

REVIEW

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

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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-1 α , IL-6, IL-1 α , 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 pyroclostin), 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 chemicals can 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

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).

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)	CCL1 (69)	CCL2 (70)	CCL26 (70)	CD40 (71)	CD40 (71)	CD69 (71)	COL3A1 (72)	CXCL10 (73)	CXCL9 (73)	EGR1 (74,75)	HIF-1 α (76)	IGF1R (77)	IL-1 α (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	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+
Quinoxifen ^a (90)	Fungicide	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+
Dazomet ^a (90)	Soil fumigant with fungicidal and nematocidal properties	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	-
3-Iodo-2-propynylbutyl-carbamate ^a (90)	Fungicide, preservative, algacide	+	-	+	+	+	+	+	+	-	+	+	-	-	-	+	-
(Z,E)-Fenpyroximate ^a (90)	Pesticide	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	-
Alachlor ^a (90)	Herbicide	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	-
Methylene bis(thiocyanate) ^b (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	-	-	+	-	-	+	+	+	+	+	+	-	-	-	-	-

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

^bTop 15 chemicals that interrelate with the most of the genes involved in the immune evasion mechanisms.

^cChemicals that showed high heterogeneity in bioaccumulation/excretion in the U.S. population.

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 $\mu\text{g/l}$ (for male sexual differentiation/development endpoint), for bisphenol A 400 $\mu\text{g/kg/day}$ (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

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-desmethylandrolensin 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-1 α , 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 μ M 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 AC₅₀ 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- γ); EGR1 (early growth response protein 1); HIF-1 α (hypoxia-inducible factor); IGF1R (insulin-like growth factor 1 receptor) and IL-1 α and IL-6 (Table 1).

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-1 α participates in mechanisms that permit prostate tumor escape, and downregulation of dampened expression of MIP-1 α might be associated with decreased IL-1 α and tumor necrosis factor- α 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-1 α , 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- β 1 and FAK (including COL3A1), the IGF-1, the HIF-1 α , the IL-6 and the IL-1 α signaling pathways (summarized in Table 2). Indeed, some pathways (e.g. chemokine, TGF- β , FAK and IL-1 α signaling pathways) are targets of multiple chemicals (Table 2). However, some pathways (e.g. PI3K/Akt, IGF-1, HIF-1 α 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 hyper-reactivity 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

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-1 α pathway	IL-6 signaling pathway	IL-1 α 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)

^a+, 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.

^aThe 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-1 α 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 11 β -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 pyraclostrobin 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 azamethiophos, 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 azamethiophos impacts genetic instability. Pyridaben is a pyridazinone derivate that is widely used as an acaricide and insecticide to control mites, white flies and aphids. Azamethiophos 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 azamethiophos 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

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-1 α 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.

^aThe 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

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

Immune evasion: prototypical disruptors	IARC classification ^b	Oral exposure ^b	Inhalation exposure ^b	Cancer hallmarks										
				Deregulated metabolism	Evasion of angiogenesis	Resistance to cell death	Genetic instability	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	+	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	+	No data
Azamephipos (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	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 1.8 × 10 ⁻² mg/m ³ . NOAEL for cancer effects is 5 mg/kg/day (EPA, RfD and NOAEL for cancer is not assessed (ATSDR) and NOAEL are not assessed	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 (RfD) 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	+	+	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
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; RfM, the National Institute for Public Health and the Environment.

^aThe 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).

^bData obtained from the TOXNET (the Toxicology Data Network) at www.toxnet.nlm.nih.gov.

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-1 α , IL-6, IL-1 α , 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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References

- Hanahan, D. et al. (2000) The hallmarks of cancer. *Cell*, 100, 57–70.
- Hanahan, D. et al. (2011) Hallmarks of cancer: the next generation. *Cell*, 144, 646–674.
- Johnson, J.P. et al. (1989) Tumor immunology: Paul Ehrlich's heritage. *Immunol. Today*, 10, S35–S37.
- Decker, W.K. et al. (2009) Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. *Cytokine Growth Factor Rev.*, 20, 271–281.
- Burdick, C.G. (1937) William Bradley Coley 1862–1936. *Ann. Surg.*, 105, 152.
- Cann, S.H. et al. (2003) Dr William Coley and tumour regression: a place in history or in the future. *Postgrad. Med. J.*, 79, 672–680.
- Levine, D.B. (2008) The Hospital for the Ruptured and Crippled: William Bradley Coley, third Surgeon-in-Chief 1925–1933. *HSS J.*, 4, 1–9.
- McCarthy, E.F. (2006) The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. *Iowa Orthop. J.*, 26, 154–158.
- Starnes, C.O. (1992) Coley's toxins in perspective. *Nature*, 357, 11–12.
- Nauts, H.C. (1989) Bacteria and cancer—antagonisms and benefits. *Cancer Surv.*, 8, 713–723.
- Thomas, L. (1959) *Discussions of Cellular and Humoral Aspects of the Hypersensitive States*. Hoeber-Harper, New York, NY.
- Burnet, F.M. (1970) The concept of immunological surveillance. *Prog. Exp. Tumor Res.*, 13, 1–27.
- Doherty, P.C. et al. (1975) H-2 compatibility is required for T-cell-mediated lysis of target cells infected with lymphocytic choriomeningitis virus. *J. Exp. Med.*, 141, 502–507.
- Janeway, C.A. et al. (2001) *Immunobiology: the Immune System in Health and Disease*. Garland Science, Churchill Livingstone, NY.
- Osada, T. et al. (2008) The effect of anti-VEGF therapy on immature myeloid cell and dendritic cells in cancer patients. *Cancer Immunol. Immunother.*, 57, 1115–1124.
- Osada, T. et al. (2012) Novel recombinant alphaviral and adenoviral vectors for cancer immunotherapy. *Semin. Oncol.*, 39, 305–310.
- Reuben, J.M. et al. (2006) Biologic and immunomodulatory events after CTLA-4 blockade with ticilimumab in patients with advanced malignant melanoma. *Cancer*, 106, 2437–2444.

18. Gao, Q. et al. (2009) Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin. Cancer Res.*, 15, 971–979.
19. Benson, D.M. Jr et al. (2010) The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. *Blood*, 116, 2286–2294.
20. Vanneman, M. et al. (2012) Combining immunotherapy and targeted therapies in cancer treatment. *Nat. Rev. Cancer*, 12, 237–251.
21. Vajdic, C.M. et al. (2009) Cancer incidence and risk factors after solid organ transplantation. *Int. J. Cancer*, 125, 1747–1754.
22. Vajdic, C.M. et al. (2009) What types of cancers are associated with immune suppression in HIV? Lessons from solid organ transplant recipients. *Curr. Opin. HIV AIDS*, 4, 35–41.
23. Kirk, G.D. et al. (2007) HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin. Infect. Dis.*, 45, 103–110.
24. Engels, E.A. et al. (2007) Systematic evaluation of genetic variants in the inflammation pathway and risk of lung cancer. *Cancer Res.*, 67, 6520–6527.
25. Kolb, H.J. et al. (1990) Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood*, 76, 2462–2465.
26. Kolb, H.J. et al.; European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia (1995) Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. *Blood*, 86, 2041–2050.
27. Strayer, D.R. et al. (1986) Familial occurrence of breast cancer is associated with reduced natural killer cytotoxicity. *Breast Cancer Res. Treat.*, 7, 187–192.
28. Bindea, G. et al. (2010) Natural immunity to cancer in humans. *Curr. Opin. Immunol.*, 22, 215–222.
29. Ferrone, C. et al. (2010) Dual roles for immunity in gastrointestinal cancers. *J. Clin. Oncol.*, 28, 4045–4051.
30. Nelson, B.H. (2008) The impact of T-cell immunity on ovarian cancer outcomes. *Immunol. Rev.*, 222, 101–116.
31. Pagès, F. et al. (2010) Immune infiltration in human tumors: a prognostic factor that should not be ignored. *Oncogene*, 29, 1093–1102.
32. Prendergast, G.C. (2008) Immune escape as a fundamental trait of cancer: focus on IDO. *Oncogene*, 27, 3889–3900.
33. de Visser, K.E. et al. (2006) Paradoxical roles of the immune system during cancer development. *Nat. Rev. Cancer*, 6, 24–37.
34. Triozzi, P.L. et al. (2000) Intratumoral injection of dendritic cells derived *in vitro* in patients with metastatic cancer. *Cancer*, 89, 2646–2654.
35. Bukur, J. et al. (2003) The role of HLA-G for protection of human renal cell-carcinoma cells from immune-mediated lysis: implications for immunotherapies. *Semin. Cancer Biol.*, 13, 353–359.
36. Pistoia, V. et al. (2007) Soluble HLA-G: are they clinically relevant? *Semin. Cancer Biol.*, 17, 469–479.
37. Kmiecik, M. et al. (2007) HER-2/neu antigen loss and relapse of mammary carcinoma are actively induced by T cell-mediated anti-tumor immune responses. *Eur. J. Immunol.*, 37, 675–685.
38. Santisteban, M. et al. (2009) Immune-induced epithelial to mesenchymal transition *in vivo* generates breast cancer stem cells. *Cancer Res.*, 69, 2887–2895.
39. Whiteside, T.L. (2006) Immune suppression in cancer: effects on immune cells, mechanisms and future therapeutic intervention. *Semin. Cancer Biol.*, 16, 3–15.
40. Knutson, K.L. et al. (2006) IL-2 immunotoxin therapy modulates tumor-associated regulatory T cells and leads to lasting immune-mediated rejection of breast cancers in neu-transgenic mice. *J. Immunol.*, 177, 84–91.
41. Ferris, R.L. et al. (2005) Human leukocyte antigen (HLA) class I defects in head and neck cancer: molecular mechanisms and clinical significance. *Immunol. Res.*, 33, 113–133.
42. Meissner, M. et al. (2005) Defects in the human leukocyte antigen class I antigen processing machinery in head and neck squamous cell carcinoma: association with clinical outcome. *Clin. Cancer Res.*, 11, 2552–2560.
43. Cavallo, F. et al. (2011) 2011: the immune hallmarks of cancer. *Cancer Immunol. Immunother.*, 60, 319–326.
44. Whiteside, T.L. (2002) Tumor-induced death of immune cells: its mechanisms and consequences. *Semin. Cancer Biol.*, 12, 43–50.
45. Uotila, P. (1996) The role of cyclic AMP and oxygen intermediates in the inhibition of cellular immunity in cancer. *Cancer Immunol. Immunother.*, 43, 1–9.
46. Grohmann, U. et al. (2003) Tolerance, DCs and tryptophan: much ado about IDO. *Trends Immunol.*, 24, 242–248.
47. Muller, A.J. et al. (2007) Indoleamine 2,3-dioxygenase in immune suppression and cancer. *Curr. Cancer Drug Targets*, 7, 31–40.
48. Rodriguez, P.C. et al. (2004) Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. *Cancer Res.*, 64, 5839–5849.
49. McKallip, R. et al. (1999) Tumor gangliosides inhibit the tumor-specific immune response. *J. Immunol.*, 163, 3718–3726.
50. Yang, L. et al. (2010) TGF-beta and immune cells: an important regulatory axis in the tumor microenvironment and progression. *Trends Immunol.*, 31, 220–227.
51. Shields, J.D. et al. (2010) Induction of lymphoidlike stroma and immune escape by tumors that express the chemokine CCL21. *Science*, 328, 749–752.
52. Mocellin, S. et al. (2004) The multifaceted relationship between IL-10 and adaptive immunity: putting together the pieces of a puzzle. *Cytokine Growth Factor Rev.*, 15, 61–76.
53. Vicari, A.P. et al. (2004) Interleukin-10 in viral diseases and cancer: exiting the labyrinth? *Immunol. Rev.*, 202, 223–236.
54. Colombo, M.P. et al. (2007) Regulatory-T-cell inhibition versus depletion: the right choice in cancer immunotherapy. *Nat. Rev. Cancer*, 7, 880–887.
55. Li, M.O. et al. (2008) TGF-beta: a master of all T cell trades. *Cell*, 134, 392–404.
56. Cohen, N. et al. (2006) GILZ expression in human dendritic cells redirects their maturation and prevents antigen-specific T lymphocyte response. *Blood*, 107, 2037–2044.
57. Akhurst, R.J. et al. (2001) TGF-beta signaling in cancer—a double-edged sword. *Trends Cell Biol.*, 11, S44–S51.
58. Young, M.R. (2004) Trials and tribulations of immunotherapy as a treatment option for patients with squamous cell carcinoma of the head and neck. *Cancer Immunol. Immunother.*, 53, 375–382.
59. Balkwill, F. et al. (2005) Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell*, 7, 211–217.
60. Zou, W. (2005) Immunosuppressive networks in the tumour environment and their therapeutic relevance. *Nat. Rev. Cancer*, 5, 263–274.
61. Teng, M.W. et al. (2008) Immune-mediated dormancy: an equilibrium with cancer. *J. Leukoc. Biol.*, 84, 988–993.
62. Kim, R. et al. (2007) Cancer immunoediting from immune surveillance to immune escape. *Immunology*, 121, 1–14.
63. Knutson, K.L. et al. (2006) Immunoediting of cancers may lead to epithelial to mesenchymal transition. *J. Immunol.*, 177, 1526–1533.
64. Reiman, J.M. et al. (2007) Tumor immunoediting and immunosculpting pathways to cancer progression. *Semin. Cancer Biol.*, 17, 275–287.
65. Zarek, P.E. et al. (2008) A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood*, 111, 251–259.
66. Waickman, A.T. et al. (2012) Enhancement of tumor immunotherapy by deletion of the A2A adenosine receptor. *Cancer Immunol. Immunother.*, 61, 917–926.
67. Zhang, J. et al. (2010) CC chemokine ligand 2 (CCL2) promotes prostate cancer tumorigenesis and metastasis. *Cytokine Growth Factor Rev.*, 21, 41–48.
68. Barsoum, I.B. et al. (2011) Hypoxia induces escape from innate immunity in cancer cells via increased expression of ADAM10: role of nitric oxide. *Cancer Res.*, 71, 7433–7441.
69. Sugaya, M. (2010) Chemokines and cutaneous lymphoma. *J. Dermatol. Sci.*, 59, 81–85.
70. Yokoyama, W.M. et al. (2003) Immune functions encoded by the natural killer gene complex. *Nat. Rev. Immunol.*, 3, 304–316.
71. Creighton, C. et al. (2003) Expression of matrix metalloproteinase 9 (MMP-9/gelatinase B) in adenocarcinomas strongly correlated with expression of immune response genes. *In Silico Biol.*, 3, 301–311.
72. Aldinucci, D. et al. (2010) The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. *J. Pathol.*, 221, 248–263.

73. Yuan, J.P. et al. (2004) mRNA expression profiling reveals a role of *Helicobacter pylori* vacuolating toxin in escaping host defense. *World J. Gastroenterol.*, 10, 1528–1532.
74. Coffelt, S.B. et al. (2009) Tumor-associated macrophages: effectors of angiogenesis and tumor progression. *Biochim. Biophys. Acta*, 1796, 11–18.
75. Gray, A. et al. (2009) Prostate cancer immunotherapy yields superior long-term survival in TRAMP mice when administered at an early stage of carcinogenesis prior to the establishment of tumor-associated immunosuppression at later stages. *Vaccine*, 27(suppl. 6), G52–G59.
76. Iwakiri, D. et al. (2009) Epstein-Barr virus (EBV)-encoded small RNA is released from EBV-infected cells and activates signaling from Toll-like receptor 3. *J. Exp. Med.*, 206, 2091–2099.
77. Pentcheva-Hoang, T. et al. (2004) B7-1 and B7-2 selectively recruit CTLA-4 and CD28 to the immunological synapse. *Immunity*, 21, 401–413.
78. Yu, H. et al. (2007) Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. *Nat. Rev. Immunol.*, 7, 41–51.
79. Park, S.J. et al. (2004) IL-6 regulates *in vivo* dendritic cell differentiation through STAT3 activation. *J. Immunol.*, 173, 3844–3854.
80. Sun, R. et al. (2004) IL-6 prevents T cell-mediated hepatitis via inhibition of NKT cells in CD4⁺ T cell- and STAT3-dependent manners. *J. Immunol.*, 172, 5648–5655.
81. Noh, K.H. et al. (2009) Activation of Akt as a mechanism for tumor immune evasion. *Mol. Ther.*, 17, 439–447.
82. Filipov, N.M. et al. (2005) Manganese potentiates *in vitro* production of proinflammatory cytokines and nitric oxide by microglia through a nuclear factor kappa B-dependent mechanism. *Toxicol. Sci.*, 84, 139–148.
83. Gollamudi, S. et al. (2012) Concordant signaling pathways produced by pesticide exposure in mice correspond to pathways identified in human Parkinson's disease. *PLoS One*, 7, e36191.
84. Carocci, A. et al. (2011) Melatonin in Parkinson's Disease. Provisional Chapter. Intech. <http://cdn.intechopen.com/pdfs-wm/46433.pdf> (1 May 2015, date last accessed).
85. Knudsen, T.B. et al. (2011) Disruption of embryonic vascular development in predictive toxicology. *Birth Defects Res. C Embryo Today Rev.*, 93, 312–323.
86. Manfo, F.P.T. et al. (2013) Protective effect of *Basella alba* and *Carpobrotus alba* extracts against maneb-induced male infertility. *Pharmaceut. Biol.*, 52, 97–104.
87. Qin, R. et al. (2011) Protection by tetrahydroxystilbene glucoside against neurotoxicity induced by MPP⁺: the involvement of PI3K/Akt pathway activation. *Toxicol. Lett.*, 202, 1–7.
88. Desplats, P. et al. (2012) Combined exposure to Maneb and Paraquat alters transcriptional regulation of neurogenesis-related genes in mice models of Parkinson's disease. *Mol. Neurodegener.*, 7, 49.
89. Cicchetti, F. et al. (2005) Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. *Neurobiol. Dis.*, 20, 360–371.
90. U.S. EPA. The U.S. Environmental Protection Agency ToxCast Phase I/II Data. <http://www.epa.gov/ncct/toxcast/data.html> (1 May 2015, date last accessed).
91. Morgan, J.B. et al. (2010) The marine sponge metabolite mycothiazole: a novel prototype mitochondrial complex I inhibitor. *Bioorg. Med. Chem.*, 18, 5988–5994.
92. Kavlock, R. et al. (2012) Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem. Res. Toxicol.*, 25, 1287–1302.
93. Walle, M.A. et al. (2013) Triclosan alters antimicrobial and inflammatory responses of epithelial cells. *Oral Dis.*, 19, 296–302.
94. Barros, S.P. et al. (2010) Triclosan inhibition of acute and chronic inflammatory gene pathways. *J. Clin. Periodontol.*, 37, 412–418.
95. Winitthana, T. et al. (2014) Triclosan potentiates epithelial-to-mesenchymal transition in anoikis-resistant human lung cancer cells. *PLoS One*, 9, e110851.
96. Ansar Ahmed, S. (2000) The immune system as a potential target for environmental estrogens (endocrine disruptors): a new emerging field. *Toxicology*, 150, 191–206.
97. Pogribny, I.P. et al. (2013) Environmental toxicants, epigenetics, and cancer. In *Epigenetic Alterations in Oncogenesis*. *Adv. Exp. Med. Biol.*, 754, 215–232.
98. Cohen, S.M. et al. (2011) Chemical carcinogenesis. *Toxicol. Sci.*, 120(suppl. 1), S76–S92.
99. Holmstrup, M. et al. (2010) Interactions between effects of environmental chemicals and natural stressors: a review. *Sci. Total Environ.*, 408, 3746–3762.
100. Oostingh, G.J. et al. (2008) A high-throughput screening method based on stably transformed human cells was used to determine the immunotoxic effects of fluoranthene and other PAHs. *Toxicol. In Vitro*, 22, 1301–1310.
101. Oostingh, G.J. et al. (2009) The cytotoxic effects of the organophosphates chlorpyrifos and diazinon differ from their immunomodulating effects. *J. Immunotoxicol.*, 6, 136–145.
102. Röder-Stolinski, C. et al. (2008) Chlorobenzene induces the NF-kappa B and p38 MAP kinase pathways in lung epithelial cells. *Inhal. Toxicol.*, 20, 813–820.
103. Röder-Stolinski, C. et al. (2008) Styrene induces an inflammatory response in human lung epithelial cells via oxidative stress and NF-kappaB activation. *Toxicol. Appl. Pharmacol.*, 231, 241–247.
104. Descotes, J. (2006) Methods of evaluating immunotoxicity. *Expert Opin. Drug Metab. Toxicol.*, 2, 249–259.
105. Krzystyniak, K. et al. (1995) Approaches to the evaluation of chemical-induced immunotoxicity. *Environ. Health Perspect.*, 103, 17.
106. Richter-Reichhelm, H.B. et al. (2002) Workshop report. Children as a special subpopulation: focus on immunotoxicity. Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV), 15–16 November 2001, Berlin, Germany. *Arch. Toxicol.*, 76, 377–382.
107. Corsini, E. et al. (2009) Immunotoxicology: opportunities for non-animal test development. *Altern. Lab. Anim.*, 37, 387–397.
108. Luster, M.I. et al. (1992) Risk assessment in immunotoxicology. I. Sensitivity and predictability of immune tests. *Fundam. Appl. Toxicol.*, 18, 200–210.
109. Luster, M.I. et al. (1993) Risk assessment in immunotoxicology. II. Relationships between immune and host resistance tests. *Fundam. Appl. Toxicol.*, 21, 71–82.
110. Koutros, S. et al. (2010) An update of cancer incidence in the Agricultural Health Study. *J. Occup. Environ. Med.*, 52, 1098–1105.
111. Fredslund, S.O. et al. (2012) Breast cancer in the Arctic—changes over the past decades. *Int. J. Circumpolar Health.*, 71, 19155.
112. Corsini, E. et al. (2013) Pesticide induced immunotoxicity in humans: a comprehensive review of the existing evidence. *Toxicology*, 307, 123–135.
113. Dietert, R.R. (2008) Developmental immunotoxicology (DIT): windows of vulnerability, immune dysfunction and safety assessment. *J. Immunotoxicol.*, 5, 401–412.
114. Vinson, F. et al. (2011) Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. *Occup. Environ. Med.*, 68, 694–702.
115. Mannelte, A.T. et al. (2012) Farming, growing up on a farm, and hematological cancer mortality. *Occup. Environ. Med.*, 69, 126–132.
116. Enzler, T. et al. (2003) Deficiencies of GM-CSF and interferon gamma link inflammation and cancer. *J. Exp. Med.*, 197, 1213–1219.
117. Finke, J. et al. (1999) Where have all the T cells gone? Mechanisms of immune evasion by tumors. *Immunol. Today*, 20, 158–160.
118. Serafini, P. et al. (2004) High-dose granulocyte-macrophage colony-stimulating factor-producing vaccines impair the immune response through the recruitment of myeloid suppressor cells. *Cancer Res.*, 64, 6337–6343.
119. Serafini, P. et al. (2004) Derangement of immune responses by myeloid suppressor cells. *Cancer Immunol. Immunother.*, 53, 64–72.
120. Korzenik, J.R. et al. (2005) Sargramostim for active Crohn's disease. *N. Engl. J. Med.*, 352, 2193–2201.
121. Curiel, T.J. et al. (2004) Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat. Med.*, 10, 942–949.
122. Kuick, R. et al. (2007) Discovery of cancer biomarkers through the use of mouse models. *Cancer Lett.*, 249, 40–48.
123. Gallagher, B. et al. (2001) Cancer incidence in New York State acquired immunodeficiency syndrome patients. *Am. J. Epidemiol.*, 154, 544–556.
124. Frisch, M. et al. (2001) Association of cancer with AIDS-related immunosuppression in adults. *JAMA*, 285, 1736–1745.

125. Biggar, R.J. et al. (2004) Cancer risk in elderly persons with HIV/AIDS. *J. Acquir. Immune Defic. Syndr.*, 36, 861–868.
126. Fung, J.J. et al. (2001) De novo malignancies after liver transplantation: a major cause of late death. *Liver Transpl.*, 7(11 suppl 1), S109–S118.
127. Boshoff, C. et al. (2002) AIDS-related malignancies. *Nat. Rev. Cancer*, 2, 373–382.
128. Kravchenko, J. et al. (2012) Transitional probability-based model for HPV clearance in HIV-1-positive adolescent females. *PLoS One*, 7, e30736.
129. Strauss, D.C. et al. (2010) Transmission of donor melanoma by organ transplantation. *Lancet Oncol.*, 11, 790–796.
130. Bugelski, P.J. et al. (2010) Critical review of preclinical approaches to evaluate the potential of immunosuppressive drugs to influence human neoplasia. *Int. J. Toxicol.*, 29, 435–466.
131. Penn, I. (2000) Post-transplant malignancy: the role of immunosuppression. *Drug Saf.*, 23, 101–113.
132. Schug, T.T. et al. (2011) Endocrine disrupting chemicals and disease susceptibility. *J. Steroid Biochem. Mol. Biol.*, 127, 204–215.
133. Germolec, D.R. (2004) Sensitivity and predictivity in immunotoxicity testing: immune endpoints and disease resistance. *Toxicol. Lett.*, 149, 109–114.
134. Inoue, A. et al. (2004) Transcription factor EGR3 is involved in the estrogen-signaling pathway in breast cancer cells. *J. Mol. Endocrinol.*, 32, 649–661.
135. Laupeze, B. et al. (2002) Polycyclic aromatic hydrocarbons affect functional differentiation and maturation of human monocyte-derived dendritic cells. *J. Immunol.*, 168, 2652–2658.
136. Karrow, N.A. et al. (2005) Oral exposure to atrazine modulates cell-mediated immune function and decreases host resistance to the B16F10 tumor model in female B6C3F1 mice. *Toxicology*, 209, 15–28.
137. NTP (1994) National Toxicology Program (NTP) Technical Report on the Toxicology and Carcinogenesis Studies of Barium Chloride Dihydrate (CAS no. 10326-27-9) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies), NTP TR 432. NIH pub. 94-3163. NTIS pub. PB94-214178. Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC.
138. Pinchuk, L.M. et al. (2007) *In vitro* atrazine exposure affects the phenotypic and functional maturation of dendritic cells. *Toxicol. Appl. Pharmacol.*, 223, 206–217.
139. Koskinen, W. et al. (1997) Factors Affecting Atrazine Fate in North Central US Soils. *Rev. Environ. Contam. Toxicol.*, 151, 117–165.
140. Dörfler, U. et al. (1997) S-triazine residues in groundwater. *Chemosphere*, 35, 99–106.
141. Gianessi, L.P. et al. (2000) Pesticide Use in US Crop Production: 1997. National Center for Food and Agricultural Policy, Washington, DC.
142. EPA (2002) Atrazine. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED). U.S. Environmental Protection Agency <http://yosemite1.epa.gov/ee/epa/ria.nsf/EIO/FOC9CFBC133BD5AC85256EE000632421> (1 May 2015, date last accessed).
143. Filipov, N.M. et al. (2005) Immunotoxic effects of short-term atrazine exposure in young male C57BL/6 mice. *Toxicol. Sci.*, 86, 324–332.
144. Steinman, R.M. (1991) The dendritic cell system and its role in immunogenicity. *Annu. Rev. Immunol.*, 9, 271–296.
145. Kortenkamp, A. et al. (2011) State of the Art Assessment of Endocrine Disrupters. Final Report, 20, V3. http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf (1 May 2015, date last accessed).
146. U.S. EPA (2005) Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/0001b. NCFE Assessment. United States Environmental Protection Agency, Washington, DC.
147. Vandenberg, L.N. et al. (2012) Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr. Rev.*, 33, 378–455.
148. Wild, C.P. et al. (2013) Measuring the exposome: a powerful basis for evaluating environmental exposures and cancer risk. *Environ. Mol. Mutagen.*, 54, 480–499.
149. Pavanello, S. et al. (2012) Biological monitoring of carcinogens: current status and perspectives. *Arch. Toxicol.*, 86, 535–541.
150. Kravchenko, J. et al. (2011) Breast cancer as heterogeneous disease: contributing factors and carcinogenesis mechanisms. *Breast Cancer Res. Treat.*, 128, 483–493.
151. Manton, K.G. et al. (2009) Cancer Mortality and Morbidity Patterns in the US Population: An Interdisciplinary Approach. Springer, New York, NY.
152. DHHS (2009) Fourth National Report on Human Exposure to Environmental Chemicals. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 520 p. <http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf> (1 May 2015, date last accessed).
153. DHHS (2013) Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, March 2013. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 324 p. http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Mar2013.pdf (1 May 2015, date last accessed).
154. DHHS (2014) Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, August 2014. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport/pdf/fourthreport_updated-tables_aug2014.pdf (1 May 2015, date last accessed).
155. IARC (2013) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Agents Classified by the IARC Monographs. International Agency for Research and Cancer, Lyon.
156. Martin, M.T. et al. (2010) Impact of environmental chemicals on key transcription regulators and correlation to toxicity end points within EPA's ToxCast program. *Chem. Res. Toxicol.*, 23, 578–590.
157. Wallace, A.D. (2012) Toxic endpoints in the study of human exposure to environmental chemicals. *Prog. Mol. Biol. Transl. Sci.*, 112, 89.
158. Houck, K.A. et al. (2009) Profiling bioactivity of the ToxCast chemical library using BioMAP primary human cell systems. *J. Biomol. Screen.*, 14, 1054–1066.
159. Kleinstreuer, N.C. et al. (2013) *In vitro* perturbations of targets in cancer hallmark processes predict rodent chemical carcinogenesis. *Toxicol. Sci.*, 131, 40–55.
160. Kaminsky, D.E. et al. (2008) Suppression of CCL2/MCP-1 and CCL5/RANTES expression by nociceptin in human monocytes. *J. Neuroimmunopharmacol.*, 3, 75–82.
161. Meek, M. et al. (2011) Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. *Regul. Toxicol. Pharmacol.*, 60, S1–S14.
162. Blaauboer, B.J. (2010) Biokinetic modeling and *in vitro-in vivo* extrapolations. *J. Toxicol. Environ. Health B Crit. Rev.*, 13, 242–252.
163. Rotroff, D.M. et al. (2010) Incorporating human dosimetry and exposure into high-throughput *in vitro* toxicity screening. *Toxicol. Sci.*, 117, 348–358.
164. Wetmore, B.A. et al. (2012) Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment. *Toxicol. Sci.*, 125, 157–174.
165. Khatami, M. (2011) Unresolved inflammation: 'immune tsunami' or erosion of integrity in immune-privileged and immune-responsive tissues and acute and chronic inflammatory diseases or cancer. *Expert Opin. Biol. Ther.*, 11, 1419–1432.
166. Khatami, M. (2008) 'Yin and Yang' in inflammation: duality in innate immune cell function and tumorigenesis. *Expert Opin. Biol. Ther.*, 8, 1461–1472.
167. Puskas, L. et al. (2005) Gene expression in thyroid tumors. In Farid, N.R. (ed) *Molecular Basis of Thyroid Cancer*. Vol. 122, pp. 265–271.
168. Keir, M.E. et al. (2008) PD-1 and its ligands in tolerance and immunity. *Annu. Rev. Immunol.*, 26, 677–704.
169. Cappello, P. et al. (2009) An integrated humoral and cellular response is elicited in pancreatic cancer by alpha-enolase, a novel pancreatic ductal adenocarcinoma-associated antigen. *Int. J. Cancer*, 125, 639–648.
170. Chang, G.C. et al. (2006) Identification of alpha-enolase as an autoantigen in lung cancer: its overexpression is associated with clinical outcomes. *Clin. Cancer Res.*, 12, 5746–5754.
171. Takashima, M. et al. (2005) Overexpression of alpha enolase in hepatitis C virus-related hepatocellular carcinoma: association with tumor progression as determined by proteomic analysis. *Proteomics*, 5, 1686–1692.

172. Cappello, P. et al. (2013) Vaccination with ENO1 DNA prolongs survival of genetically engineered mice with pancreatic cancer. *Gastroenterology*, 144, 1098–1106.
173. Amedei, A. et al. (2013) Ex vivo analysis of pancreatic cancer-infiltrating T lymphocytes reveals that ENO-specific Tregs accumulate in tumor tissue and inhibit Th1/Th17 effector cell functions. *Cancer Immunol. Immunother.*, 62, 1249–1260.
174. Amedei, A. et al. (2014) Pancreatic cancer: role of the immune system in cancer progression and vaccine-based immunotherapy. *Hum. Vaccin. Immunother.*, 10, 3354–3368.
175. Yang, S.N. et al. (2014) The effects of environmental toxins on allergic inflammation. *Allergy Asthma Immunol. Res.*, 6, 478–484.
176. Dietert, R.R. et al. (2010) Breaking patterns of environmentally influenced disease for health risk reduction: immune perspectives. *Environ. Health Perspect.*, 118, 1091–1099.
177. Kuo, P.L. et al. (2011) Ginger suppresses phthalate ester-induced airway remodeling. *J. Agric. Food Chem.*, 59, 3429–3438.
178. Kuo, C.H. et al. (2012) Immunomodulatory effects of environmental endocrine disrupting chemicals. *Kaohsiung J. Med. Sci.*, 28(7 suppl.), S37–S42.
179. Veiga-Lopez, A. et al. (2013) Developmental programming: gestational bisphenol-A treatment alters trajectory of fetal ovarian gene expression. *Endocrinology*, 154, 1873–1884.
180. Abi Salloum, B. et al. (2013) Developmental programming: impact of prenatal exposure to bisphenol-A and methoxychlor on steroid feedbacks in sheep. *Toxicol. Appl. Pharmacol.*, 268, 300–308.
181. Wei, J. et al. (2011) Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology*, 152, 3049–3061.
182. Alonso-Magdalena, P. et al. (2010) Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ. Health Perspect.*, 118, 1243–1250.
183. Maestrelli, P. et al. (2009) Mechanisms of occupational asthma. *J. Allergy Clin. Immunol.*, 123, 531–542; quiz 543.
184. Vawda, S. et al. (2014) Associations between inflammatory and immune response genes and adverse respiratory outcomes following exposure to outdoor air pollution: a HuGE systematic review. *Am. J. Epidemiol.*, 179, 432–442.
185. Clayton, R. et al. (2010) The impact of bisphenol A and triclosan on immune parameters in the U. S. Population, NHANES 2003 a 2006. *Environ. Health Perspect.*, 119, 390–396.
186. Heemskerk, V.H. et al. (1999) Insulin-like growth factor-1 (IGF-1) and growth hormone (GH) in immunity and inflammation. *Cytokine Growth Factor Rev.*, 10, 5–14.
187. Kim, J.H. et al. (2013) Synergism of antifungal activity between mitochondrial respiration inhibitors and kojic acid. *Molecules*, 18, 1564–1581.
188. Çayır, A. et al. (2012) Micronuclei, nucleoplasmic bridges, and nuclear buds induced in human lymphocytes by the fungicide signum and its active ingredients (boscalid and pyraclostrobin). *Environ. Toxicol.*, 29, 723–732.
189. Bartlett, D.W. et al. (2002) The strobilurin fungicides. *Pest Manage. Sci.*, 58, 649–662.
190. Judson, R.S. et al. (2010) In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project. *Environ. Health Perspect.* (Online), 118, 485.
191. Maltby, L. et al. (2009) Fungicide risk assessment for aquatic ecosystems: importance of interspecific variation, toxic mode of action, and exposure regime. *Environ. Sci. Technol.*, 43, 7556–7563.
192. Pereboeva, L. et al. (2013) DNA damage responses and oxidative stress in dyskeratosis congenita. *PLoS One*, 8, e76473.
193. Shadnia, S. et al. (2005) Evaluation of oxidative stress and genotoxicity in organophosphorus insecticide formulators. *Hum. Exp. Toxicol.*, 24, 439–445.
194. Navarro, A. et al. (2010) Effects of rotenone and pyridaben on complex I electron transfer and on mitochondrial nitric oxide synthase functional activity. *J. Bioenerg. Biomembr.*, 42, 405–412.
195. Ratner, V. et al. (2009) Mitochondrial dysfunction contributes to alveolar developmental arrest in hyperoxia-exposed mice. *Am. J. Respir. Cell Mol. Biol.*, 40, 511–518.
196. Boyd, J. et al. (2011) Exploring the boundaries of additivity: mixtures of NADH: quinone oxidoreductase inhibitors. *Chem. Res. Toxicol.*, 24, 1242–1250.
197. Kleinstreuer, N.C. et al. (2011) Environmental impact on vascular development predicted by high-throughput screening. *Environ. Health Perspect.*, 119, 1596.
198. Bloom, S.E. et al. (2006) Potentiation of apoptosis by heat stress plus pesticide exposure in stress resistant human B-lymphoma cells and its attenuation through interaction with follicular dendritic cells: role for c-Jun N-terminal kinase signaling. *Toxicol. Sci.*, 89, 214–223.
199. Muscarella, D.E. et al. (2003) Reversal of Bcl-2-mediated resistance of the EW36 human B-cell lymphoma cell line to arsenite-and pesticide-induced apoptosis by PK11195, a ligand of the mitochondrial benzodiazepine receptor. *Toxicol. Sci.*, 74, 66–73.
200. Fang, N. et al. (1998) Anticancer action of cube insecticide: correlation for rotenoid constituents between inhibition of NADH: ubiquinone oxidoreductase and induced ornithine decarboxylase activities. *Proc. Natl Acad. Sci. USA*, 95, 3380–3384.
201. Rowlands, J.C. et al. (1998) NADH: ubiquinone oxidoreductase inhibitors block induction of ornithine decarboxylase activity in MCF-7 human breast cancer cells*. *Pharmacol. Toxicol.*, 83, 214–219.
202. Dixit, A. et al. (2013) Minocycline, levodopa and MnTMPyP induced changes in the mitochondrial proteome profile of MPTP and maneb and paraquat mice models of Parkinson's disease. *Biochim. Biophys. Acta*, 1832, 1227–1240.
203. Santos, P.M. et al. (2009) Insights into yeast adaptive response to the agricultural fungicide mancozeb: a toxicoproteomics approach. *Proteomics*, 9, 657–670.
204. Valentich, M.A. et al. (1996) Expression of dynamin immunoreactivity in experimental pancreatic tumors induced in rat by mancozeb-nitrosomethylurea. *Cancer Lett.*, 102, 23–29.
205. Grosicka-Maciąg, E. et al. (2011) Protective effect of N-acetyl-L-cysteine against maneb induced oxidative and apoptotic injury in Chinese hamster V79 cells. *Food Chem. Toxicol.*, 49, 1020–1025.
206. Tyagi, S. et al. (2011) Neoplastic alterations induced in mammalian skin following mancozeb exposure using *in vivo* and *in vitro* models. *OMICs*, 15, 155–167.
207. Littelljohn, D. et al. (2010) Inflammatory mechanisms of neurodegeneration in toxin-based models of Parkinson's disease. *Parkinson's Dis.*, 2011, 713517. doi:10.4061/2011/713517.
208. Osaba, L. et al. (2002) Evaluation of genotoxicity of captan, maneb and zineb in the wing spot test of *Drosophila melanogaster*: role of nitrosation. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.*, 518, 95–106.
209. Van Maanen, J. et al. (1995) Modulation of nitrate-nitrite conversion in the oral cavity. *Cancer Detect. Prev.*, 20, 590–596.
210. Vandhana, S. et al. (2013) Biochemical changes accompanying apoptotic cell death in retinoblastoma cancer cells treated with lipogenic enzyme inhibitors. *Biochim. Biophys. Acta*, 1831, 1458–1466.
211. Paul, K.B. et al. (2013) Cross-species analysis of thyroperoxidase inhibition by xenobiotics demonstrates conservation of response between pig and rat. *Toxicology*, 312, 97–107.
212. Zuckerbraun, H.L. et al. (1998) Triclosan, cytotoxicity, mode of action, and induction of apoptosis in human gingival cells *in vitro*. *Eur. J. Oral Sci.*, 106, 628–636.
213. Gee, R. et al. (2008) Oestrogenic and androgenic activity of triclosan in breast cancer cells. *J. Appl. Toxicol.*, 28, 78–91.
214. Tamura, I. et al. (2012) Triclosan, an antibacterial agent, increases intracellular Zn²⁺ concentration in rat thymocytes: its relation to oxidative stress. *Chemosphere*, 86, 70–75.
215. Cullinan, M.P. et al. (2012) Long term use of triclosan toothpaste and thyroid function. *Sci. Total Environ.*, 416, 75–79.
216. Peighambarzadeh, S. et al. (2011) Presence of atrazine in the biological samples of cattle and its consequence adversity in human health. *Iran. J. Public Health*, 40, 112.
217. Zaya, R.M. et al. (2011) Exposure to atrazine affects the expression of key genes in metabolic pathways integral to energy homeostasis in *Xenopus laevis* tadpoles. *Aquat. Toxicol.*, 104, 254–262.
218. Manske, M.K. et al. (2004) Low-level atrazine exposure decreases cell proliferation in human fibroblasts. *Arch. Environ. Contam. Toxicol.*, 46, 438–444.

219. Albanito, L. et al. (2008) G-protein-coupled receptor 30 and estrogen receptor- α are involved in the proliferative effects induced by atrazine in ovarian cancer cells—RETRACTED. *Environ. Health Perspect.*, 116, 1648.
220. Ueda, M. et al. (2005) Possible enhancing effects of atrazine on growth of 7, 12-dimethylbenz (a) anthracene-induced mammary tumors in ovariectomized Sprague-Dawley rats. *Cancer Sci.*, 96, 19–25.
221. Wetzel, L.T. et al. (1994) Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fischer 344 rats. *J. Toxicol. Environ. Health A Curr. Issues*, 43, 169–182.
222. Lim, S. et al. (2009) Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. *PLoS One*, 4, e5186.
223. Kandori, H. et al. (2005) Influence of atrazine administration and reduction of calorie intake on prostate carcinogenesis in probasin/SV40 T antigen transgenic rats. *Cancer Sci.*, 96, 221–226.
224. Jiang, Y. et al. (2013) Prenatal exposure to bisphenol A at the reference dose impairs mitochondria in the heart of neonatal rats. *J. Appl. Toxicol.*, 34, 1012–1022.
225. Lee, H.-S. et al. (2012) Set, a putative oncogene, as a biomarker for prenatal exposure to bisphenol A. *Asian Pac. J. Cancer Prev.*, 13, 2711–2715.
226. Betancourt, A.M. et al. (2012) Altered carcinogenesis and proteome in mammary glands of rats after prepubertal exposures to the hormonally active chemicals bisphenol A and genistein. *J. Nutr.*, 142, 1382S–1388S.
227. Fillon, M. (2012) Getting it right: BPA and the difficulty proving environmental cancer risks. *J. Natl Cancer Inst.*, 104, 652–655.
228. Durando, M. et al. (2011) Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling rats. *J. Steroid Biochem. Mol. Biol.*, 127, 35–43.
229. Allard, P. et al. (2010) Bisphenol A impairs the double-strand break repair machinery in the germline and causes chromosome abnormalities. *Proc. Natl Acad. Sci. USA*, 107, 20405–20410.
230. Terasaka, H. et al. (2005) Cytotoxicity and apoptosis-inducing activity of bisphenol A and hydroquinone in HL-60 cells. *Anticancer Res.*, 25, 2241–2247.
231. Xu, J. et al. (2002) Bisphenol A induces apoptosis and G2-to-M arrest of ovarian granulosa cells. *Biochem. Biophys. Res. Commun.*, 292, 456–462.
232. Goodson, W.H. et al. (2011) Activation of the mTOR pathway by low levels of xenoestrogens in breast epithelial cells from high-risk women. *Carcinogenesis*, 32, 1724–1733.
233. Dairkee, S.H. et al. (2013) Bisphenol-A-induced inactivation of the p53 axis underlying deregulation of proliferation kinetics, and cell death in non-malignant human breast epithelial cells. *Carcinogenesis*, 34, 703–712.
234. Pupo, M. et al. (2012) Bisphenol A induces gene expression changes and proliferative effects through GPER in breast cancer cells and cancer-associated fibroblasts. *Environ. Health Perspect.*, 120, 1177–1182.
235. Wang, H. et al. (2013) Epithelial-mesenchymal transition (EMT) induced by TNF- α requires AKT/GSK-3 β -mediated stabilization of Snail in colorectal cancer. *PLoS One*, 8, e56664.
236. Wu, C.-H. et al. (2012) Nickel-induced epithelial-mesenchymal transition by reactive oxygen species generation and E-cadherin promoter hypermethylation. *J. Biol. Chem.*, 287, 25292–25302.
237. Graham, C.H. et al. (1999) Hypoxia-mediated stimulation of carcinoma cell invasiveness via upregulation of urokinase receptor expression. *Int. J. Cancer*, 80, 617–623.
238. Feng, Y. et al. (2012) Bisphenol AF may cause testosterone reduction by directly affecting testis function in adult male rats. *Toxicology Lett.*, 211, 201–209.
239. Ryu, J.Y. et al. (2007) Di (2-ethylhexyl) phthalate induces apoptosis through peroxisome proliferators-activated receptor-gamma and ERK 1/2 activation in testis of Sprague-Dawley rats. *J. Toxicol. Environ. Health Part A*, 70, 1296–1303.
240. Lin, C.-H. et al. (2011) Activation of Trim17 by PPAR γ is involved in Di (2-ethylhexyl) phthalate (DEHP)-induced apoptosis on Neuro-2a cells. *Toxicol. Lett.*, 206, 245–251.
241. James, N.H. et al. (1998) Suppression of hepatocyte apoptosis and induction of DNA synthesis by the rat and mouse hepatocarcinogen diethylhexylphthalate (DEHP) and the mouse hepatocarcinogen 1, 4-dichlorobenzene (DCB). *Arch. Toxicol.*, 72, 784–790.
242. Rusyn, I. et al. (2006) Modes of action and species-specific effects of di-(2-ethylhexyl) phthalate in the liver. *CRC Crit. Rev. Toxicol.*, 36, 459–479.
243. Hsieh, T.-H. et al. (2012) Phthalates induce proliferation and invasiveness of estrogen receptor-negative breast cancer through the AhR/HDAC6/c-Myc signaling pathway. *FASEB J.*, 26, 778–787.
244. Park, M.-A. et al. (2012) Cell growth of BG-1 ovarian cancer cells is promoted by di-n-butyl phthalate and hexabromocyclododecane via upregulation of the cyclin D and cyclin-dependent kinase-4 genes. *Mol. Med. Rep.*, 5, 761–766.
245. Moushumi Priya, A. et al. (2012) Induction of apoptosis and cell cycle arrest by bis (2-ethylhexyl) phthalate produced by marine *Bacillus pumilus* MB 40. *Chem. Biol. Interact.*, 195, 133–143.
246. Erkekoğlu, P. et al. (2011) Induction of ROS, p53, p21 in DEHP-and MEHP-exposed LNCaP cells-protection by selenium compounds. *Food Chem. Toxicol.*, 49, 1565–1571.
247. Erkekoğlu, P. et al. (2010) Evaluation of cytotoxicity and oxidative DNA damaging effects of di (2-ethylhexyl)-phthalate (DEHP) and mono (2-ethylhexyl)-phthalate (MEHP) on MA-10 Leydig cells and protection by selenium. *Toxicol. Appl. Pharmacol.*, 248, 52–62.
248. Isenberg, J.S. et al. (2001) Reversibility and persistence of di-2-ethylhexyl phthalate (DEHP)-and phenobarbital-induced hepatocellular changes in rodents. *Toxicol. Sci.*, 64, 192–199.
249. Rao, K.N. et al. (1997) Hepatic hyperplasia and cancer in rats: metabolic alterations associated with cell growth. *Gastroenterology*, 113, 238–248.
250. U.S. EPA (2000) List of Chemicals Evaluated for Carcinogenic Potential. U.S. EPA <http://www.epa.gov/pesticides/carlist/> (1 May 2015, date last accessed).
251. Odermatt, A. et al. (2008) Disruption of glucocorticoid and mineralocorticoid receptor-mediated responses by environmental chemicals. *CHIMIA Int. J. Chem.*, 62, 335–339.
252. U.S. EPA (2005) Maneb Facts. Prevention, Pesticides and Toxic Substances (7508C). EPA 738-F-05_XX. U.S. EPA http://www.epa.gov/op00001/reregistration/REDS/factsheets/maneb_fact.pdf (1 May 2015, date last accessed).
253. NPIC (1996) Maneb. Extension Toxicology Network. Pesticide Information Profiles. NPIC <http://extoxnet.orst.edu/pips/maneb.htm> (1 May 2015, date last accessed).
254. Kuster, M. et al. (2009) Liquid chromatography-tandem mass spectrometric analysis and regulatory issues of polar pesticides in natural and treated waters. *J. Chromatogr. A*, 1216, 520–529.
255. Miller, S.M. et al. (2000) Atrazine and nutrients in precipitation: results from the Lake Michigan mass balance study. *Environ. Sci. Technol.*, 34, 55–61.
256. Fenelon, J. et al. (1998) Transport of agricultural chemicals to ground and surface water in a small central Indiana watershed. *J. Environ. Qual.*, 27, 884–894.
257. Stoker, T.E. et al. (1999) Maternal exposure to atrazine during lactation suppresses suckling-induced prolactin release and results in prostatitis in the adult offspring. *Toxicol. Sci.*, 52, 68–79.
258. Fan, W. et al. (2007) Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine disruption in wildlife and reproductive cancers in humans. *Environ. Health Perspect.*, 115, 720–727.
259. Martin, M.T. et al. (2011) Predictive model of rat reproductive toxicity from ToxCast high throughput screening. *Biol. Reprod.*, 85, 327–339.
260. Metzler, M. et al. (2001) Chemistry of natural and anthropogenic endocrine active compounds. In *Endocrine Disruptors—Part I. The Handbook of Environmental Chemistry*. Vol. 3L, pp. 63–80.
261. Boyd, G.R. et al. (2003) Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. *Sci. Total Environ.*, 311, 135–149.
262. Kolpin, D.W. et al. (2002) Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: a national reconnaissance. *Environ. Sci. Technol.*, 36, 1202–1211.
263. Gatidou, G. et al. (2007) Simultaneous determination of the endocrine disrupting compounds nonylphenol, nonylphenol ethoxylates, triclosan and bisphenol A in wastewater and sewage sludge by gas chromatography-mass spectrometry. *J. Chromatogr. A*, 1138, 32–41.
264. Foran, C.M. et al. (2000) Developmental evaluation of a potential non-steroidal estrogen: triclosan. *Mar. Environ. Res.*, 50, 153–156.

265. Ishibashi, H. et al. (2004) Effects of triclosan on the early life stages and reproduction of medaka *Oryzias latipes* and induction of hepatic vitellogenin. *Aquat. Toxicol.*, 67, 167–179.
266. NICNAS (2006) Diethylhexyl Phthalate (DEHP) Factsheet. CAS: 117-81-7. NICNAS.
267. Jobling, S. et al. (1995) A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. *Environ. Health Perspect.*, 103, 582–587.
268. Hao, C. et al. (2013) Perinatal exposure to diethyl-hexyl-phthalate induces obesity in mice. *Front. Biosci. (Elite Ed.)*, 5, 725–733.
269. IARC (1982) Monograph on the Evaluation of Carcinogenic Risk to Humans. Some Industrial Chemicals and Dyestuffs. Di(2-ethylhexyl) Phthalate. International Agency for Research and Cancer, Lyon.
270. IARC (2000) Monograph on the Evaluation of Carcinogenic Risk to Humans. Some Industrial Chemicals. Di(2-ethylhexyl) Phthalate. International Agency for Research and Cancer, Lyon, pp. 41–148.
271. Tomasetti, C. et al. (2015) Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*, 347, 78–81.
272. Bisson, W.H. (2012) Editorial: computational chemogenomics in drug design and discovery. *Curr. Top. Med. Chem.*, 12, 1867–1868.
273. Akushevich, I. et al. (2012) New stochastic carcinogenesis model with covariates: an approach involving intracellular barrier mechanisms. *Math. Biosci.*, 236, 16–30.
274. Moolgavkar, S.H. et al. (1981) Mutation and cancer: a model for human carcinogenesis. *J. Natl Cancer Inst.*, 66, 1037–1052.
275. Tan, W.-Y. (1991) *Stochastic Models for Carcinogenesis*. CRC Press Series: Statistics: A Series of Textbooks and Monographs. Vol. 116. Marcel Dekker, Inc. New York, Basel, Hong Kong. pp. 264.
276. Luebeck, E.G. et al. (2002) Multistage carcinogenesis and the incidence of colorectal cancer. *Proc. Natl Acad. Sci. USA.*, 99, 15095–15100.
277. Little, M.P. et al. (2003) A stochastic carcinogenesis model incorporating genomic instability fitted to colon cancer data. *Math. Biosci.*, 183, 111–134.
278. Kravchenko, J. et al. (2012) Evaluating the number of stages in development of squamous cell and adenocarcinomas across cancer sites using human population-based cancer modeling. *PLoS One*, 7, e37430.