REVIEW ARTICLE

Environmental Chemical, Pancreatic Toxicity and Metabolic Disorder Review

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ABSTRACT

This review examined traditional and modern methodologies for characterizing pancreas-mediated metabolic dysfunctions and associated diseases resulting from exposures to environmental factors, including environmental chemicals and nutritional factors. The current status, challenges and potential solutions for using the pancreas in toxicity screening of metabolically disrupting chemicals were addressed, highlighting the need for advanced toxicity screening through New Approach Methodologies (NAMs) and advanced *in vitro* models. In addition, the review emphasized the necessity for toxicity screening of aggregate exposures and cumulative risks of environmental chemicals and nutritional factors for comprehensive and holistic human health risk assessment.

INTRODUCTION

The pancreas plays a pivotal role in the onset, development and progression of metabolic syndrome, which is characterized by obesity, insulin resistance, hypertension and dyslipidemia and a precursor to severe health conditions such as steatosis, Type 2 Diabetes (T2D), cardiovascular diseases and various cancers [1].

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The surge in metabolic disorders parallels the significant increase in environmental chemical production and exposure over the past four decades, such as Vinyl Chloride (VC) [2], Bisphenol A (BPA) [3], Phthalates [4], arsenic [5] and nutritional factors such as High-Fat Diets (HFD) [6]. These studies also demonstrated the crucial role of the pancreas in regulating metabolic processes, making it a critical organ for studying the impact of environmental chemical on metabolic syndrome and disease.

Pancreas as a target organ for toxicity testing of environmental chemicals of concern for metabolic syndrome and disease

Evidence of environmental chemical disrupting the pancreas functions dates back to the early 1940s when alloxan, a glucose analogue, was found to induce type 1 diabetes in rabbits by destroying insulin-producing cells [7]. Workers in a Swedish Vinyl Chloride (VC) plant also showed an excess of pancreas tumors [2]. Table 1 summarizes 16 key studies on the effects of environmental chemicals on pancreas-mediated metabolic syndromes and diseases from 1976 to 2018.

Table 1. Table 1 summarizes 16 key studies on the effects of environmental chemicals on pancreas-mediated metabolic syndromes and diseases from 1976 to 2018. These studies were identified based on relevance to pancreatic toxicity, scientific rigor and impact and years of publications.

Environmental chemical	Pancreatic function	Approach	Adverse health outcome	Experimental model	Year
Alloxan	Insulin-producing-cells	Traditional toxicology	Destruction of insulin-producing	*In vivo*	2008
Streptozotocin	β cell apoptosis	Traditional toxicology	Type-I diabetes	*In vivo*	2001
Vinyl chloride	Tumor incidence	Epidemiological data	Pancreatic tumors	Epidemiological data	1976
Bisphenol A (BPA)	β cell function	Traditional toxicology	Insulin resistance	*In vivo*	2011
Perfluorooctanoic Acid (PFOA)	Metabolic pathways	Traditional toxicology	Liver and pancreatic dysfunction	*In vivo*	2013
Arsenic	Insulin secretion	Traditional toxicology	Glucose metabolism	*In vivo*	2011
Phthalates	Insulin resistance	Epidemiology data	Insulin resistance	Epidemiological data	2007
Organophosphates	Glucose and insulin homeostasis	Traditional toxicology	Altered glucose and insulin homeostasis	*In vivo*	2005
Cadmium	Insulin secretion	Traditional toxicology	Impaired insulin secretion	*In vivo*	2009
PCBs	Glucose metabolism	Traditional toxicology	Alters glucose metabolism	Epidemiological data	2005
Dioxins (TCDD)	Insulin secretion	Traditional toxicology	Impairs glucose tolerance	*In vivo*	2016
Lead	Glucose homeostasis	Epidemiology data	Disrupts insulin secretion	Epidemiological data	2013
Mercury	Oxidative stress	Epidemiology data	β cell damage	Epidemiological data	2013
PAHs	Glucose homeostasis	Traditional toxicology	Insulin resistance	*In vivo* (animal)	2004
DDT	Glucose homeostasis	Epidemiology data	Increased risk of diabetes	Epidemiological data	2010
Chlorpyrifos	Insulin signaling	Traditional toxicology	Disrupts glucose metabolism	*In vivo*	2018

Pesticides and metals were prominently represented, with 3 pesticides and 4 metals examined. Studying a wide range of chemicals helped identify multiple pathways through which environmental chemicals can impact pancreatic function, leading to a broader understanding of environmental health risks. Traditional endpoints, such as insulin secretion, glucose metabolism and tumor incidence, were the primary focus of these studies, providing reliable indicators of pancreatic dysfunction and metabolic health impacts. The majority of studies utilized traditional toxicology approaches with an emphasis on toxicity endpoints or adverse health outcomes obtained from *in vivo* animal models or human epidemiological data, which offered a holistic view of the toxic effects on the pancreas, considering the complexities of whole-organism interactions and real-life exposure scenarios.

Efficiently screening chemicals for toxicity using the pancreas as the target required appropriate animal models, in which the phenotypes and pathogeneses of the animal's condition resembled the human disease under investigation. Overall, these studies that were conducted before 2018 highlighted the early stages of research on the relationships between environmental chemical exposure and pancreatic function and a need for more research using New Approach Methods (NAMs) and advanced *in vitro* systems to complement the existing approaches.

Utilizing integrated modern methodologies to provide mechanistic insides into pancreatic toxicity

To address limitations of traditional endpoints and *in vivo* studies, integrating modern methodologies, such as NAMs and developing effective *in vitro* models, have been

extensively applied in the past decade to provide mechanistic insights on environmental chemical mediated pancreatic toxicity. Table 2 is a summary of some key studies using High-Throughput Screening (HTS), Omics technologies, computational modeling, and advanced *in vitro* systems for enhancing our understanding of how environmental chemicals impact pancreatic function, toxicity and adverse health outcome. For instances, studies conducted by Xu et al. demonstrated the potential of HTS in screening a broad range of compounds, including pesticides, industrial chemicals, and metals [8], identifying several that impaired insulin secretion and β-cell viability. The development and application of computational models [9], was crucial in predicting the effects of various chemicals on pancreatic β-cell function. These models integrated data from multiple sources, allowing for the simulation of β-cell responses and identification of potential toxicants without extensive *in vitro* or *in vivo* testing. The study on maturation of human embryonic stem cell-derived pancreatic progenitors into functional islets [10], investigated the effects of toxicants on insulin secretion and β-cell. In addition, the co-culture models of pancreatic β-cells and α-cells was developed to study their interactions in the presence of toxicants such as phthalates and organochlorine pesticides [11]. The advanced *in vitro* models provided valuable information on cellular interactions and collective responses to environmental chemicals, highlighting the complexity of pancreatic responses to toxic insults. In a recent transcriptomics study [12], cell viability was found to be moderately affected after BPA, Bisphenol-F (BPF) and Perfluorooctanesulfonic acid (PFOS) exposure, indicating most of the selected chemicals studied caused functional alterations in pancreatic α-cells for the first time. These studies demonstrated that HTS is an efficient tool for identifying harmful chemicals affecting pancreatic function and Omics profiling can provide detailed insights into molecular expression and pathway changes due to chemical exposure, which is essential for understanding mechanisms of pancreatic toxicity. In addition, computational modeling of NAMs and pathway-based data offer a promising approach to predict chemical toxicity, reducing the reliance on extensive *in vitro* or *in vivo* testing. Advanced *in vitro* models are valuable for identifying environmental chemicals, documenting their toxicity and allowing biochemical and toxicological investigations into the underlying mechanisms, such as pancreatic β-cells for testing of chemical toxicity relevant with certain types of diabetes mellitus in both humans and experimental animals. Current *in vitro* differentiation protocols can efficiently generate glucose-responsive insulin-secreting β-like cells that are not fully mature but are valuable for high-throughput toxicity screening. Human pluripotent stem cell (hPSC) culture has proven to be a powerful tool for *in vitro* toxicity testing, overcoming many limitations of other β-cell models. In summary, integrating modern methodologies, such as NAMs and advanced *in vitro* models, enable more accurate characterization of environmental chemical mediated pancreatic toxicity and metabolic syndromes for improving early detection of toxic effects and ultimately contributing to better protection of human health from environmental exposures.

Table 2. List of some key studies using NAMs and *in vitro* systems for enhancing the understanding of how environmental chemicals impact pancreatic function, toxicity and adverse health outcomes.

Chemical name	Pancreatic function	Approach	Adverse outcomes	Experimental system	Year
BPA	Signaling and glucose metabolism	Transcriptomics	Changes in genes expression and pathways	*In vitro*	2020
VC+HFD	Metabolic dysfunction	Proteomics	Metabolic dysfunction	*In vivo*	2018
Phthalates, organochlorine pesticides	Cellular interactions	Co-culture model	Collective responses to toxicants	*In vitro*	2016
Pesticides	Insulin secretion	HTS	β-cell viability	*In vitro*	2019
Pesticides, heavy metals, industrial solvents	ß-cell function	Computational modeling	Predicted the chemcial effects onß-cell function,	*In vitro*	2018
BPA, BPF, PFOS and etc.	Pancreatic a-cellbiology	Tanscriptomics	Altered pancreatic a-cell function	*In vivo*	2023
Natural product inhibitors	Pancreatic ß-cell function	HTS	Inhibition of pancreatic ß-cell function	*In vitro*	2019

Impacts of the interplay between environmental chemical and nutritional factor on metabolic dysfunction

HFD is well-established as a significant factor promoting metabolic dysfunction and is even considered a major contributor to the development of metabolic syndrome [6]. Numerous examples demonstrate that developmental exposures to metabolically disrupting chemicals can be exacerbated by high-fat diets later in life, underscoring the increased susceptibility to obesity and other metabolic diseases resulting from exposures to environmental chemicals [13]. For instance, developmental exposure to Polycyclic Aromatic Hydrocarbons (PAH) leads to obesity, insulin resistance, and inflammation, particularly when followed by a high-fat diet in adulthood [14].

The insulin resistance induced by BPA may be additive with a HFD [15]. These emerging data support the idea that developmental exposures to environmental chemicals alter the susceptibility set point for metabolic diseases by HFD and the interplay between HFD and chemicals might potentiate the development of metabolic syndromes. In a recent proteomic study, the pancreas proteome of mice exposed to occupational chemical of VC and HFD, singly and in combinations, was compared to that of normal mice fed a Low-Fat Diet (LFD) on a global scale. This comparison aimed to identify differentially expressed cytokines, enzymes and phosphorylated AKT kinases, focusing on a subset of proteins crucial to metabolic dysfunctions mediated by the pancreas. This comparative approach in protein profiling greatly facilitated the identification of dysregulated proteins associated with specific biological conditions, including metabolic syndromes. The quantitative measurement and comparison of proteins that provide mechanistic insights were essential for uncovering and distinguishing the roles of altered proteins in the pathogenesis of metabolic syndrome induced by VC and HFD.

This study provided novel insights into VC toxicity mechanisms and characterized the interactive health effects of VC and HFD on pancreas-mediated metabolic disorder for the first time. To comprehend the molecular basis and toxicity pathways underpinning the development of metabolic syndrome and disease in the pancreas, it's essential to collectively investigate both nutritional and environmental chemical exposures, such as HFD and various chemicals. Additionally, the research necessitated a reevaluation of occupational safety guidelines for the occupational toxicant of VC to protect occupational worker safety, which directly impacted human health risk assessments and regulatory contexts.

CONCLUSION

The pancreas is a valuable but complex target for environmental toxicity testing. Current research has provided robust but sometimes limited insights. To gain a deeper mechanistic understanding and more detailed data on the impacts of environmental chemicals on pancreatic function, it is necessary to expand the use of modern techniques such as New Approach Methodologies (NAMs) and *in vitro* model. Future investigations should delve into the molecular targets and pathways within the AOP framework for effective screening of environmental chemicals for their potential to disrupt metabolism and enabling earlier diagnosis and treatment of metabolic syndromes and associated diseases.

The connections between high-fat diet consumption and occupational exposures are only beginning to be elucidated. It is generally accepted that the risk of metabolic syndromes and diseases may be increased by occupational exposures to chemicals such as Vinyl Chloride (VC). In-depth studies are warranted to explore interactive health effects of occupational toxicants and lifestyle factors, such as HFD, on the pancreas pathways, function and physiology between occupational toxicants and lifestyle factors, such as HFD, for directly impacting human health risk assessments and regulatory contexts and protecting occupational worker safety.

The endocrine system consists of not only the pancreas, but alo liver, and adipose tissue which are also frequently affected simultaneously by environmental chemicals. The system, collectively rather than as individual tissues or organs, regulate overall metabolism. Therefore, for a systematic understanding of metabolic syndromes and diseases mediated by the pancreas, it is essential to integrate environmental exposure data linked to metabolic disruptions originating from the liver and adipose tissues. Translating findings from the pancreas to other metabolically active tissues, especially the liver and adipose tissue is critical to validate data and findings obtained from the pancreas to achieve a systematic understanding of how environmental factors mediate metabolic syndromes and diseases at the systematic level. A comprehensive examination of multiple endpoints and tissues is essential for defining the actions, mechanisms and toxicities of suspected environmental chemicals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Tsai HJ, Chang JS. Environmental risk factors of pancreatic cancer. J Clin Med. 2019;8(9):1427.
2. Lenzen S. The mechanisms of alloxan-and streptozotocin-induced diabetes. Diabetologia. 2008;51(2):216-226.
3. Alonso-Magdalena P, Ropero AB, Soriano S, García-Arévalo M, Ripoll C. Bisphenol-A acts as a potent estrogen *via* non-classical estrogen triggered pathways. Mol Cell Endocrinol. 2012;355(2):201-207.
4. Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult US males. Environ Health Perspect. 2007;115(6):876-882.
5. Paul DS, Walton FS, Saunders RJ, Stýblo M. Arsenic-induced diabetes and pancreatitis in animal models. Toxicol Appl Pharmacol. 2011;257:372-381.
6. Hariri N, Thibault L. High-fat diet-induced obesity in animal models. Nutr Res Rev. 2010;23:270-299.
7. Byren D, Engholm G, Englund A, Westerholm P. Mortality and cancer morbidity in a group of Swedish VCM and PCV production workers. Environ Health Perspect. 1976;17:167-170.
8. Fisher RA. Advances in biokinetic models and computational toxicology. Toxicol Res. 2018;7:821-830.
9. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I. Reversal of diabetes with insulin-producing cells derived *in vitro* from human pluripotent stem cells. Nat Biotechnol. 2014;32(11):1121-1133.
10. Kim SM, Lee EJ, Jung HS, Han N, Kim YJ. Co-culture of α TC-6 cells and β TC-1 cells: Morphology and function. Endocrinol Metab. 2015;30:92–97.
11. Al-Abdulla R, Ferrero H, Boronat-Belda T, Soriano S, Quesada I. Exploring the effects of metabolism-disrupting chemicals on pancreatic α-cell viability, gene expression and function: A screening testing approach. Int J Mol Sci. 2023;24:1044.
12. Wei J, Li Y, Ying C, Chen J, Song L. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. Endocrinology. 2011;152:3049-3061.
13. Khalil A, Villard PH, Dao MA, Burcelin R, Champion S. Polycyclic aromatic hydrocarbons potentiate high-fat diet effects on intestinal inflammation. Toxicol Lett. 2010;196:161-167.
14. Moon MK, Jeong IK, Oh TJ, Ahn HK, Kim HH. Long-term oral exposure to bisphenol A induces glucose intolerance and insulin resistance. J Endocrinol. 2015;226:35-42.
15. Ge Y, Bruno M, Nash MS, Coates NH, Chorley BN. Vinyl chloride enhances high-fat diet-induced proteome alterations in the mouse pancreas related to metabolic dysfunction. Toxicol Sci. 2023;193:103-114.

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