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Review

REVIEW

Chemical compounds from anthropogenic environment and immune evasion mechanisms: potential interactions

Julia Kravchenko[1,*], Emanuela Corsini[2], Marc A.Williams[3], William Decker[4], Masoud H.Manjili[5], Takemi Otsuki[6], Neetu Singh[7], Faha Al-Mulla[8], Rabeah Al-Temaimi[8], Amedeo Amedei[9], Anna Maria Colacci[10], Monica Vaccari[10], Chiara Mondello[11], A. Ivana Scovassi[11], Jayadev Raju[12], Roslida A.Hamid[13], Lorenzo Memeo[14], Stefano Forte[14], Rabindra Roy[15], Jordan Woodrick[15], Hosni K.Salem[16], Elizabeth P. Ryan[17], Dustin G. Brown[17], William H.Bisson[18], Leroy Lowe[19] and H.Kim Lyerly[1,20]

[1]Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA; [2]Dipartimento di Scienze Farmacologiche e Biomolecolari, School of Pharmacy, Università degli Studi di Milano, 20133 Milan, Italy; [3]MEDCOM Army Institute of Public Health, Toxicology Portfolio - Health Effects Research Program, Aberdeen Proving Ground, Edgewood, Baltimore, MD 21010, USA; [4]Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX 77030, USA; [5]Department of Microbiology and Immunology, Massey Cancer Center, Virginia Commonwealth University, Richmond, VA 23298, USA; [6]Department of Hygiene, Kawasaki Medical School, Kurashiki 701-0192, Japan, [7]Advanced Molecular Science Research Centre, King George's Medical University, Lucknow, Uttar Pradesh 226003, India, [8]Department of Pathology, Kuwait University, Safat 13110, Kuwait, [9]Department of Experimental and Clinical Medicine, University of Firenze, Firenze 50134, Italy, [10]Center for Environmental Carcinogenesis and Risk Assessment, Environmental Protection and Health Prevention Agency, 40126 Bologna, Italy, [11]Institute of Molecular Genetics, National Research Council, Pavia 27100, Italy, [12]Toxicology Research Division, Bureau of Chemical Safety, Food Directorate, HPFB, Health Canada, Ottawa, Ontario K1A0K9, Canada, [13]Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor 43400, Malaysia, [14]Mediterranean Institute of Oncology, 95029 Viagrande, Italy, [15]Molecular Oncology Program, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC 20057, USA, [16]Urology Department, Kasr Al-Ainy School of Medicine, Cairo University, El Manial, Cairo 12515, Egypt, [17]Department of Environmental and Radiological Health Sciences, Colorado State University/ Colorado School of Public Health, Fort Collins, CO, 80523-1680, USA, [18]Environmental and Molecular Toxicology, Environmental Health Sciences Center, Oregon State University, Corvallis, OR 97331, USA, [19]Getting to Know Cancer, Nova Scotia, Canada and [20]Department of Pathology, Duke University Medical Center, Durham, NC 27710, USA

*To whom correspondence should be addressed. Tel: +1 919 668 6809; Fax: +1 919 681 7970; Email: julia.krauchanka@duke.edu

Correspondence may also be addressed to William H. Bisson. Tel: +1 541 737 5735; Fax: +1 541 737 0497; Email: bissonw@science.oregonstate.edu

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Abstract

An increasing number of studies suggest an important role of host immunity as a barrier to tumor formation and progression. Complex mechanisms and multiple pathways are involved in evading innate and adaptive immune responses, with a broad spectrum of chemicals displaying the potential to adversely influence immunosurveillance. The evaluation of the cumulative effects of low-dose exposures from the occupational and natural environment, especially if multiple chemicals target the same gene(s) or pathway(s), is a challenge. We reviewed common environmental chemicals and

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discussed their potential effects on immunosurveillance. Our overarching objective was to review related signaling pathways influencing immune surveillance such as the pathways involving PI3K/Akt, chemokines, TGF-β, FAK, IGF-1, HIF-1α, IL-6, IL-1α, CTLA-4 and PD-1/PDL-1 could individually or collectively impact immunosurveillance. A number of chemicals that are common in the anthropogenic environment such as fungicides (maneb, fluoxastrobin and pyroclostrobin), herbicides (atrazine), insecticides (pyridaben and azamethiphos), the components of personal care products (triclosan and bisphenol A) and diethylhexylphthalate with pathways critical to tumor immunosurveillance. At this time, these chemicals are not recognized as human carcinogens; however, it is known that they these chemicalscan simultaneously persist in the environment and appear to have some potential interfere with the host immune response, therefore potentially contributing to promotion interacting with of immune evasion mechanisms, and promoting subsequent tumor growth and progression.

Abbreviations

CCL	chemokine C–C motif ligand
DC	dendritic cell
DEHP	diethylhexylphthalate
EPA	Environmental Protection Agency
IARC	International Agency for Research on Cancer
IL	interleukin
NK	natural killer
TGF-β	transforming growth factor-beta

Introduction

Individuals are routinely exposed to various combinations of chemicals at low doses; however, the combined, long-term effects of such exposures on human health remain unclear. The non-governmental and not-for-profit organization known as 'Getting to Know Cancer' (www.gettingtoknowcancer.org) solicited and then selected teams of scientists to review the possibility and consider the hypothesis that chemicals common in the anthropogenic environment chemicals may contribute to human carcinogenesis, even though they are not considered human carcinogens by the International Agency for Research on Cancer (IARC). An overarching framework of this analysis was a review of environmental chemical carcinogenesis, with specific points of focus on one of the individual characteristics of cancer cells widely recognized by modern cancer scientists as one of the 'hallmarks of cancer' (1,2). Although each of the individual hallmarks is reviewed in companion reviews by scientist with expertise in each hallmark, this specific review is focused on the more recently recognized emerging hallmark of cancer 'immune evasion mechanisms of carcinogenesis' (2) and the potential interactions of these mechanisms with environmental chemicals.

The 'hallmarks of cancer' originally described in a seminal publication by Hanahan *et al.* (1) included sustained proliferative signaling, evasion of suppressed growth, activation of invasion and metastasis, enabling replicative immortality, induction of angiogenesis, resistance to cell death and underlying genomic instability and inflammation. Of note, immune evasion was not listed among these original 'hallmarks'; however, Hanahan *et al.* (2) recognized that tumor evasion from immune system recognition and destruction is an emerging hallmark of cancer in their most recent update. These changes have occurred as observational data from genetically engineered mice to clinical epidemiology studies suggested that the 'immune system operates as a significant barrier to tumor formation and progression, at least in some forms of non-viral induced cancer' (2). Consequently, multiple chemicals from the anthropogenic environment may contribute to carcinogenesis through this mechanism.

In part, because this element of carcinogenesis has been only recently widely recognized, there is a paucity of data in animal models, in human cell model systems and in clinical studies that are related to putative associations between the immune response to tumor cells and exposures to various chemicals from the anthropogenic environment. Nonetheless, the specific assessment of environmental exposures that might affect immunosurveillance faces many challenges, so this is a relatively new area of research. For example, we cannot currently list the precise chemicals that affect immune evasion mechanisms due to an insufficient knowledge base in this relatively novel field. Consequently, additional investigations will be needed to demonstrate the impact of environmental chemical exposures on the immune system to better understand whether or not it can be compromised or dysregulated with a subsequent loss of an effective tumor immunosurveillance network. Nonetheless, this review is an opportunity to recognize and discuss this knowledge gap. In this review, we discuss a number of environmental chemicals of interest based on reports of their potential interactions with the mechanisms involved in immunosurveillance.

Overview of immune evasion as a hallmark of cancer: immunologic perspective and mechanisms

Since the late 19th century, rare spontaneous tumor regressions were noted in patients following episodes of infection, which suggested that immune response could inhibit or modify the behavior of cancers (3). However, early attempts at treating cancer patients by simply giving them bacterial extracts failed because the nature and role of host immunity in cancer remission was not well understood, and a simplistic view that a 'toxic factor' contained in the bacterial extracts was the one that prevailed (4–10). The more sophisticated concept of tumor immune surveillance was introduced in the mid-20th century (11,12) as the host immune system was characterized as capable of both recognizing and responding to nascent transformed cells in an organism and destroying them. Later, molecular mechanisms of antigen processing and presentation and the role of the major histocompatibility complex in this process were discovered (13), with the realization that a variety of tumor-associated and tumor-specific antigens contained within membrane and intracellular compartments of tumor cells could serve as targets of the immune system. More recently, it has been recognized that the presence of antigen alone is insufficient to generate a potent immune response, and activation by costimulatory molecules may also be required for effective immune stimulation (14). Finally, potent immunomodulatory checkpoints, both at the activation phase and the effector phase, have been recognized, and therapeutic blockade of the checkpoints has resulted in dramatic antitumor responses in clinical studies, creating a

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new era of enthusiasm for immune-based therapies targeting cancer (15–20).

A number of clinical observations have also supported the evidence for intrinsic immunosurveillance of tumors. For example, in immunodeficient patients with advanced human immunodeficiency virus infection with low levels of circulating $CD4^+$ T cells often developed malignancies known to be associated with viral infections (e.g. Kaposi's sarcoma, non-Hodgkin's lymphoma, invasive cervical carcinoma and anal cancer) (21,22) and also with some non-viral etiologies (e.g. increased risk of lung cancer after adjusting for smoking status) (23,24). An important role of T cells in preventing recurrent leukemia following allogeneic bone marrow transplantation was also reported (25,26). Other observations have been less profound; nonetheless, a low natural killer (NK) cell activity has been reported in patients with breast cancer that had a family history of this tumor and in their first-degree relatives that were clinically asymptomatic (27). Recent clinical studies also supported the existence of an antitumoral immune response in cancer patients (28–30) and an important role of cytotoxic T cells (CTLs) and NK cells in this process (30,31). These findings are complemented by the development of cancer vaccines and studies of new combination of these with immunological inhibitory checkpoints (17–20). This combination of data has resulted in a contemporary view of cancer as a disorder of cell growth, survival and movement, with a major facilitator of that progression being disruption and dysregulation of the immune response (32).

In trying to characterize the immune response to tumors, it must be understood that both innate and adaptive immunities participate in the control of tumor cell death and survival. Innate response typically used germ line-encoded receptors to respond to highly conserved structural motif found on pathogens, whereas adaptive responses rely on specialized undergoing specific somatic mutations to generate highly specific, high-affinity immunologic receptors such as T-cell receptors and immunoglobulins that can be highly specific to pathogens and generate immunologic memory. Highly specialized and professional antigen-presenting cells, termed dendritic cells (DCs), play a central role in activation of the adaptive immune response and the highly efficient eradication of tumor cells. DCs do this by taking up foreign antigens, becoming activated by appropriate costimulation and migrating to lymphoid organs to present their antigenic payload to adaptive immune cells (33–36).

Although the recognized immunomodulatory elements can modify this adaptive response to the tumor, additional methods of immune escape can occur due to specific behavior of the tumor cells. For example, an effective antigen-specific immune response may lead to epigenetic changes within the tumor that can result in loss of expression of tumor antigens. This process represents a form of tumor escape from the host's immune control mechanisms (37,38). In addition, the malignant cells are advantage if they can create a microenvironment that creates poor conditions to stimulate T cells or poor conditions for the function of tumor-specific cytotoxic T cells (39).

The molecular mechanisms of evading host immunity have become increasingly clear and include a variety of strategies such as (i) loss of antigen processing and presentation via downregulation of surface molecule expression (e.g. low-affinity T cells recognizing tumor-associated antigens), (ii) modulation of the systemic immune response by production of immunosuppressive cytokines and other factors (e.g. tumor-induced immune suppression) and (iii) tumor escape and relapse under immune pressure by recruiting immunosuppressive cells into the tumor microenvironment (39–43). Among the tumor-released soluble factors and cytokines that can augment the normal immune response are tumor necrosis factor-alpha (44), small molecules of prostaglandin E2, histamine and epinephrine (45). In addition, tumor release of indoleamine 2,3-dioxygenases (46,47), arginase I (48), tumor-associated gangliosides (49–51), interleukin (IL)-10 (52–56), transforming growth factor-beta (TGF-β) (57) and granulocyte-macrophage colony-stimulating factor (58) are also detected. Moreover, tumor microenvironments that favor chronic inflammation enable a population of tumor cells to escape from antitumor immunity, thus supporting carcinogenic progression (33,59,60).

Recent transplantation experiments showed that cancer cells that had originated in immunodeficient animals were often unable to initiate secondary tumors in syngeneic immunocompetent hosts. In contrast, cancer cells from tumors that originated in immunocompetent animals could initiate tumors when adoptively transferred in both immunocompetent and immunodeficient mice (61,62). These observations suggest the existence of tumor 'immunoediting', which is a form of tumor escape. This means that when highly immunogenic cancer cells are eliminated by immunocompetent hosts, weakly immunogenic cancer cells can escape host immunity with a capacity to form tumors in both immunodeficient and immunocompetent hosts, thus conferring immunological protection of the tumor cells from immunological detection and destruction (2,63). Another broader process, i.e. 'immunosculpting', includes immune-mediated changes in the tumor including amino acid substitutions in key antigenic proteins that can promote functional cellular reprogramming (e.g. epithelial to mesenchymal transition) with both mutations and non-permanent cytokine production (64).

Environmental exposures to chemicals and immune evasion mechanisms

As part of the 'Halifax Project' initiative that was instigated by the Getting to Know Cancer, we selected chemicals based on preestablished criteria that were provided to each team. Specifically, we were tasked to identify 'prototypical' chemicals with disruptive potential that are common in anthropogenic environment but not known as established human carcinogens (i.e. not IARC class 1 carcinogens). We also looked for chemicals that may potentially target the genes/pathways related to an immune evasion hallmark of cancer (Table 1). The objective of this review is to discuss possible pathways that could be involved in the modulation of immunosurveillance rather than to provide a full toxicological evaluation of the chemicals.

It is now understood that exposure to many naturally occurring and anthropogenic chemicals can influence the initiation and/or progression of tumors in animals and humans (97). In addition to genotoxic and/or epigenetic mechanisms of this process that are now well established, immunotoxic and immunomodulatory effects can be considered (97,98). Immunotoxicity can be defined as any modulation (activation, suppression or deviation) of immune responses by chemicals that cannot be related to the infection with a certain type of the pathogen (99). For some chemicals, significant immune effects occur at doses that are below those where acute cellular toxicity is observed (100–103). Most of *in vivo* immunological experiments are usually performed on healthy adult animals. However, immunotoxic effects may change when the immune system is compromised due to existing disease or when immune system is not yet fully developed (i.e. in young individuals) (104–106).

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Table 1. Examples of the chemicals that interrelate with the genes involved in immune evasion mechanisms

Chemical	Where chemical is used	ADORA1 (65–67)	AKT1 (68)	CCL2 (69)	CCL26 (70)	CD40 (71)	CD69 (71)	COL3A1 (72)	CXCL10 (73)	CXCL9 (73)	EGR1 (74,75)	HIF-1α (76)	IGF1R (77)	IL-1α (78)	IL-6 (79–81)
Maneb[a] (82–90)	Foliate fungicide	–	+	+	+	–	+	+	+	+	–	–	+	+	+
Pyridaben[a] (83,90–92)	Insecticide	–	–	+	+	+	+	+	+	+	+	+	–	+	–
Pyraclostrobin[a] (90)	Foliate fungicide	+	–	+	+	+	+	+	+	+	–	–	–	+	–
Fluoxastrobin[a] (90)	Fungicide	–	–	+	+	+	+	–	+	+	+	+	–	+	–
Zoxamide[a] (90)	Fungicide	–	–	+	+	+	+	+	+	+	–	–	–	+	+
Propargite[a] (90)	Pesticide	–	–	+	+	+	+	+	+	+	–	–	–	+	+
Quinoxyfen[a] (90)	Fungicide	–	–	+	+	+	+	+	+	+	–	–	–	+	+
Dazomet[a] (90)	Soil fumigant with fungicidal, herbicidal and nematicidal properties	–	–	+	+	+	+	+	+	+	–	–	–	+	–
3-Iodo-2-propynylbutyl-carbamate[a] (90)	Fungicide, preservative, algaecide	+	–	+	+	+	+	–	+	+	–	–	–	+	–
(Z,E)-Fenpyroximate[a] (90)	Pesticide	–	–	+	+	+	+	+	+	+	–	–	–	+	–
Alachlor[a] (90)	Herbicide	–	–	+	+	+	+	+	+	+	–	–	–	+	–
Methylene bis(thiocyanate)[a] (90)	Fungicide, disinfectant, microbicide	–	–	+	+	+	+	+	+	+	–	–	–	+	–
Tebupirimfos[a] (90)	Pesticide	–	–	+	+	+	+	+	+	+	–	–	–	+	–
Thiodicarb[a] (90)	Insecticide	–	–	+	+	+	–	+	+	+	–	–	–	+	+
Trifloxystrobin[a] (90)	Fungicide	–	–	+	+	+	+	+	+	+	–	–	–	+	–
Triclosan[b] (90,93–95)	Preservative and antiseptic agent: in soaps, toothpastes, mouthwashes, acne medications, deodorants, in kitchen utensils, toys, medical devices	–	–	+	–	+	+	+	+	+	–	–	–	+	–
2,4-Dichlorophenoxyacetic acid (2,4-D)[b] (90)	Pesticide metabolite	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Carbaryl[b] (90)	Pesticide metabolite	–	–	+	+	+	–	–	+	–	–	–	–	–	–
Cypermethrin[b] (90)	Pesticide metabolite	–	–	+	–	–	–	+	–	+	–	–	–	–	–
Bisphenol A[b] (90,96)	Production of polycarbonate plastics and epoxy resins. It is used in food and drink packaging (e.g. water and infant bottles), medical devices, in lacquers to coat metal food cans, bottle tops and water supply pipes	–	–	+	–	+	+	+	+	+	–	–	–	–	–

The list of these chemicals is obtained from the ToxCast data (90).

[a]Top 15 chemicals that interrelate with the most of the genes involved in the immune evasion mechanisms.

[b]Chemicals that showed high heterogeneity in bioaccumulation/excretion in the U.S. population.

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In fact, the concordance between immunotoxicity and carcinogenicity of chemical compounds can be as high as 81% ($P = 0.019$), suggesting that immunotoxic chemicals may also be carcinogenic (107–109). Thus, the following can be postulated: (i) if a chemical is immunotoxic and it modulates innate and adaptive cell-mediated immunity, then that chemical could affect immunosurveillance; (ii) if the effect of a chemical on the immune system is independent of its genotoxic/epigenetic effects, that chemical could increase cancer risk alone by impacting changes induced by other factors and/or exposures; (iii) exposures to chemicals that dramatically increase the number of tumor cells can overwhelm immune surveillance and (iv) a compromised immunity may be inefficient in managing the development and progression of tumor cells. This would permit greater likelihood of tumor cells escaping host immunity and establishing a malignant condition.

A number of chemicals with immunotoxic potential have been identified in previous studies and shown to increase the risk of cancer for exposed individuals. For example, perfluorinated compounds, polychlorinated biphenyls and organochlorine pesticides might increase cancer risk, especially among individuals that have genetic polymorphisms associated with metabolism of those compounds (110–113). Others have shown that maternal and perinatal exposures to pesticides were associated with increased risk of lymphoma later in life (114,115). Factors other than exposures to chemicals from anthropogenic environment can potentially interfere with the relationships between chemical compounds and the host immune response and might thus modify the risk of tumor development and progression. An example of such a modifying factor is the immune status of the organism at the time of chemical exposure. Animal studies showed that an immunocompromised status was associated with a higher risk of spontaneous and chemically induced tumors (60,116–122). And chemically induced immunosuppression might impact the ability of an animal to reject cancer cells, depending on the severity of immunosuppression (109) and the type of defect (e.g. defects in both NK and T-cell functional activity) (61,62).

However, information on the role of coexisting immunosuppression, relative susceptibility to chemical exposures and their effects on malignant risk are sparse for human. Clinical observations of human immunodeficiency virus-infected patients and organ transplant recipients that had displayed increased risk of malignant development or transformation are consistent with the role of immunosurveillance in carcinogenesis (123–130). These observations led to the hypothesis that immunodeficient or immunosuppressed individuals might have a higher risk of tumor development when exposed to chemicals that affect immune responsiveness compared with immunocompetent individuals.

On an individual level, many disparate factors influence the capacity of any particular compound to affect host immunity. These include genetic variability in the capacity to metabolize chemicals, coexisting immunosuppressive conditions (e.g. human immunodeficiency virus-infected individuals or patients receiving immune-suppressive medications), the age of an individual on exposure to the chemical (e.g. *in utero*, in children, in adults), differential dose, route and duration of exposure and the frequency of exposure (131,132). But if a sufficiently large population (i.e. number of people) is exposed to certain environmental chemicals, even the most modest impacts on immunosurveillance competence might increase the risk of disease (e.g. cancer) at the population level (133). Chemical compounds can affect the immune response through different pathways. For example, certain endocrine-disrupting chemicals can increase breast cancer risk through genes that are involved in estrogen-dependent induction of immune evasion, including estrogen receptor-mediated genes (EGR3) (134).

Polycyclic aromatic hydrocarbons inhibit differentiation and maturation of DCs (135). Moreover, phytoestrogens, phthalates, bisphenol A, parabens and various pesticides, herbicides and fungicides accumulate in human tissues and in wildlife, thus increasing the time of exposure. For example, atrazine, which is a widely used broad-spectrum chloro-s-triazine herbicide, impacts the maturation of DCs (136,137) and decreases expression levels of major histocompatibility complex class I (138). Moreover, atrazine persists in the soil and surface water for several months (139–142) and its effects on the immune system can persist long after initial exposure (143,144).

In addition to the complicating impact of bioaccumulation, the non-monotonic dose response to these chemicals makes evaluation of the health impacts of such chemicals even more challenging (145). Since the effects seen at high doses of exposure cannot be used for extrapolations into the low-dose range, direct low-dose testing is required to evaluate the effects. In the risk assessment procedure, the low-dose effects are observed at the doses near the lower end of the dose–response curve. The low-dose estimates for each chemical are based on various parameters of dose–response analysis, including the reference dose, which is an estimate (with uncertainty that can span an order of magnitude) of a daily oral exposure to the human population, including susceptible populations, which is likely to be without an appreciable risk of deleterious effects during a lifetime. The reference dose is generally derived from the no observed adverse effect level or lowest observed adverse effect level. Both the no observed adverse effect level and lowest observed adverse effect level are two commonly used toxicological endpoints (146) (presented in Table 4). Generally, the reference dose is used in the U.S. Environmental Protection Agency's (EPA) non-cancer health assessments. Additionally, the no observed adverse effect level is a concentration of a chemical or compound that is associated with no observed adverse effects in tested organisms, and the lowest observed adverse effect level is a concentration of a chemical or compound that is associated with the lowest observed level of adverse effects in test organisms.

In a recent study, the low-dose effects have been observed in chemicals from a number of classes, with the affected health endpoints covering a large range of targets (147): for example, the low-dose cutoff for atrazine was 200 μg/l (for male sexual differentiation/development endpoint), for bisphenol A 400 μg/kg/day (for immune system, prostate, mammary gland, brain development, reproduction and metabolism), for maneb 5 mg/kg/day (for testosterone release) and for triclosan 12 mg/kg/day (for altered uterine responses to ethinyl estradiol). However, it is a challenging task to identify the levels of chemicals that could be considered 'low dose' and have no adverse effects on human health because multiple factors and conditions could influence such low-dose exposures. Additionally, individuals are exposed to many environmental chemicals over the lifetime, along with other stressors and anthropogenic exposures in a cumulative manner (referred to as the 'human exposome'), so the evaluation of the health effects that result from multiple acute, subacute, chronic and subchronic occupational and non-occupational exposures remains a significant challenge (148,149).

Another factor that makes chemical exposure studies in carcinogenesis challenging is the latency period. This is because the moment of exposure that is required for cancer initiation

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and the development of a tumor (or the latency period) vary from ~7 to 35 years, depending on the cancer type, specific organ and tissue site and the grade of the tumor. For example, the shortest latency is often observed in the settings of pancreatic and cervical cancer, and the longest latency is seen in the settings of prostate and grade I breast cancer (150,151). Moreover, when multiple chemical compounds act synergistically, the effects can occur at much lower doses compared with the dose at which a single chemical exposure might exert a detectable health effect in human subjects.

The National Report on Human Exposure to Environmental Chemicals (152–154) provides some information on population heterogeneity by the level of bioaccumulation and excretion of various compounds (155). For instance, ~5% of the U.S. population have 3–10 times higher concentrations of certain chemicals in their blood, serum or urine that might be explained by either higher exposures and/or altered individual metabolic capacity. Examples of such compounds that demonstrate a highly heterogeneous distribution in a population include benzophenone-3 (used as a sunscreen in lotions, conditioners, cosmetics and in plastic surface coatings) and triclosan (2,4,4′-trichloro-2′-hydroxyphenyl ether, which is a preservative and antiseptic agent used in soaps, toothpastes, mouthwashes, acne medications, deodorants, kitchen utensils, toys and medical devices). Other examples are pesticide metabolites including 2,4- and 2,5-dichlorophenols, phytoestrogens (e.g. daidzein, genistein and *O*-desmethylangolensin that are present in soy-based foods) and butyl parabens (used as preservative and food and pharmaceutical industry flavoring additives as well as in personal care and cosmetic products). Additional examples include ethyl paraben (an antifungal preservative also known as food additive E214) and *n*-propyl paraben (used as a preservative in water-based cosmetics and as food additive E216), metabolites of pesticides [e.g. the cypermethrin-related chemicals *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid and 3-phenoxybenzoic acid], metabolites of organophosphorus (e.g. dimethylphosphate, dimethylthiophosphate and dimethyldithiophosphate) and organochlorine insecticides (e.g. 2,4,5-trichlorophenol, which is also used as a wood preservative and for chlorinating drinking water). Other compounds that display a highly heterogeneous population distribution include dibromochloromethane (a disinfection by-product in drinking water and swimming pools), 2,2′,4,4′,5-pentabromodiphenyl ether (a fire retardant), phthalate metabolites like mono-ethylphthalate and mono-2-ethylhexyl phthalate (that are used as plasticizers in adhesives, detergents, solvents, vinyl tiles and flooring, personal care products, plastic bags, intravenous injection medical tubing and children's toys). Finally, 1-hydroxynaphthalene (1-naphthol), which is a metabolite of carbaryl, is used in plasticizers, dyes, synthetic leather tanning chemicals and in moth repellents. It also displays heterogeneity in bioaccumulation and excretion studies in the U.S. population (155).

Note that compared with currently unrecognized human carcinogenic chemicals, bioaccumulation and excretion of compounds that are already recognized as human carcinogens (155) appear to be less heterogeneous in the U.S. population. This allows one to hypothesize that known carcinogenic compounds may have more unified bioaccumulation and excretion patterns in the population, which also assists in recognizing them already as carcinogens.

The U.S. EPA's ToxCast program (http://www.epa.gov/ncct/toxcast/) and the Tox21 collaboration (http://www.epa.gov/ncct/Tox21/) with the National Toxicology Program and National Institutes of Health Chemical Genomics Center have reported a large number of *in vitro* high-throughput screening assays and high-content screening information for numerous environmental chemicals (156,157). One important focus of ToxCast is the measurement of chemically induced perturbation of critical cellular signaling pathways that may represent potential modes of chemical toxicity (158).

In vivo animal model studies have suggested the following genes with the highest odds ratios for the potential disruption of immunosurveillance: receptor designated opioid receptor-like 1 (for thyroid tumor), chemokine C–C motif ligand 2 (CCL2; for spleen and liver tumors) and IL-1α, interferon-γ-inducible 9-kd (CXCL9) and 10-kd protein (CXCL10) (for liver and thyroid tumors) (159). These genes are associated with effective immune response in both animals and humans (160). When multiple chemicals impact antitumor immune responses, the resultant cumulative effects of these exposures may impart a greater relative risk of carcinogenesis and tumor development, particularly in the context of multiple exposures affecting the same genetic targets (161).

Immune evasion mechanisms: opportunities for target genes and pathways

The list of chemicals and the targets that they disrupt is based on EPA's 2009 ToxCast data. The EPA-screened chemicals included in Table 1 carried the highest scores for the ToxCast immune system disruption counts with the respective number of activated associated genes. A dose of ~100 μM of each individual chemical was used in each assay. The potency of an assayed chemical that gave a positive (i.e. gene activation) response was summarized using the AC_{50} value (i.e. at a concentration of 50% of the maximal activity) or the lowest effective concentration values. Note that the use of nominal potency in determining hazard identification has been challenged because *in vitro* assays cannot account for *in vivo* impacts of a compounds bioavailability, metabolic clearance and exposure (162). The *in vitro* to *in vivo* extrapolation using information on human dosimetry and exposure is valuable in assessing the validity of high-throughput *in vitro* screening to provide hazard predictions at the level of the organism (163,164).

We referred to the ToxCast database to determine which chemicals aligned with immune system evasion mechanisms that were relevant in carcinogenesis. Since chronic inflammation and immune responsiveness in carcinogenesis are both linked to, and initiated at the premalignant stages of tumor development (165,166), it is understandable that ToxCast data sets describe pathways that are related to both inflammation and immune evasion as putative immune disruption mechanisms (158,159). We selected the pathways that were related specifically to immune evasion as a cancer hallmark by comparative analysis of existing studies in the settings of both inflammation and immunosurveillance with the results on immune disruption presented by ToxCast. Consequently, several genes from the ToxCast immune disruption list were selected since they were associated with immune evasion based on an overview of the literature: for example, ADORA1 (adenosine A1 receptor); AKT1 (v-akt murine thymoma viral oncogene homolog 1 or protein kinase alpha); CCL2; CCL26; CD40, CD69, COL3A1 (type III collagen of extracellular matrix); CXCL10 (interferon-inducible protein-10); CXCL9 (monokine induced by interferon-gamma); EGR1 (early growth response protein 1); HIF-1α (hypoxia-inducible factor); IGF1R (insulin-like growth factor 1 receptor) and IL-1α and IL-6 (Table 1).

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Specifically, ADORA1 was involved in the immune response to thyroid cancer (167) by encoding adenosine receptors that inhibited T-cell responses. This was achieved in part by augmenting FOXP3 expression in $CD4^+$ helper T cells (65). Another study has also shown that tumors grew slower in ADORA (i.e. ADORA2A) knockout mice (66). Other examples included the participation of CCL2 in immune system evasion by recruiting immune suppressor cells to the tumor microenvironment (67), and CCL26, which helped to promote a Th2-dominant tumor microenvironment that was beneficial for tumor cells (69). Similarly, others showed that CD69, which is among the earliest cell-surface expressed molecules, was induced during lymphocyte activation (70), and COL3A1, which might be involved in tumor cell evasion of immune surveillance (71). Finally, another group found that CXCL10, which is the ligand for CXCR3, was a chemoattractant for activated T cells (72). Moreover, the expression of the EGR1 gene participates in immune evasion mechanisms of infectious agents (73), although its role in tumor evasion (e.g. as a tumor suppressing factor) remains unclear (74). IL-1α participates in mechanisms that permit prostate tumor escape, and downregulation of dampened expression of MIP-1α might be associated with decreased IL-1α and tumor necrosis factor-alpha during the advanced stages of cancer (75). Finally, IL-6 is crucial for both tumor growth and immunosuppression (78). IL-6 also inhibits maturation of DCs, and NK cell activation, and may promote NK cell anergy (79,80).

Additional pathways contribute to immune surveillance that is also associated with carcinogenesis and tumor progression. These pathways include activation of the PI3K/AKT pathway, which represents a new mechanism of immunological tumor escape (81). For HIF-1α, the studies have linked hypoxia-induced accumulation of D-subunits with expression of ADAM10 and decreased surface major histocompatibility complex class I polypeptide-related sequence A levels that can lead to tumor cell resistance to innate immune effector-mediated lysis (68). The local immune response of Epstein–Barr virus-associated tumors to infiltrating T cells might be suppressed by enhancing cytokine and cellular growth factors like IGF1 (76).

The collection of genes involved suggests several candidate-signaling pathways that are capable of participating in chemically induced immune evasion. These pathways include PI3K/Akt, chemokine pathways (e.g. CCL2, CCL26, CXCL9, CXCL10), TGF-β1 and FAK (including COL3A1), the IGF-1, the HIF-1α, the IL-6 and the IL-1α signaling pathways (summarized in Table 2). Indeed, some pathways (e.g. chemokine, TGF-β, FAK and IL-1α signaling pathways) are targets of multiple chemicals (Table 2). However, some pathways (e.g. PI3K/Akt, IGF-1, HIF-1α and IL-6) have greater chemical-specific involvement. In addition, signaling pathway cross talk might play a role in affecting host immunity.

There are also intracellular signaling pathways that are critical in regulating DC differentiation, survival and activity, which could be activated or inhibited through signal-mediated cross talk. For example, the MAPK (mitogen-activated protein kinase signaling cascade) pathway cross talks with CCL2, Akt, IL-6 and IGF-1. The PI3K/Akt (phosphatidylinositol-3-kinase/protein kinase B) pathway cross talks with IGF-1 and IL-6. Also, the JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3) pathway cross talks with IL-6. Additionally, chemicals in the environment affect several candidate immune evasion pathways that are involved in antitumor immunity. For example, CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and the PD-1/PDL-1 (programmed death-ligand 1) signaling pathways are involved in the immune evasion of tumor cells. Monoclonal antibodies inhibiting these pathways have demonstrated the effectiveness of anticancer effects in certain types of tumor (77,168). The α-enolase (ENO1) antigen that is coded by the ENO1 gene has been recently detected in pancreatic (169), lung and hepatocellular cancers (170,171). ENO1 has also been tested as a vaccine target (172–174); it has the cross talks with CXCL9, CXCL10 and CD40. Consequently, these pathways represent excellent candidates for further studies of the effects of disruptive or agonistic chemicals of the immune response in human carcinogenesis.

Factors other than exposures to chemicals from anthropogenic environment can potentially interfere with the relationship between chemical compounds and host immunity, which might modify the risk of tumor development and progression. One such factor is the immunological status of the organism at the time of environmental chemical exposure. Animal studies showed that an immunocompromised state was associated with a higher risk of spontaneous and chemically induced tumors (60,116–122). Chemically induced immunosuppression can impact the ability of an animals to reject cancer cells, and this depends on the extent of immunosuppression (109) and the type of defect (e.g. defects in one or in both NK and T-cell functional behavior) (61,62). However, information on the role of coexisting immunosuppression in the human system and their susceptibility to chemical exposures is sparse and is currently insufficient to suggest the role of immunosuppression in chemical carcinogenesis.

Environmental chemicals that impact multiple pathways associated with immune dysfunction may also increase the risk of diseases other than cancer. The dysfunction of the immune system caused by some endocrine-disrupting chemicals may lead to lower effectiveness of immune response to infection or to the allergy and autoimmune diseases due to the hyperreactivity of immune response (175). For example, exposures to pesticides, solvents and air pollutants have been shown to be associated with the immune response dysregulation and inflammatory dysfunction and contributed to higher risk of asthma and allergies (176). Specifically, human bronchial epithelial cells treated with butylbenzyl phthalate, bis(2-ethylhexyl) phthalate, dibutyl phthalate and diethyl phthalate increased bronchial smooth-muscle cell proliferation and migration, suggesting a role of these chemicals in asthma airway remodeling (177,178). There are also increasing evidence from the animal studies that *in utero* or neonatal exposures to bisphenol A are associated with higher risk of immune system dysregulation and metabolic syndrome that may develop later in life (179–182). Another example can be a pesticide-induced asthma in agriculture workers that may be due to the indirect effects of pesticides on the immune system, including interfering with the Th1/Th2 balance or pesticide-induced oxidative stress (183). For addition, certain environmental chemicals may cause the changes in response of immune system to infectious agents, thus increasing risk of adverse outcomes of respiratory infections (184). For example, it has been shown that higher bisphenol A levels were associated with lower levels of anticytomegalovirus antibodies in humans, thus suggesting that exposure to this chemical may attenuate antiviral immunity (185).

Cross talk between immune evasion and other hallmarks of cancer

Based on the number of variables involved in this field and the paucity of data in this area of research, we believe that future research will need to focus on environmentally relevant

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Table 2. Candidate-signaling pathways potentially involved in chemically induced tumorigenesis and related to immune evasion hallmark: three chemicals from different groups are selected as examples

Chemical	PI3K/Akt signaling pathway	Chemokine signaling pathway (CCL2, CCL26, CXCL9, CXCL10)	TGF-β signaling pathway (COL3A1)	FAK pathway (COL3A1)	IGF-1 signaling pathway	HIF-1α pathway	IL-6 signaling pathway	IL-1α pathway
Maneb (fungicide)	+[a] (85,87)	+ (85)	+ (83,85,86)	+ (85)	+ (84)	–	+ (82,83)	+ (83)
Pyridaben (insecticide)	–	+ (83,92)	+ (83)	+ (83)	–	+ (91,92)	–	+ (92)
Triclosan (preservative and antiseptic agent)	–	+ (93)	+ (94)	+ (95)	–	–	–	+ (93)

'+', the pathway is likely involved when the organism is exposed to respective chemical; '–', the pathway is unlikely involved when the organism is exposed to respective chemical.

[a]The involvement of the candidate pathways that are constructed from the data on every single gene is described in the ToxCast data (90) (as shown in Table 1).

low-dose exposures to mixtures of chemicals that are known to have a disruptive impact on immune system tumor surveillance and elimination. Given that the pathways involved in immune evasion might also participate in other hallmarks of cancer, we undertook a mapping exercise to identify cross-hallmark relationships that have been reported for the key mechanisms and the disruptive chemicals that we identified. This was done by a cross-validation study to show how the target pathways and/or chemical disruptors (i.e. those that potentially interact with the pathways involved in immune evasion) might also be involved in other cancer hallmarks (Tables 3 and 4). In particular, this heuristic could be useful for researchers who would like to try to predict potential synergies that might emerge when testing low-dose exposures to mixtures of chemicals for this purpose.

To conduct this cross-hallmark activity, our team selected nine prototypic chemicals drawn from a list of 20 chemicals (as listed in Table 1). The prototypic chemicals chosen were maneb, pyridaben, pyraclostrobin, fluoxastrobin, azamethiophos, triclosan, atrazine, bisphenol A and diethylhexyl phthalate. Several examples of the interrelations of the pathways involved in immune evasion and other cancer hallmarks are presented in Table 3. This analysis shows that some of the mechanisms and pathways that are important for the immune system in cancer are also highly relevant for aspects of cancer's biology. For example, chemical exposures that affect chemokine signaling pathways could also deregulate metabolism, the evasion of antigrowth signaling, angiogenesis, resistance to cell death, sustained proliferative signaling, tissue evasion and metastasis, tumor-promoting inflammation and affect the tumor microenvironment. Similarly, the disruption of the HIF-1α and of the PI3K/Akt pathways can influence most of the other hallmarks of cancer. Disruption of the IGF-1 signaling pathway could affect metabolism, evade antigrowth signaling, resistance to cell death, sustained proliferative signaling, tissue evasion, tumor-promoting inflammation and tumor microenvironment hallmarks.

Table 4 shows where there have been reports of cross-hallmark effects by the chemicals that we selected. For example, maneb displays the widest spectrum of potential effects on multiple pathways among fungicides, i.e. it has complementary effects on dysregulated metabolism, sustained proliferative signaling, genetic instability and tumor promoting inflammation. Two other fungicides (pyraclostrobin and fluoxastrobin) affected only the hallmarks of genetic instability and tumor-promoting inflammation. Among fungicides, currently only maneb is reported to exhibit limited carcinogenicity in humans as determined by the U.S. EPA (250), but it remains 'not classifiable as to its carcinogenicity to humans' by the IARC (155). Maneb is also a cortisol disruptor that inhibits 11β-HSD2 (251). Maneb was registered in the USA in 1962 for use on food (including potatoes and tomatoes) and ornamental crops to prevent their damage in the field and to protect the harvested crops from deterioration during storage and transportation (252,253). Pyraclostrobin and fluoxastrobin (the chemical class of strobins) have been used since the early 2000s; therefore, there are less data available on these fungicides compared with longer periods of observation for maneb. Pyraclostrobin is a broad-spectrum fungicide that is used in both agricultural (cereal grains, fruits and vegetables) and non-agricultural settings (e.g. flowers and grass, including golf courses). Pyraclostrobin is one of the most frequently applied fungicides for grapes, apricots, tomatoes, sweet cherries and plums. Fluoxastrobin is used to prevent diseases in crops such as wheat, barley, corn, soybean, potato, tomato, pepper, strawberry and turf plots (i.e. in the context of landscaping). It is likely that both fluoxastrobin and pyroclostrobin are also endocrine-disrupting fungicides (254).

In addition to immune system evasion, atrazine (a triazine herbicide that is used primarily in corn production) may also interfere with other hallmarks including dysregulated metabolism, genetic instability, sustained proliferative signaling and tumor-promoting inflammation. Similar to the classification ascribed to maneb, atrazine is listed by IARC as 'not classifiable as to its carcinogenicity to humans' (155). Atrazine is the most common pesticide contaminant of ground and surface water in the USA (255,256). Since 2000, atrazine has been reported as an endocrine disruptor for both androgen- and estrogen-mediated processes (257,258).

Additionally, two insecticides, pyridaben and azamethiphos, have broader potential effects related to cancer hallmark pathways, in addition to their effects on immunosurveillance, i.e. pyridaben exposure can dysregulate metabolism and tumor-promoting inflammation. Moreover, exposure to azamethiphos impacts genetic instability. Pyridaben is a pyridazinone derivate that is widely used as an acaricide and insecticide to control mites, white flies and aphids. Azamethiphos is a widely used organophosphate pesticide in the control of cockroaches and flies in buildings and warehouses. This compound was also used in fish farming to control external parasites in Atlantic salmon. Neither pyridaben nor azamethiphos are listed by the IARC as carcinogens (155). However, the majority of insecticides are designed to be disruptors of various physiological functions in insects; therefore, these compounds are likely disruptive for humans, too. Recent studies showed that pyridaben can activate the estrogen receptor alpha in experimental rodents (259).

Triclosan and bisphenol A are commonly found in personal care products. Bisphenol A is a monomer that is also used in the production of polycarbonates and epoxy resins for coating

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Table 3. Interrelations of the pathways involved in immune evasion and other cancer hallmarks (as described in Hanahan *et al.* 1,2)[a]

Immune evasion mechanisms: priority targets	Deregulated metabolism	Antigrowth signaling evasion	Angiogenesis	Genetic instability	Resistance to cell death	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor-promoting inflammation	Tumor microenvironment
Chemokine signaling pathway (CCL2, CCL26, CXCL9, CXCL10) (69,70,73,90,159)	±	No data (for CCL26 and CXCL9) + (for CCL2 and CXCL10)	+	No data	+	–	+	± (for CXCL10), – (for CXCL9), + (for CCL2 and CCL26)	+	+
ADORA1 (65–67,90)	No data	No data	No data	No data	+	No data	+	No data	–	+
HIF-1α pathway (76,90)	±	+	+	+	±	+	+	+	+	+
PI3K/Akt signaling pathway (68,90)	±	+	+	+	+	+	+	+	+	+
IGF-1 signaling pathway (77,90,186)	+	±	–	No data	+	–	+	+	+	+

Pathways that have opposing action with a particular hallmark (i.e. when the activation of the same genes has procarcinogenic effect when considering immune evasion hallmark and anticarcinogenic effect when considering one of the 10 other cancer hallmarks) were denoted using '–', and the pathways with procarcinogenic effects were denoted using '+'. When the results were mixed (i.e. showing both procarcinogenic and anticarcinogenic potential), the symbol '±' was used.

[a]The involvement of the candidate pathways that are constructed from the data on every single gene is described in the ToxCast data (90) (as shown in Table 1).

beverage and food packages, baby milk bottle and optical lenses (260). It is 'not classifiable as to its carcinogenicity to humans' by the IARC (155). Triclosan is a broad-spectrum antimicrobial agent. In addition to its use in personal care products, triclosan is also used in carpets and sportswear production. These chemicals are among the most frequently detected compounds in waters downstream of densely urbanized areas (261,262). Compounds like triclosan and bisphenol A act as endocrine disruptors, e.g. bisphenol A has antiandrogenic (263) and triclosan has androgenic and antiestrogenic activities (264,265). As shown in Table 4, bisphenol A affects nearly all hallmarks of cancer, except of the tumor microenvironment hallmark for which the data are still currently unknown. The effect of triclosan might dysregulate metabolism, genetic instability, sustained proliferative signaling and tumor-promoting inflammation.

Diethylhexylphthalate (DEHP), which is one of the most extensively used phthalates worldwide in the plastic, coating and cosmetics industries, is another class of compounds that might promote hallmarks of cancer (266). DEHP influences resistance to cell death, evasion of antiproliferative signaling, sustained proliferative signaling and tumor-promoting inflammation as hallmarks of cancer. Since the mid-1990s, DEHP was reported as an endocrine disruptor (267). Perinatal exposure to DEHP might also be associated with an increased incidence of obesity due to its endocrine disrupting impact during the developmental 'window of susceptibility' that affects adipogenesis (268). In 2000, the designation of DEHP as 'possibly carcinogenic to humans' (based on animal studies) has been changed to 'cannot be classified as to its carcinogenicity in humans' (269,270).

Overall, this heuristic shows that a number of chemicals that we considered also have the potential to interact with several other cancer hallmark pathways. Therefore, researchers who plan to consider these chemicals for exposure research on mixtures should carefully evaluate these potential synergies.

Further studies

Cancer has a complex and multifactorial etiology impacted by both inherited factors and environmental exposures over the life course of an individual. Although genetic risks have been identified, most studies suggest that substantial contributions to cancer risk are derived from the environment. This viewpoint remains consistent with the recent observations that cancer risk is associated with the potential number of stem cells divisions needed to maintain a tissue integrity (271). Coupled with the importance of evaluating an already extensive (and expanding) number of chemicals of unknown cancer-promoting potential, there is a clear need for more efficient *in vitro* screening tools that should be complemented with *in silico* virtual ligand screening approaches to help construct a target and pathway-based understanding of specific chemicals or groups of chemicals (159,272). Specific genes and pathways could be further measured by experiments that are designed to arrive at quantified information for each chemical studied.

Due in part to low relative risks attributed to low-dose exposures and the knowledge that multiple chemicals have the potential to contribute to these exposures over sustained and durable periods of time, it remains challenging to evaluate the effects of such exposures on human health by classical epidemiological approaches. Dose–response analyses could provide information on quantitative 'sensitivity' of each 'barrier' (e.g. apoptosis and DNA repair system) following exposure to specific chemicals or to complex mixtures of chemicals, both in the context of immune system evasion mechanisms, and other cancer

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Table 4. Reports of cross-hallmark effects of selected chemicals[a]

				Cancer hallmarks									
Immune evasion: prototypical disruptors	IARC classification[b]	Oral exposure[b]	Inhalation exposure[b]	Deregulated metabolism	Evasion of antigrowth signaling	Angiogenesis	Genetic instability	Resistance to cell death	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor-promoting inflammation	Tumor microenvironment
Pyraclostrobin (187–189)	Inadequate data for an assessment of human carcinogenic potential	Systemic NOAEL is 100 mg/kg/day	Not assessed	–	No data	No data	+	No data	No data	No data	No data	+	No data
Fluoxastrobin (189–192)	Group B2: probable human carcinogen	Systemic NOAEL is 70–237 mg/kg/day	Not assessed	No data	No data	–	+	No data	No data	No data	No data	+	No data
Azamethiphos (193)	Not listed as carcinogen	Not assessed	Not assessed		No data	No data	+	No data	No data	No data	No data	No data	No data
Pyridaben (194–201)	Group E: evidence of noncarcinogenicity for human	NOAEL for systemic toxicity is 50 mg/kg/day	Not assessed	±	No data	–	No data	–	No data	–	No data	+	No data
Maneb (202–208)	Group B2: probable human carcinogen	RfD for non-cancer effects is 0.005 mg/kg/day (EPA). NOAEL for non-cancer effects is 5 mg/kg/day (EPA, RIVM). RfD and NOAEL for cancer is not assessed (ATSDR)	Tolerable concentration in air for non-cancer effects is 1.8×10^{-2} mg/m^3. NOAEL for non-cancer effects is 10 mg/m^3 (RIVM) and not assessed by ATSDR (due to insufficient data). For cancer effects, RfD and NOAEL are not assessed	+	No data	–	+	–	No data	+	No data	+	No data
Triclosan (209–215)	Not yet determined	Systemic NOAEL is 30–52.4 mg/kg/day	Not assessed	±	No data	–	+	–	No data	+	No data	+	No data
Atrazine (216–223)	Not likely to be carcinogenic to human	RfD is 3.5×10^{-2} mg/kg/day. NOAEL for decreased body weight is 3.5 mg/kg/day	Not assessed	±	No data	No data	+	No data	No data	+	No data	+	No data
Bisphenol A (224–238)	Group 3: not classifiable as to its carcinogenicity to human	RfD is 5×10^{-2} mg/kg/day. NOAEL for decreased body weight is not assessed	Not assessed	+	+	+	+	±	+	+	No data	+	No data
Diethylhexyl phthalate (239–249)	Not classified as to its carcinogenicity to human	Not assessed	Not assessed	+	+	No data	No data	±	No data	+	No data	+	No data

Chemicals that were found to have opposing actions in a particular hallmark (i.e. anticarcinogenic) were denoted using '–', whereas disruptors that were found to have a procarcinogenic action were denoted using '+'. When the effects were mixed (i.e. reports showing both procarcinogenic potential and anticarcinogenic potential), the sign '±' was used. ATSDR, the Agency for Toxic Substances and Disease Registry; NOAEL, the no observed adverse effect level; RfD, the reference dose; RIVM, the National Institute for Public Health and the Environment.

[a]The involvement of the candidate pathways that are constructed from the data on every single gene is described in the ToxCast data (90) (as shown in Table 1).

[b]Data obtained from the TOXNET data (the Toxicology Data Network) at www.toxnet.nlm.nih.gov.

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hallmarks. Attempts at quantifying these measured 'barriers' can be incorporated into models of carcinogenesis (273).

Future studies should focus on linking population data on cancer-specific incidence and mortality (e.g. for cancers of breast, prostate, testicular, ovarian and thyroid, wherein the risk of developing that cancer is affected by endocrine-disrupting chemicals). Studies should also focus on information of the measured characteristics of immune system evasion, and other established hallmarks of cancer, which collectively could be further incorporated into biologically motivated models of carcinogenesis, in a manner similar to those developed by Moolgavkar *et al.* (274) and Tan (275). Further extensions of these models were developed over the past decade including the two-stage clonal expansion model, the multistage clonal expansion model and other biologically motivated models of human carcinogenesis (150,276–278). These models are capable of providing valuable insight into the relative risks of environmental exposures.

In this article, we have reviewed some common chemicals that are known or suspected to be present in anthropogenic environment. We have also discussed their potential effects on host immunity and proposed mechanisms by which they potentially interact with specific hallmark pathways. Based on a comprehensive review of the literature on environment and health, we recognized that immune evasion has only been recently widely accepted as an emerging cancer hallmark, and we suggest that it may be among the least studied of the hallmarks. The literature describing the potential effects of chemical exposures on the immune evasion, in particular the impact in the context of low-dose exposures from ubiquitous anthropogenic environmental chemicals, is sparse.

The causal relationship between chemical exposures from compounds that are not currently recognized as human carcinogens and the increased risk of cancer development (including the potential impacts of such chemicals on the pathways that are related to immune evasion mechanisms) cannot be formally established at this time. However, based on available studies, several candidate-signaling pathways that are related to the host immune response can be identified for further study, e.g. the pathways involving PI3K/Akt, chemokines, TGF-β, FAK, IGF-1, HIF-1α, IL-6, IL-1α, CTLA-4 and PD-1/PDL-1. At least several groups of environmentally ubiquitous chemical contaminants—including fungicides (maneb, fluoxastrobin, pyroclostrobin), herbicides (atrazine), insecticides (pyridaben and azamethiphos), personal care products (triclosan and bisphenol A) and the extensively used industrial compound DEHP—are among those that might potentially interrelate with mechanisms of tumor immunosurveillance.

Although none of these chemicals are currently recognized as human carcinogens, as ubiquitous in anthropogenic environment and as eliciting a long-term and low-dose exposure, the research of these chemicals may be valuable. Ultimately, we should know whether or not these exposures interfere with the host immune response and thus augment the risk of tumor cell survival. Further detailed studies, including screening of lesions at the premalignant stage of development, will help shed more light on this topic. This will be made possible by determining the role of such exposures and their influence on host immunity and in the evaluation of their potential to increase the risk of carcinogenesis and tumor development.

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