to the NOAEL of $29\ \text{mg kg}^{-1}\ \text{day}^{-1}$ determined in a 2 year study of toxicity and carcinogenicity in rats [65, 67]. Based on this NOAEL, an acceptable daily intake of up to $0.3\ \text{mg kg}^{-1}\ \text{day}^{-1}$ was established for humans (safety factor 100) by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Meeting of Pesticide Residues (JMPR) [103]. Since malathion in doses of 10 to $20\ \text{mg kg}^{-1}\ \text{day}^{-1}$ fed to rats for 4 weeks altered blood glucose and insulin values, Panahi et al. [67] suggested that the previously determined NOAEL and the derived acceptable daily intake dose [103] for humans should be re-evaluated. At present, the US EPA oral RfD for malathion is set at $20\ \mu\text{g kg}^{-1}\ \text{day}^{-1}$ [104], and this was determined using a study of volunteers who had an oral intake of 8, 16 or 24 mg/day of malathion. In this study, the NOAEL was 16 mg/day (equivalent to $0.27\ \text{mg kg}^{-1}\ \text{day}^{-1}$ for a person of 60 kg). The reported RfD of the JMPR ($0.3\ \text{mg kg}^{-1}\ \text{day}^{-1}$) [103], however, did not include this NOAEL value because they argued that, considering the age of the study, it was likely that the administered malathion contained toxic impurities. Although the RfD of malathion is debatable, this illustrates that the malathion concentrations producing diabetogenic effects in rat might be relevant to humans, and further research on its potential to interfere with processes involved with diabetes development and progression could give valuable information for risk assessment.

For all other compounds discussed in this review the studied concentrations are high compared with exposure levels of the general population and with concentrations

that cause, for example, teratological, reproductive and developmental effects or cancer. For instance, the RfD for TCDD was very recently proposed to be set at $0.7\ \text{pg kg}^{-1}\ \text{day}^{-1}$ based on LOAEL ($\pm 20\ \text{pg kg}^{-1}\ \text{day}^{-1}$) values in human studies looking at endocrine related endpoints (sperm count and thyroid-stimulated hormone concentrations), but is still under review by the US EPA [105]. In acute in vivo studies investigating effects on beta cell function, concentrations of $1\text{--}50\ \mu\text{g/kg}$ are used [79], which are far higher than the RfD. The suggested diabetogenic potential might thus be a minor factor in the risk assessment of these compounds, because other deleterious effects are observed at much lower concentrations. However, some effects manifest themselves acutely, while others manifest themselves more chronically. The time period necessary for a compound to exert its diabetogenic properties in humans has not been investigated so far, but for the example of TCDD only acute (several hours to 10 days) in vivo effects on rabbits were monitored [79]. Because of the lack of information, it is not currently possible to draw conclusions regarding the importance of the diabetogenic effect of these compounds relative to other observed harmful effects.

Based on the findings for certain compounds, such as bisphenol A and malathion, inclusion of the diabetogenic properties might be interesting for estimations of safe acceptable daily intake or RfD values. Because the concentrations of compounds used in mechanistic studies are much higher than those commonly encountered in the environment, these mechanistic studies cannot provide direct information on compound toxicity in human-relevant exposure scenarios. In assessing the risk of a compound, direct extrapolation of concentration levels from simple experimental studies is not always accurate, since more complex exposure scenarios should be considered, such as long-term exposure to low concentrations, mixture effects and exposure during critical stages of development. Moreover, although the applied concentrations are higher than the exposure levels for the human population, specific effects of compounds on the pancreatic beta cell are indicative of a targeted interaction with certain regulatory pathways [102]. The pathways that are altered by, for instance, TCDD might also be triggered by other dioxin-like compounds (e.g. dioxin-like PCBs, polychlorinated dibenzofurans, polybrominated dibenzodioxins/furans). Additionally, since humans are exposed to a variety of compounds, mixtures may exert an effect even at NOAELs of individual compounds. Many compounds act by binding through receptors (oestrogenic compounds to ERs, dioxin-like compounds to the aryl hydrocarbon receptor, etc), which may lead to additive or synergistic effects of the individual compounds.

Table 2 Overview of the experimental set up and model species used in the discussed mechanistic studies

Compound	Mechanistic studies				US EPA			
	Exposure conditions	Model species	Ref	Background information	NOAEL (N) LOAEL (L)	Org	UF	RfD
Bisphenol A	In vitro	0.1/1 nmol/l	Isolated islets or single beta cells, mouse	Quesada et al. [48] Nadal et al. [51]	Concentrations in human serum: 0.2–1.6 ng/ml (0.88–7.0 nmol/l) [43]	Rat	1,000	50 $\mu\text{g kg}^{-1} \text{day}^{-1}$
	In vivo	10/100 $\mu\text{g kg}^{-1} \text{day}^{-1}$	Mouse	Alonso-Magdalena et al. [47]	Concentrations in human urine: Mean: 1.33 ng/ml (5.85 nmol/l) [107]			
Malathion	In vitro	25/125/625 $\mu\text{g/ml}$	Isolated islets, rat	Vosough-Ghanbari et al. [66]	Estimated lethal dose (human): 858 mg/kg [67]	Human	10	20 $\mu\text{g kg}^{-1} \text{day}^{-1}$
		3/15/75 mg/kg, injected 1 h before in vitro testing	Isolated islets, rat	Panahi et al. [67]	Accidental exposure: 10 $\mu\text{g/l}$ [67]			
	In vivo	5/10/20 mg $\text{kg}^{-1} \text{day}^{-1}$	Rat	Poumouhammadi et al. [65]	Concentration in blood after overdose poisoning: 175–517 $\mu\text{g/ml}$ [67]			
Diazinon	In vivo	15/30/60 mg/kg	Rat	Vosough-Ghanbari et al. [66]	JMPR/WHO report [108]: Acute daily intake dose: 0–0.3 mg/kg	NR	NR	NR
				Ghafoor-Rashidi et al. [58]	Acute RID: 2 mg/kg			
Dimethoate	In vivo	20/40 mg $\text{kg}^{-1} \text{day}^{-1}$ (subchronic)	Rat	Kamath and Rajimi et al. [64]	JMPR/WHO report [108]: Acute daily intake dose: 0–0.005 mg/kg	Rat	300	0.2 $\mu\text{g kg}^{-1} \text{day}^{-1}$
				Novelli et al. [75]	Acute RID: 0.03 mg/kg			
TCDD	In vitro	1 $\mu\text{g/kg}$, injected 24 h before in vitro testing	Isolated islets, rat	Novelli et al. [75]	JMPR/WHO report [108]: Acute daily intake dose: 0–0.002 mg/kg	Human	30	0.7 $\mu\text{g kg}^{-1} \text{day}^{-1}$
		0.05/0.5/1.0 nmol/l	INS-1E	Piaggi et al. [81]	Lethal dose (rat): 125 $\mu\text{g/kg}$ [75]			
Aroclor 1254	In vivo	1/50 $\mu\text{g/kg}$	Rabbit	Ebner et al. [79]	NR	Monkey	300	20 ng $\text{kg}^{-1} \text{day}^{-1}$
	In vitro	5/10 $\mu\text{g/ml}$	RINm5F	Fischer et al. [85] Fischer et al. [86]	0.005 mg $\text{kg}^{-1} \text{day}^{-1}$			
PCB-153	In vitro	5/10 $\mu\text{g/ml}$	RINm5F	Fischer et al. [85] Fischer et al. [86]	NR	NR	NR	NR
				Fischer et al. [85] Fischer et al. [86]	NR			
PCB-47	In vitro	5/10 $\mu\text{g/ml}$	RINm5F	Fischer et al. [85] Fischer et al. [86]	NR	NR	NR	NR

Table 2 (continued)

Compound	Mechanistic studies				US EPA				
	Exposure conditions	Model species	Ref	Background information	NOAEL (N) LOAEL (L)	Org	UF	RfD	
Cadmium	In vitro	0.5/1 mmol/l 5/20 $\mu\text{mol/l}$	Isolated pancreas, rat Isolated islets, mouse	Chafghazi et al. [89] Nilsson et al. [90]	Estimated daily intake (US): 0.30–0.35 $\mu\text{g kg}^{-1}$ day^{-1} [109] Mean levels (≥ 20 years; NHANES 1999–2002): 0.468 $\mu\text{g/l}$ (4.164 mmol/l) (blood) 0.273–0.281 $\mu\text{g/l}$ (2.429–2.5 mmol/l) (urine) [109]	0.005 $\text{mg kg}^{-1} \text{day}^{-1}$ (N; water) 0.01 $\text{mg kg}^{-1} \text{day}^{-1}$ (N; food)	Human	10	0.5 $\mu\text{g kg}^{-1} \text{day}^{-1}$ (water) 1 $\mu\text{g kg}^{-1} \text{day}^{-1}$ (food)
	In vivo	0.6 mg kg^{-1} day^{-1} (chronic) 0.5/1.0/2.0 mg kg^{-1} day^{-1} (subchronic)	Rat Rat	Edwards and Prozialeck [88] Lei et al. [91]					
Arsenic	In vitro	0.5/1 mmol/l	Pancreatic islets, human; MIN6 Isolated pancreatic beta cells, rat	MacFarlane et al. [94] Diaz-Villaseñor et al. [97]	NOAEL (rat): 4.0 mg kg^{-1} day^{-1} [110]	0.0008 $\text{mg kg}^{-1} \text{day}^{-1}$ (N) 0.014 $\text{mg kg}^{-1} \text{day}^{-1}$ (L)	Human	3	0.3 $\mu\text{g kg}^{-1} \text{day}^{-1}$
	In vivo	1/5 $\mu\text{mol/l}$ 0.05/0.1/0.25/0.5 $\mu\text{mol/l}$ 3.4 $\text{mg kg}^{-1} \text{day}^{-1}$	INS-1 832/13 Rat	Fu et al. [98] Izquierdo-Vega et al. [92]					
Mercury	In vitro	2/5 $\mu\text{mol/l}$ (MeHg) 0.2/0.5/1 $\mu\text{mol/l}$ (HgCl_2 and MeHg) 1 $\mu\text{mol/l}$ (HgCl_2 and MeHg)	HIT-T15; isolated islets, mouse HIT-T15 Isolated islets, mouse	Chen et al. [99] Chen et al. [100] Chen et al. [100]	Mean urinary mercury concentration in urban pediatric population [100]: 0.2–11.7 $\mu\text{g/l}$ (1.0–58.3 nmol/l) Occupation exposure (blood) [100]: Control: 1.60 \pm 0.20 $\mu\text{g/l}$ (7.98 \pm 1.00 nmol/l) Exposed: 10.72 \pm 1.34 $\mu\text{g/l}$ (53.44 \pm 6.68 nmol/l), 8.08 \pm 1.15 $\mu\text{g/l}$ (40.28 \pm 5.73 nmol/l) Total mercury concentration in hair of diseased population (Japan) [100]: 2.08–36.5 $\mu\text{g/l}$ (10.37–181.96 nmol/l)	0.226/0.317/0.633 $\text{mg kg}^{-1} \text{day}^{-1}$ (L; HgCl_2)	Rat	1,000	0.3 $\mu\text{g kg}^{-1} \text{day}^{-1}$ (HgCl_2)
	In vivo	50/500 $\mu\text{g kg}^{-1}$ day^{-1} (HgCl_2) 20 $\mu\text{g kg}^{-1}$ day^{-1} (MeHg)	Mouse	Chen et al. [100]		0.857–1.472 $\mu\text{g kg}^{-1} \text{day}^{-1}$ (benchmark dose; MeHg)	Human	10	0.1 $\mu\text{g kg}^{-1} \text{day}^{-1}$ (MeHg)

Background information that was provided in (most of) the mechanistic studies to explain the choice of the exposure dose is summarised. To compare the doses used in the experimental studies, the US EPA reference dose, with the NOAEL or LOAEL values, model species (Org) and uncertainty factors (UF) on which their calculations were based was derived from the Integrated Risk Information system of the US EPA [106]. Compounds are discussed in order of appearance

For the IUPAC names of chemicals mentioned in this table, please see ESM Table 1

NR, not reported

Concluding remarks and future directions

The prevalence of diabetes mellitus is currently at epidemic proportions and is a cause of great concern, not only for human health, but also because of its social and economic implications. Although genetic predisposition, obesity, diet and lack of exercise are commonly accepted causes of the development of type 2 diabetes, it is argued that these factors alone cannot fully explain the rapid rise in the prevalence of diabetes. The environment and, more specifically, environmental pollutants are mentioned as major interfering candidates. Although a large variety of compounds have been shown to be epidemiologically correlated with the occurrence of type 2 diabetes, detailed mechanistic information on how these pollutants interfere with insulin metabolism is lacking. Therefore, the present review gives an overview of the available information linking environmental pollutants with type 2 diabetes, specifically focusing on the crucial player in diabetes development, the beta cell. Although the data are sparse and fragmented, pancreatic beta cells are clearly at risk to be targeted by pollutants. Therefore, more research efforts on the interaction of compounds with beta-cell function and/or mass in animal models at human relevant concentrations are needed to further evaluate the hypothesis that environmental pollutants can be additional risk factors for diabetes development. Disentangling the pollutant's modus operandi aids to the elucidation of the underlying pathways that regulate beta cell function and hereby might reveal key regulator and signalling genes and molecules targeted by and susceptible for xenobiotic chemicals. Mechanistic studies in combination with long term *in vivo* exposures at low doses and multigenerational studies in animal models, will definitely ameliorate risk assessment. Simultaneously, more targeted epidemiological research should be undertaken and broadened towards the general population. Only with in-depth information on different exposure scenarios and effect levels can conclusions be made concerning human risk.

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