The challenges of linking chemical exposures to carcinogenesis

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Table of Contents

Abstract

Environmental chemical exposures contribute to cancer risk through diverse mechanisms influenced by both intrinsic and extrinsic factors. This essay explores how genetic variation, metabolic enzyme activity, and epigenetic regulation intersect with lifestyle, diet, and exposure timing to shape individual susceptibility to carcinogenesis. Using cigarette smoke, arsenic, and bisphenol A (BPA) as case studies, it highlights genotoxic and non-genotoxic pathways of action. The complexity of cancer development, long latency periods, and variability in biological responses pose significant challenges to attributing causality. Current hazard-based classification systems often fail to capture real-world exposure contexts. As understanding of carcinogenic mechanisms advances, especially in areas like epigenetics and endocrine disruption, risk-based frameworks are needed to more accurately assess cancer risk from chemical exposures.

Introduction

Human exposure to environmental chemicals is an unavoidable aspect of modern life, due to their ubiquitous presence in air, water, food, and consumer products. Although more than 160 million distinct chemicals have been cataloged globally, only 129 have been directly linked to human cancer and officially classified by the International Agency for Research on Cancer as "known human carcinogens" (IARC, 2024). This discrepancy highlights a critical challenge in cancer epidemiology: despite widespread exposure to potentially hazardous chemicals, not all exposed individuals develop cancer. This variability in cancer risk is influenced by a combination of biological, lifestyle, and environmental factors that modulate individual susceptibility to carcinogenesis.

Cancer is a significant burden on Canadians, both in terms of public health and economic impact. According to the Canadian Cancer Society, an estimated 247,100 new cancer cases will be diagnosed in Canada in 2024, with two out of five Canadians expected to be diagnosed with cancer at some point in their lives (Canadian Cancer Society, 2024). The economic burden of cancer in Canada is also substantial; in 2021, it was estimated to cost $26.2 billion CAD, encompassing direct healthcare costs as well as lost productivity and other indirect impacts to families (Garaszczuk et al., 2022). Given the high incidence and economic impact of cancer, understanding modifiable risk factors—including environmental chemical exposures—is essential for effective prevention and intervention strategies. Despite the clear importance of understanding cause and effect relationships between chemical exposures and carcinogenesis, this remains an exceedingly difficult feat due to the highly contextual nature of these relationships.

The process of cancer development is inherently complex and interconnected, involving multiple stages, responses and pathways that differ between individuals, ethnic populations and global regions. Genetic variability, for example, plays a crucial role in cancer susceptibility, with polymorphisms in a wide range of genes involved in cancer metabolism, development and response,

such as in metabolic enzymes, DNA repair mechanisms, immune responses and oncogenes (Talseth-Palmer & Scott, 2011). Additionally, epigenetic factors such as DNA methylation and histone modifications add further complexity, enabling differential regulation of the already complex genetic landscape (Barrow & Michels, 2014). Beyond these intrinsic factors, extrinsic elements such as cumulative chemical exposures, lifestyle choices, dietary habits, sleep patterns, and chronic stress levels play critical roles in modulating cancer risk (Anand et al., 2008).

Furthermore, linking environmental chemical exposure to cancer development poses substantial toxicological and methodological challenges. Carcinogenesis is a prolonged, multi-stage process that may span years or decades, complicating the direct attribution of specific cancers to individual exposures. Furthermore, human studies are often hindered by confounding factors, animal model studies by species-specific variations in susceptibility, and *in vitro* models lack the interconnected physiology of a whole organism, which together obscure causative links between environmental chemicals and cancer. The evolving understanding of what constitutes a carcinogen has also led to concerns over endocrine disrupting chemicals in more recent years, which cause indirect cancer-promoting effects rather than traditional DNA-damaging effects (Gore et al., 2015). These insights necessitate the continuous re-evaluation of regulatory frameworks governing chemical safety, as new information and modes of action of carcinogenesis emerge.

This review examines the interplay between individual susceptibility factors and environmental exposures, as well as the evolving landscape of toxicological research that shapes our understanding of cancer risk. This is an enormous topic, and therefore not every possible factor is discussed. Here, the examples of cigarette smoke, arsenic and bisphenol A are used as case studies as these three chemicals represent a diverse range of carcinogenic mechanisms, exposure sources, and public health implications, making them ideal examples to illustrate the complexities of environmental chemical exposure and cancer risk.

Section 1: Short Overview of Selected Chemicals

1.1 Bisphenol A (BPA)

BPA is an industrial chemical that is widely used in the manufacturing of polycarbonate plastics and epoxy resins (Seachrist et al., 2016). BPA was commonly found consumer products like food and beverage containers, water bottles, toys, and the linings of metal cans. In 2008 BPA was determined to meet the criteria of Section 64 (a) and (c) of the Canadian Environmental Protection Act, 1999 which defines a substance as toxic due to harmful effects on the environment and to human health (Government of Canada, 2024). Currently, baby bottles containing BPA are banned in Canada and there are ongoing exposure monitoring efforts for the general public, however BPA is still used a variety of polycarbonate plastics in consumer goods and was recently detected in 90% of Canadian urine samples tested (Government of Canada, 2024; Rogers, 2021). Concerns about exposure are mainly due to BPA's action as an estrogenic endocrine disrupting chemical (EDC). By binding to estrogen receptors, BPA can interfere with the body's hormonal signaling pathways, potentially leading to abnormal cellular growth and differentiation (Seachrist et al., 2016). After a review on the safety of BPA in 2007, the National Institute of Health in the United States concluded that BPA was likely to be associated with increased malignancies, though there was insufficient data to conclude specifically whether it was carcinogenic (Seachrist et al., 2016). Unlike direct DNA-damaging carcinogens, BPA may exert its cancer-promoting effects through hormonal dysregulation, making it a non-genotoxic chemical of concern.

1.2 Cigarette Smoke

Cigarette smoke contains a complex mixture of over 9500 chemicals, including over 60 known carcinogens like polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and heavy metals (Hecht, 2006; CDC, 2010). Cigarette smoke is a classic example of a genotoxic carcinogen, as many of its

components cause direct damage to DNA bases by forming DNA adducts (DeMarini, 2004). A DNA adduct is when a chemical covalently binds to a DNA base, and if not rapidly repaired, can lead to mutations during DNA replication. Cigarette smoke is well-established as a cause of various cancers and is considered one of the most avoidable risk factors for cancer development (DeMarini, 2004). Smoking-associated genotoxic effects have been found in 8 different organ sites: oral, esophagus, larynx, lungs, pancreas, bone marrow, bladder, and uterus.

1.3 Arsenic

Arsenic is a naturally occurring element found in the earth's crust, and as such can leach into and contaminate drinking water, soil, and food. The most common route of human exposure is through drinking water in regions with high natural arsenic levels, as well as through dietary sources like rice and seafood (Tapio & Grosche, 2006). Unlike traditional genotoxic carcinogens, arsenic does not form DNA adducts and mainly exerts its carcinogenic effects through indirect mechanisms (Speer et al., 2023). Particularly, arsenic known for creating reactive oxygen species during metabolism through disruption of the electron transport chain, among other mechanisms (Tapio & Grosche, 2006; Speer et al., 2023). Reactive oxygen species can directly cause damage to DNA by oxidizing DNA bases which can lead to mutations and DNA strand breaks. Long-term arsenic exposure is associated with an increased risk of several cancers, including skin, bladder, lung, and liver cancers (Chen et al., 1992).

Section 2: Individual Susceptibility to Cancer

2.1 *Intrinsic Factors*

2.1.1 Genetic Variability

DNA damage and subsequent repair are normal occurrences in the body which result from metabolic processes and environmental factors (Lewis & Dimri, 2023). DNA damage does not explicitly lead to carcinogenesis if damage occurs at levels which do not overwhelm repair capabilities. Cells in the

human body experience an estimated 20,000 DNA damaging events per day, which are typically repaired by specific DNA repair pathways depending on the kind of damage (Lindahl & Wood, 1999). For instance, base excision repair (BER) is responsible for removing and replacing damaged bases, single-strand base repair (SSBR) repairs and rejoins single-strand breaks, while homologous recombination (HR) and non-homologous end joining (NHEJ) repair double-strand breaks. Additionally, mismatch repair (MMR) corrects incorrect nucleotide insertions and deletions (Chae et al., 2016). The relationship between DNA repair mechanisms and cancer is nuanced. Loss of function in DNA repair can lead to cancer initiation when DNA damage does occur, while gain-of-function alterations can also contribute to cancer progression due to chemotherapy resistance in cancer cells (Chae et al., 2016). Individual differences in susceptibility to cancer often arise from genetic polymorphisms in these DNA repair genes. Variations in genes involved in BER, HR, NHEJ, and MMR can alter the capability of DNA repair processes, influencing an individual's ability to address damage caused by environmental carcinogens like cigarette smoke and arsenic. For example, polymorphisms in the *XRCC1* gene, which plays a crucial role in SSBR and BER, have been associated with an increased risk of lung cancer in smokers (Chen et al., 2002; Chen et al., 2015). *XRCC1* polymorphisms can reduce the effectiveness of the enzyme's activity in these repair mechanisms, leading to the accumulation of DNA adducts and DNA strand breaks. *ERCC2* polymorphisms is another example of a genetic trait that leads to increased risk of carcinogenesis. *ERCC2* is also involved in BER and those with polymorphisms have been shown to be more vulnerable to ROS-induced DNA damage from chronic arsenic exposure (Banerjee et al., 2007).

Polymorphisms in oncogenes and tumor suppressor genes are further crucial factors that influence an individual's susceptibility to cancer. Proto-oncogenes are involved with normal biological processes as growth factors, transcription factors or other transducers. One example is the RAS gene family, which encode proteins involved in cell signalling that control cell growth and cell

death (NCI, 2022). If these genes have uncontrolled increases in activity, they can become oncogenes which promote dysregulated cell growth and proliferation – hallmarks of cancer cells (Kontomanolis et al., 2020). Tumor suppressor genes, such as *TP53* and *BRCA1*, are involved with cell cycle checkpoints and induce targeted apoptosis, preventing uncontrolled cell division. Variations in these genes can decrease an individual's ability to repair DNA damage before cell division to prevent propagation of mutated DNA (Kontomanolis et al., 2020). For example, BPA mimics the effects of endogenous estrogen and binds the transcription factor estrogen receptor alpha, encoded by the *ESR1* gene, which is known to be involved with cell proliferation regulation (Liao et al., 2013). Excessive estrogen receptor alpha activation can increase the risks of hormone-related cancer development in an indirect way by promoting the proliferation of cells with mutated DNA (Dumitrascu et al., 2020).

Phase 1 and 2 metabolic enzymes play critical roles in the biotransformation of carcinogens. Polymorphisms in the genes encoding these enzymes can lead to differences in the bioactivation or detoxification of carcinogens. For example, PAHs in cigarette smoke are Phase 1 metabolized by CYP1A1, CYP1A2 and CYP1B1 into bioactivated metabolites, such as diol epoxides, which are capable of forming DNA adducts if they are produced faster than Phase 2 enzymes can metabolize them into an excretable form (Luo et al., 2021; Moorthy et al., 2015). Individuals with certain gain-of-function polymorphisms in the *CYP1A1* gene, such as in the *CYP1A1 m1* and *m2* variants, showed increased smoking-related lung cancer risk in an Egyptian population, perhaps due to increased bioactivation of PAHs (Hussein et al., 2014). Glutathione S-transferases (GSTs) are another critical family of enzymes involved in detoxifying reactive metabolites, including those produced by CYP-mediated bioactivation. Compounds undergo detoxification through conjugation reactions with the phase II enzymes to form stable polar products that are readily eliminated (Koh et al., 2011). Genetic polymorphisms in GST genes can lead to reduced or absent enzyme activity, compromising the body's ability to metabolize carcinogens into excretable forms. For instance, the absence of the *GSTM1* gene,

known as the GSTM1 null genotype, has been linked to an increased risk of lung cancer in smokers. Individuals lacking functional GSTM1 are less capable of forming excretable glutathione conjugates with reactive intermediates derived from compounds such as PAHs, leading to a higher accumulation of DNA adducts and a greater risk of carcinogenesis (Liu et al., 2014). BPA metabolism is also influenced by genetic variability in metabolic enzymes. BPA is primarily processed through phase II reactions involving UDP-glucuronosyltransferases (UGTs), which convert BPA into its inactive and excretable forms (Nachman et al., 2014). Individuals carrying polymorphisms of *UGT2B15* show decreased enzymatic activity (Hanoika et al., 2011), thus slower elimination of BPA and potentially higher likelihood for estrogenic receptor interactions.

2.1.2 Epigenetics

Inherited, spontaneous or environmentally induced epigenetic alterations are increasingly being recognized as early molecular events in cancer initiation. The most commonly described epigenetic modification in cancer is DNA methylation at cytosine residues, although chromatin remodelling is also heavily involved. DNA methylation and histone modifications often work together to silence or activate gene transcription (Herceg, 2007). Although tumor suppressor gene silencing by DNA methylation occurs frequently in cancer, genome-wide hypomethylation is one of the hallmark events of early cancer formation (Herceg, 2007). Likely, hypomethylation events lead to aberrant activation of oncogenes. While alterations in the epigenome can occur during adulthood, the epigenome is most vulnerable to external factors during embryogenesis because DNA synthesis is high and DNA methylation patterns required for normal tissue development are highly regulated and established during early development (Dolinoy et al., 2007). The Developmental Origins of Health and Disease (DOHAD) hypothesis provides a model where environmental exposures during development increase susceptibility to cancer in adulthood, not by inducing genetic mutations, but by influencing the programming of the epigenome. Using the example of cigarette smoke, studies have shown promoter

hypermethylation of the tumour suppressor gene *p16* in lung cancers of cigarette smokers (Belinsky, 2004). Presumably, if *in utero* exposure to cigarette smoke caused epigenetic alterations to *p16* expression, this could cause later in life cancer onset should a second carcinogenic exposure occur and tumour suppressor activity is decreased. There are also several other factors which can lead to individual differences and susceptibilities to epigenetic dysregulation of cancer-related genes. For example, genetic polymorphisms in DNA methyltransferase enzymes (DNMTs) and epigenetic drift during normal ageing can lead to a loss of DNA methylation regulation (Herceg, 2007). Epigenetic drift is a well-established gradual hypomethylation event that occurs with age and increases susceptibilities to age-related diseases and cancers (Teschendorff et al., 2013).

Arsenic exposure has a particularly important epigenetic mechanism. DMNTs catalyze the transfer of a donor methyl group from *S*-adenosylmethionine (SAM) onto cytosine residues. The metabolism and excretion of arsenic requires methylation of inorganic arsenic into mono-methylarsonic acid, which uses up multiple equivalents of SAM-donated methyl groups for this process (Reichard & Puga, 2010). Therefore, during excessive or chronic arsenic metabolism, reserves of SAM which are otherwise used for normal DNA methylation maintenance become depleted. This can have profound regulation consequences on epigenetic control of oncogenes, and can be exacerbated if exposure occurs in an individual experiencing age-related epigenetic drift or who already has low DNMT activity due to genetic polymorphisms.

2.2 Extrinsic Factors

2.2.1 Differences in Exposures

Even when individuals are exposed to the same carcinogens, individual cancer susceptibility can be shaped by the timing, duration, and intensity of exposures. Firstly, there are certain windows of susceptibility over the course of a lifetime where an individual may be more vulnerable to environmental carcinogens. As mentioned previously, *in utero* is a particularly sensitive time for the

epigenome. Additionally, adolescent women are vulnerable during puberty as breast tissue proliferation during this time increases the chance that breast cells will be adversely affected by EDCs such as BPA (Totzkay et al., 2023). As people age, they may also become more susceptible to carcinogen exposures due to cumulative DNA damage, a natural decline in DNA repair capacity and epigenetic drift (Solary et al., 2022).

Different types and durations of exposures can also contribute to individual susceptibility to carcinogenesis. Chronic low-dose vs. acute high-dose exposures often result in different risk estimates for known carcinogens (ATSDR, 2022; Halmes et al., 2000). Under this framework, chronic exposures to low levels of arsenic in drinking water can lead to a gradual accumulation of arsenic in bodily tissues, leading to increases in oxidative damage at those sites and inhibition of DNA repair enzymes which increases carcinogenesis risk (Singh et al., 2011). In contrast, acute low-level exposures may also induce immediate changes to gene expression or cause DNA damage but can be subsequently repaired or reserved without overwhelming repair machinery capabilities. Conventional cancer risk assessments generally rely on the assumption that cancer risk increases as a function of cumulative dose (Halmes et al., 2000). However, though the relationship between exposure and cancer risk often follows dose-response curves**,** it is now better understood that these curves are not always linear (Korchevskiy & Korchevskiy, 2022). Non-monotonic dose-responses—where low doses potentially exert more significant or differing effects than higher doses—are observed with endocrine disruptors like BPA, complicating traditional risk assessments (Vandenberg et al., 2012). Therefore, individual risk from carcinogen exposure is highly dependent on dose, timing, duration and unique dose-response curve of the carcinogen.

Synergistic effects occur when two or more chemicals interact in a way that amplifies their combined toxicological impact, often leading to an enhanced risk of cancer. Many metabolic enzymes, such as CYPs, can be induced or inhibited by exposure to chemicals (Hakkola et al., 2020). This is

most well-known in the context of causing significant drug-drug interactions, though the same principles apply for multiple carcinogen exposures. For example, arsenic exposure is known to induce CYP1A1 expression (Wu et al., 2008). This induction of CYP1A1 primes the individual for bioactivation of any subsequent carcinogenic exposures because as previously mentioned, many carcinogens actually require Phase 1 metabolism into their bioactivated form to exert carcinogenic effects. The carcinogenicity of PAHs found in cigarette smoke are dependent upon bioactivation by CYP1A1 (Hecht, 2006), therefore arsenic and cigarette smoke are known have synergistic effects (Wu et al., 2008). Other interactions are also possible, whereby exposure to one carcinogen results in the inhibition of a critical CYP required for the detoxification of a second carcinogen that has direct DNA damaging effects. Even if two individuals had the exact same carcinogen exposure, prior exposures to chemicals can lead to individual susceptibilities to cancer development.

2.2.2 Lifestyle Factors

In addition to intrinsic factors and exposure types, lifestyle choices play a significant role in modulating individual cancer risk. Diet is a particularly important factor. Pro-inflammatory and hyper-insulinemic diets such as high-fat/high-sugar intake have been shown to be linked with many different kinds of cancer in epidemiological studies (Steck & Murphy, 2020; Hajjii-Louati et al., 2021). Conversely, certain preventative measures such as increased dietary fibre or antioxidant intake may decrease the risk of colorectal cancers (Reynolds et al., 2019; Harvard Health, 2024). In fact, approximately 4-8% of all cancers can be attributed to obesity, a disease characterized by chronic low-grade inflammation, making obesity a specific risk factors for cancer development and progression (Pati et al., 2023; Hildebrant et al., 2023). There are several potential mechanisms by which obesity, diabetes and others metabolic dysfunctions contribute to a pro-cancer environment. Firstly, pro-inflammatory cells release growth factors and promote angiogenesis, which are favourable for cancer promotion (Coussens & Werbs, 2010). According to the Warburg effect, cancer cells utilize

aerobic glycolysis for their energy supply, and therefore hyperglycemia is favourable for their proliferation (Avgerinos et al., 2019; Luengo et al., 2021). Furthermore, adipose tissue act as an endocrine organ because it is a site for the aromatization of testosterone into estrogen, which in excess can have oncogenic effects via the activation of the transcription factor estrogen receptor alpha (Avgerinos et al., 2019).

Another potential mechanism for the link between obesity and cancer is through the involvement of peroxisome proliferator-activated receptors (PPARs). PPARs are a group of ligand-activated transcription factors which, play a crucial role in lipid metabolism, energy balance, and inflammation (Vitale et al., 2016). PPARα is expressed in the liver, kidney, small intestine, heart and muscle, where it activates fatty acid metabolism (Tachibana et al., 2008). PPARγ has two isoforms: PPARγ1 and PPARγ2. PPARγ1 is expressed in the colon and immune cells. PPARγ2 is expressed in adipose tissue and regulates adipocyte differentiation. The role of PPARs in cancer is complex, as they have many diverse functions and have been attributed to both tumour suppression and tumour proliferation in different contexts, species and tissues (Tachibana et al., 2008). Generally, PPARα and PPARγ-activation is thought to be anti-inflammatory. Additionally, PPARγ activation has been shown to lead to reduced cancer cell proliferation in a variety of tumour models (Grommes et al., 2004). Conversely, obesity has been shown to be associated with a reduction in PPARα and PPARγ activation and expression (Daynes & Jones, 2002; Wang et al., 2022; Vargas-Sánchez et al., 2020), providing further evidence that obesity is an inflammatory and pro-carcinogenic state. Obesity and metabolic dysregulation can impact PPAR signalling in a variety of tissue types and dysregulation of these signalling pathways may lead to cancer cell proliferation (Tachibana et al., 2008; Hernandez-Quiles et al., 2024). Obesity, diabetes and other metabolic dysfunctions are caused, in part, by lifestyle choices – though of course there are intrinsic dispositions as well, such as PPAR-related genetic mutations. Specifically, four different PPARγ loss-of-function mutations have been shown to be

associated with colon cancer in humans (Sarraf et al., 1999), while several gain-of-function mutations have been associated with bladder cancer in humans (Rochel et al., 2019). This underscores the complexity of the role of PPAR signalling in carcinogenesis, and that individual differences in regulation and chemical exposures can pre-dispose an individual to specific kinds of cancer. For example, arsenic exposure has been shown to inhibit PPARγ expression in a mouse fibroblast preadipocyte cell line (Wang et al., 2005). Conversely, BPA exposure activated PPARγ in a human macrophage cell line and upregulated lipid metabolism-related genes (Gao et al., 2020). Finally, when known PPARγ agonists were administered to bronchial epithelial cells that had been pre-exposed to cigarette smoke, several inflammatory markers were found to be significantly decreased, indicating a potential protective role of PPARγ to lung inflammation in smokers (Wang et al., 2018). Overall, individuals suffering from metabolic dysfunction and PPAR dysregulation may have a more favourable environment for cancer cell growth and proliferation following exposures to carcinogenic chemicals such as cigarette smoke, arsenic or BPA. However, assigning a specific directionality to the role of PPARs in cancer is extremely context-dependant.

Finally, sleep and stress are other important factors to consider when discussing lifestyle factors contributing to individual susceptibility to cancer. Chronic stress triggers the release of glucocorticoids like cortisol, which can lead to immune suppression and increased inflammation, both of which can promote carcinogenesis (Eckerling et al., 2021). Poor sleep quality or insufficient sleep has been associated with an increased risk of several cancers, potentially due to its effects on immune function. In fact, in 2007, the IARC has classified that shift work involving circadian interruption was “probably carcinogenic to humans” (IARC, 2020). Therefore, combining stress or sleep disturbances with other chemical exposures can exacerbate or act synergistically to individual susceptibility to cancer.

Section 3: Toxicological Challenges in Linking Environmental Chemicals to Cancer Risk

3.1 Complexity of Carcinogenesis

The process of carcinogenesis occurs in multiple stages—initiation, promotion, and progression—each of which can be influenced by environmental exposures. During the initiation stage, a carcinogen induces permanent genetic alterations, such as mutations, which can result in irreversible DNA damage (Abel & DiGiovanni, 2010). However, not all initiated cells progress to clonal expansion, and the presence of mutations alone does not guarantee the development of cancer. As previously mentioned, exposure to PAHs in tobacco smoke can result in the formation of DNA adducts, but the progression to cancer depends on subsequent factors and stages of carcinogenesis (Hecht, 2006). The non-guarantee that chemicals which cause initiated cells will then turn into cancer make direct attribution to a specific exposure difficult. The promotion stage involves the clonal expansion of initiated cells as a result of hyperproliferation and inflammation in the tumour microenvironment (Abel & DiGiovanni, 2010). Clonal expansion is when an initiated cancer cell rapidly multiples before host immune and repair mechanisms can reverse or induce apoptosis. Promoting agents, which are often non-genotoxic, stimulate initiated cell proliferation. BPA can act as a promoter by interacting with estrogen receptors, leading to increased cell proliferation in estrogen-sensitive tissues like the breast. Importantly, BPA does not directly induce DNA mutations but instead promotes the expansion of already initiated cells, complicating the direct attribution of BPA to cancer development (Weber Lozada & Keri, 2011). Individual factors discussed in the previous section are crucial at this stage for determining cancer outcome. The progression stage marks the accumulation of additional genetic and epigenetic changes which silence tumour-suppressor genes, activate oncogenes, promote angiogenesis, and epithelial-to-mesenchymal transition thereby promoting metastasizing of cancer cells (Abel & DiGiovanni, 2010). Arsenic exposure, as previously discussed, can result in DNA hypomethylation which can favour the progression of cancer by potentially activating oncogenes

(Reichard & Puga, 2010). Finally, because cancer must progress through this variety of stages, there is often long latency periods between exposures and cancer (Páez et al., 2012). This prolonged period of disease development, with many factors involved with the progression from one stage to another further complicates direct attributions of specific chemical exposures to carcinogenicity.

3.2 Limitations of Epidemiological and Experimental Studies

Epidemiological studies play a critical role in assessing the carcinogenic risks of environmental chemicals, but they are often subject to confounding variables that complicate the interpretation of results. Factors that were previously discussed in Section 2 leading to individual susceptibilities make it difficult to predict carcinogenic risk of a single exposure. Statistical analyses control for these confounders, yet even advanced statistical methods such as multivariable regression analysis may not fully account for all sources of bias because it relies on prior knowledge and understanding of confounding variables, often leading to residual confounding (Becher, 1992). Experimental studies, while valuable for establishing mechanistic pathways, also face significant limitations. *In vivo* animal models often provide insights into chemical carcinogenicity, but species-specific differences in metabolism, DNA repair mechanisms, and immune responses can lead to results that do not accurately predict human outcomes. Rodent models are commonly used to study chemical-induced cancer, yet the metabolic pathways in rodents may differ significantly from those in humans, leading to either an underestimation or overestimation of carcinogenic risks (Kirchmair et al., 2015; Caporossi & Papaleo, 2015). The metabolism of BPA for example, may differ between humans and rodents, as it is speculated that glucuronidation and excretion of BPA is more rapid in humans, leading to potentially higher toxicity in rodents (Caporossi & Papaleo, 2015). Similarly, *in vitro* studies, while crucial for understanding molecular mechanisms of carcinogenesis, lack the complexity of a whole organism. These studies do not account for systemic interactions such as tissue-specific susceptibilities, immune responses, or the metabolic processes that influence how chemicals

are activated or detoxified in the body (Katt et al., 2016). This lack of physiological context makes it challenging to translate *in vitro* findings directly to human cancer risk.

To provide an example of how findings between various models can differ, there has been much conflicting evidence in the case of BPA carcinogenicity which has led to difficulties in risk assessment globally. Seachrist et al. (2016) reviews the epidemiological, *in vivo* and *in vitro* evidence for BPA and carcinogenesis, and concludes that there is strong evidence in *in vivo* and *in vitro* models of a connection, this has yet to be proven in humans. In fact, in 2023 a more recent review states "there is no clear evidence of associations between BPA and cancer in humans" (Prueitt et al., 2023). However, another recent review states that results from the CLARITY-BPA study (a U.S. federal government research initiative) indicate that low-dose and developmental exposures increase human cancer risk (Khan et al., 2021). The CLARITY-BPA report itself does not attempt to interpret findings. One epidemiological study, which is often cited, investigated blood levels of BPA in Korean women and breast cancer occurrence found no statistical difference between levels of BPA in cases compared to controls (Yang et al., 2009). However, this epidemiological finding does not rule out the possibility for BPA being involved in carcinogenesis, because as previously discussed, there are different period of susceptibility which may shape carcinogenesis risk that are not considered from measuring serum BPA levels of women in adulthood. *In vitro* experiments have shown that BPA exposure increased the proliferation, migration and invasion of human ovarian cancer cells (Xie et al., 2023). In an *in vivo* rat model, exposure to BPA *in utero* increased mammary tumour susceptibility in an induced-carcinogenesis mammary gland cell model, indicating that BPA may enhance cancer proliferation/progression (Weber Lozada & Keri, 2011). However, these findings in *in vivo* and *in vitro* models don't necessarily indicate that BPA is carcinogenic in humans. The model, methods, routes of exposure, timing and duration of exposure, metabolism and species-specific differences all make inferring human outcomes difficult.

3.3 Evolving Understanding of Carcinogen Classification

In recent decades, the classification of carcinogens has come under scrutiny due to evolving scientific understanding. Historically, global agencies such as the IARC and the United Nations Global Harmonized System (GHS) of Classification and Labeling of Chemicals have relied on hazard identification approaches to classify chemicals. These classifications often do not account for actual human exposure levels or specific risk decision frameworks (Boobis et al., 2016). A statement to the public from Cancer Research UK (2012) summarized this as "the IARC does hazard identification, not risk assessment", meaning that identifying a chemical's carcinogenic potential does not provide information about the magnitude of public risk (Boobis et al., 2016). For example, chemicals with widely differing potencies, like processed meat and sulfur mustard gas, are placed into the same category (Group 1), which can lead to public misperceptions about their relative risks (Boobis et al., 2016). This has raised concerns that hazard-identification classification systems are of poor relation to cancer preventative measures, and lead to difficulty in translating classifications into health policies which reflect realistic risk (The Lancet Oncology, 2016).

Many of current classification systems were developed in an era when chemicals that directly damage genetic material, such as nitrosamines in cigarette smoke, were the main focus of carcinogenicity (Boobis et al., 2016). However, as more chemicals were tested using long-term rodent experiments, non-genotoxic carcinogens emerged. These carcinogens act through mechanisms such as changes to cell proliferation or chronic inflammation, which may involve non-linear dose-responses, where cancer risk is strongly dependent on exposure context (Bevan & Harrison, 2017). Appropriate regulation of carcinogenic substances requires understanding their mode of action, particularly whether they exhibit a threshold effect. Genotoxic carcinogens are understood to have no specific threshold of harm, as carcinogenicity increases linearly with dose (Nohmi, 2018). Non-genotoxic carcinogens, however, often have a threshold dose, meaning below a specific dose there is

no measurable adverse effect, and the elicited response may not increase linearly with dose (Nohmi, 2018). Therefore, it is possible that a non-genotoxic carcinogen may have an exposure dose range which could theoretically be considered to be completely safe, yet still be classified as a "known human carcinogen" by the IARC. Given this important discrepancy in dose-responses models between genotoxic and non-genotoxic carcinogens, there is inadequate distinguishment between their potential risks using classification systems (Boobis et al., 2016).

A key development has been the identification of 10 key characteristics of carcinogens, which better reflect the complexity of carcinogen mode of actions (Smith et al., 2016). These characteristics, summarized in Table 1, allow for a broader understanding of how both genotoxic and non-genotoxic chemicals can contribute to cancer risk. As previously discussed, chemicals that alter DNA repair enzyme activity or cell proliferation without causing DNA mutations may still contribute to cancer risk through indirect pathways. This evolving understanding emphasizes the importance of moving away from hazard-based classification and adopting risk-based assessment frameworks that take into account actual human exposure and biological context. For many chemicals, there remain key characteristics where not enough research has been conducted yet, and further carcinogenic modes of action may still be uncovered. For example, research regarding the capability of chemicals to alter the epigenome is especially lacking (Potera, 2016). Furthermore, it is possible that in future decades, even more modes of action of carcinogenesis

will be elucidated, leading to an even more refined view of which chemicals are carcinogenic

and under what circumstances. As understanding of the various modes of action for carcinogens increases, ideally the ability to assign risk to specific carcinogenic exposures will also increase.

Table 1: Key Characteristics of Carcinogens (Adapted from Smith et al., 2016)

Characteristic	Examples of Relevant Evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with electrophilic structure, forming DNA/protein adducts
2. Is genotoxic	DNA damage (strand breaks, mutations), intercalation, cytogenetic changes
3. Alters DNA repair	Disruption of DNA repair machinery (e.g., replication, base excision repair)
4. Induces epigenetic alterations	Changes in DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Formation of oxygen radicals, oxidative stress, macromolecular damage
6. Induces chronic inflammation	Increased cytokine/chemokine production, elevated myeloperoxidase activity
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Activation/inactivation of receptors (e.g., ER, AhR), modulation of ligands
9. Causes immortalization	Inhibition of cellular senescence, transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, alterations in cellular energetics

Conclusion

Understanding the link between environmental chemical exposures and cancer development is a multifaceted challenge that requires consideration of both intrinsic biological factors and extrinsic environmental exposures. From direct DNA damage, as seen with cigarette smoke, to non-genotoxic pathways, such as the hormone disruption caused by BPA or the oxidative stress induced by arsenic, it is clear that the mechanisms of chemical carcinogenesis are varied and complex. Individual susceptibility to cancer is dependent upon both intrinsic factors, such as genetic variability and epigenetics, and extrinsic factors, including exposure and lifestyle choices. Genetic polymorphisms or epigenetic regulations in metabolic enzymes like CYP1A1 and GSTM1, for example, can significantly affect how individuals metabolize and detoxify carcinogens, influencing their overall cancer risk. Similarly, environmental and lifestyle factors, such as diet, stress, and obesity, play crucial roles in modulating cancer risk. Metabolic dysfunction, driven by obesity and conditions like diabetes, further interacts with environmental exposures, creating a favorable environment for cancer cell proliferation.

There are substantial toxicological challenges in directly linking chemical exposure to carcinogenesis. The initiation, promotion, and progression stages of cancer development complicate direct attribution to specific exposures, particularly when there are long latency periods between exposure and disease manifestation. Moreover, epidemiological studies are often confounded by various factors, and experimental studies, whether *in vivo* or *in vitro*, fail to fully predict human systems. Furthermore, traditional hazard-based systems fail to account for exposure levels, dose-response relationships, and biological context of chemical carcinogenesis. This can lead to public confusion regarding the relative risks of different chemicals. Risk assessment frameworks may be a better capture the nuanced ways chemicals interact with individual susceptibilities and real-world exposure. Finally, the understanding of modes of action of carcinogenesis may continue to expand as new research emerges in fields such as epigenetics.

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