Review



# From Mutation to Metabolism: Environmental and Dietary Toxins as Upstream Drivers of Mitochondrial Dysfunction and Chronic Disease

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*Review*

# From Mutation to Metabolism: Environmental and Dietary Toxins as Upstream Drivers of Mitochondrial Dysfunction and Chronic Disease

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**Abstract**

Environmental and dietary exposures contribute to the modern burden of cancer, atherosclerotic cardiovascular disease (ASCVD), and type 2 diabetes mellitus (T2DM). While mutagenesis remains central to carcinogenesis, many exposures impair mitochondrial function—disrupting electron transport, depolarizing membranes, damaging mitochondrial DNA, and amplifying reactive oxygen species. These mitochondrial injuries converge on oxidative stress, chronic inflammation, endothelial dysfunction, and insulin resistance, thereby linking diverse hazards (industrial solvents, pesticides, heavy metals, air pollution) and dietary patterns (ultra-processed foods, high glycemic load) to common chronic diseases. This narrative review synthesizes human epidemiology with mechanistic evidence to map exposures → mitochondrial injury → disease end points, grading the strength of evidence and distinguishing hazard from risk. We highlight robust associations (e.g., benzene–leukemia, PM2.5–ASCVD, cadmium–CVD/T2DM) and areas of uncertainty (e.g., EMF, omega-6 oils). By centering mitochondria, we offer a unifying framework for prevention policy and clinical practice, and outline research priorities for exposomic measurement, mitochondrial biomarkers, and intervention trials.

**Keywords:** mitochondria; oxidative stress; environmental exposures; carcinogens; heavy metals; PM2.5; ultra-processed foods; insulin resistance; cancer; atherosclerosis; type 2 diabetes

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**Series Note**

This article is part of the *From Mutation to Metabolism* series, which re-examines chronic disease etiology through the lens of metabolic and mitochondrial dysfunction. In the first installment—*From Mutation to Metabolism: Root Cause Analysis of Cancer's Initiating Drivers* (Preprints 2025, DOI:10.20944/preprints202509.0903.v1)—we proposed a systems-based framework identifying upstream drivers such as toxins, dietary stressors, micronutrient deficiencies, and hormonal imbalances. The present review expands on that foundation by focusing specifically on environmental and dietary toxins as upstream initiators of mitochondrial injury, oxidative stress, and systemic metabolic disruption, connecting these mechanisms to cancer, atherosclerotic cardiovascular disease, type 2 diabetes, and other chronic illnesses.

**Highlights (Key Points)**

- Many established carcinogens also damage mitochondria, driving oxidative stress, inflammation, and insulin resistance.
- Shared mitochondrial mechanisms plausibly link toxins to cancer, ASCVD, T2DM, neurodegeneration, and skin aging.
- Diet patterns (high carbohydrate intake, ultra-processed foods, excess omega-6 seed oils) function as metabolic/toxic stressors.
- Risk mitigation should combine exposure reduction with mitochondrial support within an integrative framework.

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This review explores the underrecognized role of environmental toxins in chronic disease development. By focusing on mitochondrial damage—rather than genetic mutations—as a shared mechanism linking cancer, heart disease, and type 2 diabetes, this work offers a new framework for understanding the modern epidemic of chronic illness. The document systematically reviews categories of toxins and the biological pathways they disrupt, including oxidative stress, inflammation, and insulin resistance. This reference is intended for health professionals, researchers, and informed readers seeking a science-based, integrative view of toxic-driven disease.

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## Introduction

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Chronic diseases such as cancer, heart disease, and type 2 diabetes mellitus (T2DM) have become the leading causes of morbidity and mortality worldwide. Although often treated as distinct conditions, these diseases share a common and often overlooked foundation—environmental and industrial toxins.

For decades, the dominant theory of cancer pathogenesis has centered on genetic mutations. While mutations are real, this view is increasingly seen as narrow and incomplete. A growing body of evidence now reveals that many carcinogens—substances officially classified as known or probable human carcinogens by authoritative agencies such as the World Health Organization's International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (EPA), and the National Toxicology Program (NTP)—inflict damage far beyond the genome. Compounds such as benzene, formaldehyde, cadmium, aflatoxins, and radon are not only mutagenic but also disrupt cellular function at multiple levels.

In particular, many of these toxins directly impair mitochondrial function, compromising cellular energy production and triggering cascades of oxidative stress, chronic inflammation, and metabolic imbalance. These mitochondrial and non-genetic injuries represent a powerful and underappreciated mechanism of disease.

Moreover, the health impact of these toxins is not confined to cancer. Mounting research shows that the same carcinogens contributing to tumor development also play major roles in cardiovascular disease, neurodegenerative disorders, liver disease, and endocrine dysfunction. In other words, carcinogens damage more than just DNA—they damage the heart, the brain, the liver, and virtually every organ system.

This book focuses on recognizing and understanding this hidden link: how toxins contribute to the development of chronic diseases through mitochondrial and systemic cellular damage. While prevention, detoxification, and therapeutic strategies are important topics, they are beyond the scope of this volume. The goal here is to reframe our understanding of chronic illness by highlighting an often-ignored but scientifically supported mechanism—one that may fundamentally alter how we approach modern disease.

## 1. Industrial Chemicals

1. **Benzene**, commonly found in plastics, detergents, pesticides, and cigarette smoke, has well-documented toxic effects on overall health. Its mechanisms of toxicity include damaging mitochondrial DNA (mtDNA), disrupting the electron transport chain (ETC), promoting oxidative stress, increasing reactive oxygen species (ROS), causing genetic mutations, and impairing glucose metabolism [1–5]**.** Long-term overexposure to benzene can lead to a wide range of diseases, including but not limited to:
    - **Cancer Risk**: Causes leukemia by damaging bone marrow and inducing chromosomal aberrations [1–7].
    - **Heart Disease Risk**: Increases oxidative stress, leading to endothelial dysfunction and atherosclerosis [8,9].
    - **T2DM Risk**: Alters pancreatic beta-cell function, increases insulin resistance, and promotes chronic inflammation [10,11].
    - **Aging (Skin)**: Causes dryness, reduced elasticity, early signs of aging like wrinkles and fine lines, disrupts the skin barrier and collagen production, increases susceptibility to environmental damage, and may lead to dermatitis, irritation, and potential skin cancer through oxidative stress [11].
2. **Formaldehyde,** commonly found in building materials, furniture, and cosmetics, with well-documented toxic effects on overall health. Its mechanisms of toxicity include forming DNA crosslinks, disrupting mitochondrial DNA (mtDNA) replication, and altering glucose homeostasis [1–5,12]**.** Despite regulations, formaldehyde exposure often exceeds national standards in various environments, particularly in China, the world's largest producer and

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consumer of formaldehyde [13]. Long-term overexposure to formaldehyde can lead to a wide range of diseases, including but not limited to:

- **Cancer Risk**: Linked to nasopharyngeal cancer and leukemia [12,14–16].
- **Heart Disease Risk**: Promotes vascular stiffness and oxidative stress [14,15,17,18].
- **T2DM Risk**: Increases insulin resistance by disrupting mitochondrial function and inducing inflammation in adipose tissue [17,18].
- **Aging (Skin)**: Causes irritation and inflammation, accelerating collagen breakdown, leading to premature wrinkles, loss of skin tone, contact dermatitis, eczema, sensitization, dryness, and skin irritation [19,20].

3. **Phthalates:** widely used plasticizers in consumer products, commonly found in plastics, food packaging, and cosmetics, have well-documented toxic effects on overall health [1–5,21–23]. Their mechanisms of toxicity include mimicking estrogen, interfering with mitochondrial membrane potential, increased oxidative stress and impairing insulin signaling. Long-term overexposure to formaldehyde can lead to a wide range of diseases, including but not limited to:

- **Cancer Risk**: Linked to hormone-dependent cancers.
- **Heart Disease Risk**: Disrupts lipid metabolism and accelerates plaque formation [24–26].
- **T2DM Risk**: Promotes insulin resistance, dyslipidemia, and beta-cell dysfunction [27].
- **Aging (Skin)**: Disrupts hormones, contributing to acne, premature aging, altered skin elasticity, fine lines, dullness, and reduced hydration.

**2. Pesticides**

1. **Glyphosate：** one of the world's most commonly used herbicides (e.g., Roundup), has well-documented toxic effects on overall health [1–5]. Its mechanisms include impairing mitochondrial complex II, reducing ATP production, and affecting glucose metabolism. Long-term overexposure to formaldehyde can lead to a wide range of diseases, including but not limited to:

- **Cancer Risk**: Probable carcinogen linked to lymphoma [28,29].
- **Heart Disease Risk**: Contributes to vascular dysfunction and hypertension [30,31].
- **T2DM Risk**: Alters gut microbiota, disrupts insulin signaling, and promotes chronic inflammation and insulin resistance [32–34].
- **Aging (Skin)**: Linked to dermatitis, skin irritation, and potential disruptions in skin microbiota and causes inflammation, which accelerates skin thinning and sensitivity [29,35–37].

2. **Atrazine：** one of the world's most commonly used herbicides, has well-documented toxic effects on overall health [1–5,38,39]. Its mechanisms include increasing reactive oxygen species (ROS), damaging mitochondrial DNA (mtDNA) leading to mitochondrial dysfunction, and interfering with insulin receptor function, disrupting endocrine system, leading to following diseases.

- **Cancer Risk**: Linked to breast and ovarian cancers [40,41].
- **Heart Disease Risk**: Increases atherosclerotic cardiovascular disease risk [42–44].
- **T2DM Risk**: Associated with insulin resistance, metabolic syndrome, and disrupted lipid metabolism [45,46].
- **Aging (Skin)**: Atrazine induces oxidative stress and damage, impairing skin repair mechanisms and leading to chronic inflammation, premature aging, and early wrinkle formation.

**3. Heavy Metals**

1. **Lead:** Sources of lead exposure include paint, contaminated water, and industrial emissions. As a common staple food, rice can be a significant source of lead exposure in

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some populations due to irrigation with contaminated water. Lead exposure increases risks of cancer, ASCVD, T2DM, and aging (including skin aging) by inducing oxidative stress, DNA damage, vascular inflammation, and disrupting glucose metabolism. Lead exposure accelerates cellular senescence and collagen degradation, disrupts mitochondrial function, shortens telomeres, and degrades collagen, contributing to systemic and skin aging, emphasizing the need to minimize environmental lead exposure and detox for better health and longevity [1–5].

- **Cancer Risk**: Linked to kidney and brain cancers.
- **Heart Disease Risk**: Promotes arteria [47–51]l stiffness and hypertension, increases ASCVD risk and mortality [47–51].
- **T2DM Risk**: Impairs pancreatic beta-cell function and exacerbates insulin resistance [52–56].
- **Aging (Skin)**: Reduces skin elasticity, inhibits collagen production, causes discoloration, and may lead to sagging skin, uneven tone, hair loss, and brittle nails [57].

2. **Mercury:** Mercury exposure primarily comes from contaminated fish and seafood, industrial emissions, gold mining, mercury-containing products (e.g., dental amalgams, cosmetics), and occupational or environmental contamination. Mercury exposure increases risks of cancer, ASCVD, T2DM, and aging (including skin aging) by inducing oxidative stress, chronic inflammation, mitochondrial dysfunction, and DNA damage [1–5]. These mechanisms accelerate cellular senescence, disrupt glucose metabolism, damage vascular and skin integrity, and promote carcinogenesis.
   - **Cancer Risk**: Linked to kidney and skin cancers [58].
   - **Heart Disease Risk**: Increases oxidative stress and endothelial dysfunction [59,60].
   - **T2DM Risk**: Disrupts insulin secretion, reduces beta-cell viability, and increases systemic inflammation, increases insulin resistance [61–63].
   - **Aging (Skin)**: Causes skin rashes, depigmentation, inflammation, mercury-induced erythema, pigmentation disorders, and reduced skin resilience, accelerating the aging process [64].
3. **Cadmium:** Common sources of cadmium exposure include contaminated food (especially rice, leafy vegetables, and shellfish), cigarette smoke, industrial emissions, and occupational exposure in mining, smelting, and battery production. Cadmium exposure increases risks of cancer, ASCVD, T2DM, and aging (including skin aging) by inducing oxidative stress, chronic inflammation, and DNA damage, while disrupting glucose metabolism and endothelial function. It accelerates cellular senescence, impairs collagen synthesis, and promotes carcinogenesis and vascular dysfunction, contributing to systemic and skin aging [1–5].
   - **Cancer Risk**: Causes lung, prostate, and kidney cancers [65–71].
   - **Heart Disease Risk**: Promotes vascular calcification and hypertension [47,72–77].
   - **T2DM Risk**: Induces pancreatic beta-cell damage and impairs glucose uptake in muscle cells [52–55,78,79].
   - **Aging (Skin)**: Accelerates skin aging by triggering oxidative stress, breaking down skin proteins, impairing wound healing, and increasing wrinkle depth [80,81].

**4. Airborne Pollutants**

1. **Particulate Matter (PM2.5)** Air pollution (PM2.5) increases risks of cancer, ASCVD, T2DM, systemic and skin aging by inducing oxidative stress, chronic inflammation, DNA damage, and cellular dysfunction, emphasizing the need for protective measures and air quality improvement [1–5].
   - **Cancer Risk**: Linked to lung cancer and other types of cancer [82–85].
   - **Heart Disease Risk**: Increases ASCVD, myocardial infarction and arrhythmias [86–90].

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- **T2DM Risk**: Linked to insulin resistance and systemic inflammation through oxidative stress [91–95].
- **Aging (Skin)**: penetrates deep into the skin, causing mitochondrial dysfunction, oxidative damage, inflammation, hyperpigmentation, reduced elasticity, and exacerbating acne, eczema, wrinkles, pigmented spots and skin aging [96–99].

**5. Food Additives and Contaminants**

1. **Nitrosamines:** Nitrosamines, found in tobacco, and contaminated water, and processed meats, and even common prescription drugs [100–105], increase risks of cancer, ASCVD, T2DM, and aging (including skin aging) by impairing mitochondrial complexes, disrupting insulin signaling, and increasing reactive oxygen species (ROS) [1–5].
   - **Cancer Risk**: Linked to stomach and colorectal cancer [106–110].
   - **Heart Disease Risk**: Promotes arterial damage [111].
   - **T2DM Risk**: Alters beta-cell function and increases systemic inflammation [112–114].
   - **Aging (Skin)**: Increases skin cancer risk, exacerbates inflammation, impairs collagen synthesis, and accelerates skin sagging and wrinkle formation [113,115].
2. **Aflatoxins:** Aflatoxin contamination, a common foodborne toxin from fungi in grains, nuts, and dairy, significantly increases risks of cancer (especially liver cancer), ASCVD, T2DM, and aging (including skin aging) by causing DNA damage, oxidative stress, mitochondrial dysfunction—depolarizing mitochondrial membranes, reducing ATP production, and altering glucose metabolism—inflammation, and disrupted metabolic processes [1–5].
   - **Cancer Risk**: Strongly associated with liver cancer.
   - **Heart Disease Risk**: Contributes to vascular inflammation.
   - **T2DM Risk**: Impairs beta-cell viability and increases insulin resistance.
   - **Aging (Skin):** Impairs skin repair processes, weakens the skin barrier, disrupts pigmentation, and causes uneven tone and reduced skin integrity.

**6. Household Chemicals and Personal Care Products**

1. **Parabens:** Parabens, widely used preservatives in cosmetics, personal care products and processed foods, increase risks of cancer (especially hormone-related, with parabens detected in 99% of human breast tissue samples [116]), ASCVD, T2DM, autism [117] and aging (including skin aging) by mimicking estrogen [118], disrupting mitochondrial membrane potential, and impairing glucose uptake [1–5]. Parabens has been found in 99% of human breast tissue samples.
   - **Cancer Risk**: Linked to breast cancer [116,119–121].
   - **Heart Disease Risk**: Promotes vascular inflammation [122].
   - **T2DM Risk**: Disrupts insulin sensitivity and promotes adipocyte dysfunction [123–126].
   - **Aging (Skin)**: Disrupts hormonal balance, leading to acne, dryness, reduced skin elasticity, premature aging, and sensitization that may result in dermatitis. Increases mortality risks [127–130].
2. **Triclosan,** a common antimicrobial found in personal care products (such as antibacterial soaps and toothpaste) and household items, increases risks of cancer, ASCVD, T2DM, and aging (including skin aging) by disrupting thyroid [131] and other endocrine function [132], impairing mitochondrial activity, promoting oxidative stress, impairing insulin signaling, and altering lipid and glucose metabolism [1–5,133–136].
   - **Cancer Risk**: Potentially promotes skin cancer [137–141].
   - **Heart Disease Risk**: Impairs vascular function, disrupts lipid metabolism, leading to cardiovascular and renal damage [142].
   - **T2DM Risk**: Increases insulin resistance and beta-cell dysfunction, and fatty liver [143,144].

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- **Aging (Skin)**: Disrupts the skin microbiome, increases oxidative stress, and causes eczema, skin irritation, loss of natural hydration, and accelerated aging signs [145–147].

**7. Radiation and Electronic Emissions**

1. **Radon,** a radioactive gas from soil and building materials, increases risks of cancer (especially lung cancer), ASCVD, T2DM, and aging (including skin aging) through mechanisms such as DNA damage, oxidative stress, chronic inflammation, and mitochondrial dysfunction [1–5].
   - **Cancer Risk**: Leading cause of lung cancer after smoking [148,149].
   - **Heart Disease Risk**: Increases risks for cerebral (stroke) and cardiovascular disease risks [150–154].
   - **Aging (Skin):** Induces oxidative damage, weakens the skin's cellular structure, and increases the risk of premature aging and skin cancer [155,156].
2. **Electromagnetic Fields (EMF):** Electromagnetic fields (EMF) from electronic devices and power lines increase risks of cancer, ASCVD, T2DM, and aging (including skin aging) by inducing oxidative stress, DNA damage, mitochondrial dysfunction, increasing ROS, impairing insulin receptor signaling, promoting inflammation, and disrupting cellular signaling and metabolic processes [1–5].
   - **Cancer Risk**: Increases cancer risk [157–159].
   - **Heart Disease Risk**: Alters cardiac electrical stability, may increase CVD risk [160,161].
   - **T2DM Risk**: Disrupts glucose metabolism by interfering with mitochondrial function in insulin-sensitive tissues [162,163].
   - **Aging (Skin)**: Induces oxidative stress, impairs mitochondrial function, slows skin cell renewal, and weakens the skin barrier, increasing sensitivity to environmental stressors [164–166].

**8. Toxins Used in Cancer Therapy**

1. **Cisplatin,** primarily from chemotherapy or environmental contamination, increases risks of secondary cancers, ASCVD, T2DM, and accelerated aging, including skin aging. Its mechanisms include oxidative stress, DNA damage, mitochondrial dysfunction, and chronic inflammation, which disrupt cellular repair, impair endothelial function, promote insulin resistance, and degrade skin collagen and elastin. Additionally, cisplatin depletes antioxidants and damages stem cell populations, exacerbating systemic and skin aging processes [1–5,167,168].
   - **Cancer Risk**: Is a chemotherapeutic agent but also a carcinogen [169] and may cause secondary malignancies [170,171].
   - **Heart Disease Risk**: Causes cardiotoxicity [172–176].
   - **T2DM Risk**: Damages pancreatic beta-cells and impairs insulin secretion [177–181].
   - **Aging (Skin):** Damages DNA and mitochondrial function, causing dryness, pigmentation changes, reduced skin resilience, and increased sensitivity to UV radiation [182,183].

**9. Dietary Toxins**

1. **High Carbohydrate Diet:** In addition to the above traditionally recognized toxins, dietary high carbohydrate intake has been receiving increasing attention as to their link to increased risks of chronic diseases, including cancer, cardiovascular diseases, diabetes and accelerated aging, through several mechanisms including hyperglycemia, advanced glycation end products (AGEs) formation, insulin resistance, increased inflammation, leaky gut and mitochondrial dysfunction. High carb diet increases risks for many diseases including but not limited to:

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- **Cancer Risk**: Increases cancer risk, including breast cancer [184–187] and colon, bladder, and diabetes-related cancers [188].
- **Heart Disease Risk**: Increases cardiovascular disease risk [189–191].
- **T2DM Risk**: Increased type 2 diabetes mellitus risk [192–197].
- **Aging (Skin):** Increases risks of accelerated skin aging, increased collagen damage, wrinkles, skin atrophy [198–200].

2. **High Ultra-Processed Foods Intake:** increase risks of cancer, ASCVD, T2DM, and aging by promoting chronic inflammation, oxidative stress, hormonal imbalances, and gut dysbiosis while lacking essential nutrients. **Cancer Risk**: Increases risk for various cancers [201–204].**Heart Disease Risk**: Increases cardiovascular disease risk [205–211].**T2DM Risk**: Increases type 2 diabetes mellitus risk [212–216]. **Aging:** Accelerates biological aging, shortens telomere, and increased overall mortality [217–220], as well as accelerated skin aging [221].
3. **High Intake of Omega-6 Rich Seed Oils in the Diet:** Emerging research suggests high dietary intake of omega-6-rich seed oils (e.g., soybean, sunflower, and corn oils) may increase risks of cancer, ASCVD, T2DM, and aging by promoting chronic inflammation, oxidative stress, and an imbalance in the omega-6 to omega-3 ratio. These oils generate pro-inflammatory eicosanoids, exacerbate insulin resistance, and increase lipid peroxidation, leading to cellular damage and accelerated aging. Reducing omega-6 intake and restoring omega-3 balance is critical for lowering these risks and improving health.
   - **Cancer Risk**: Increases risk for various cancers [222–225].
   - **Heart Disease Risk**: Increases cardiovascular disease risk [226,227].
   - **T2DM Risk**: Increases type 2 diabetes mellitus risk [222].

**Key Takeaways**

- **T2DM Risk**: Many of these toxins disrupt insulin sensitivity, glucose metabolism, and pancreatic beta-cell function through oxidative stress and mitochondrial dysfunction.
- **Interconnected Risks**: The overlap between cancer, heart disease, and T2DM highlights the critical role

## Discussion

The impact of toxins on human health extends beyond the direct induction of genetic mutations. These substances target mitochondria, impairing their ability to produce ATP and regulate ROS. Mitochondrial damage lies at the heart of systemic pathologies, linking cancer, heart disease, and T2DM in a shared network of dysfunction.

1. **Cancer**: Toxins such as benzene, formaldehyde, and heavy metals are well-documented carcinogens. They induce DNA damage, disrupt repair mechanisms, and increase oxidative stress, creating an environment conducive to cancer development. However, their mitochondrial effects amplify this risk by impairing cellular energy homeostasis and promoting chronic inflammation—a hallmark of cancer progression.
2. **Heart Disease**: Many toxins, including particulate matter, pesticides, and heavy metals, damage vascular endothelial cells and increase arterial stiffness through oxidative stress and mitochondrial dysfunction. By disrupting mitochondrial signaling, these substances impair the heart's energy supply and contribute to hypertension, atherosclerosis, and myocardial dysfunction.
3. **Type 2 Diabetes Mellitus**: The link between toxins and T2DM is increasingly evident, with substances such as phthalates, cadmium, and glyphosate implicated in insulin resistance and beta-cell dysfunction. Toxins disrupt mitochondrial function in insulin-sensitive tissues, leading to impaired glucose uptake and systemic metabolic imbalances.

The interconnected nature of these diseases highlights the role of toxins as systemic disruptors. They act on multiple pathways simultaneously, reinforcing the need for a holistic approach to

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prevention and treatment. Addressing mitochondrial health, reducing environmental exposures, and improving cellular resilience through nutrition and lifestyle changes are essential steps in mitigating the impact of these toxins.

## Conclusion

The pervasive presence of environmental and industrial toxins presents a significant challenge to global health. These substances not only induce genetic mutations but also cause widespread mitochondrial dysfunction, fueling the development of cancer, heart disease, T2DM, and other chronic illnesses. Recognizing the shared mechanisms underlying these conditions underscores the importance of a unified approach to disease prevention and management.

Efforts to mitigate the impact of these toxins must include regulatory policies to reduce exposure, advancements in medical research to address mitochondrial damage, and public health initiatives promoting awareness and prevention. Furthermore, leveraging strategies such as antioxidant therapies, detoxification protocols, and lifestyle modifications can enhance mitochondrial resilience and improve overall health outcomes. By addressing the root causes of chronic disease, we can move toward a future where these illnesses are not only managed but also prevented.

The evidence is clear: protecting mitochondrial health is central to combating the interconnected epidemics of cancer, heart disease, and T2DM, offering hope for improved public health and longevity.

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