Causes of genome instability: the effect of low dose chemical exposures in modern society

REVIEW

Causes of genome instability: the effect of low dose chemical exposures in modern society

Sabine A.S.Langie, Gudrun Koppen[*], Daniel Desaulniers[1],
Fahd Al-Mulla[2], Rabeah Al-Temaimi[2], Amedeo Amedei[3], Amaya Azqueta[4],
William H.Bisson[5], Dustin Brown[6], Gunnar Brunborg[7], Amelia K.Charles[8], Tao Chen[9],
Annamaria Colacci[10], Firouz Darroudi[11], Stefano Forte[12], Laetitia Gonzalez[13],
Roslida A.Hamid[14], Lisbeth E.Knudsen[15], Luc Leyns[13], Adela Lopez de Cerain
Salsamendi[4], Lorenzo Memeo[12], Chiara Mondello[16], Carmel Mothersill[17],
Ann-Karin Olsen[7], Sofia Pavanello[18], Jayadev Raju[19], Emilio Rojas[20], Rabindra Roy[21],
Elizabeth Ryan[6], Patricia Ostrosky-Wegman[20], Hosni K.Salem[22], Ivana Scovassi[16],
Neetu Singh[23], Monica Vaccari[10], Frederik J.Van Schooten[24], Mahara Valverde[20],
Jordan Woodrick[21], Luoping Zhang[25], Nik van Larebeke[26,27],
Micheline Kirsch-Volders[13], Andrew R.Collins[28]

Environmental Risk and Health Unit, Flemish Institute for Technological Research (VITO), Boeretang 200, 2400 Mol, Belgium,
[1]Health Canada, Environmental Health Sciences and Research Bureau, Environmental Health Centre, Ottawa, Ontario
K1A0K9, Canada, [2]Department of Pathology, Kuwait University, Safat 13110, Kuwait, [3]Department of Experimental and Clinical
Medicine, University of Firenze, Florence 50134, Italy, [4]Department of Pharmacology and Toxicology, Faculty of Pharmacy,
University of Navarra, Pamplona 31009, Spain, [5]Environmental and Molecular Toxicology, Environmental Health Sciences
Center, Oregon State University, Corvallis, OR 97331, USA, [6]Department of Environmental and Radiological Health Sciences/
Food Science and Human Nutrition, College of Veterinary Medicine and Biomedical Sciences, Colorado State University/
Colorado School of Public Health, Fort Collins, CO 80523-1680, USA, [7]Department of Chemicals and Radiation, Division
of Environmental Medicine, Norwegian Institute of Public Health, PO Box 4404, N-0403 Oslo, Norway, [8]Hopkins Building,
School of Biological Sciences, University of Reading, Reading, Berkshire RG6 6UB, UK, [9]Division of Genetic and Molecular
Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, USA, [10]Center
for Environmental Carcinogenesis and Risk Assessment, Environmental Protection and Health Prevention Agency, Bologna
40126, Italy, [11]Human and Environmental Safety Research, Department of Health Sciences, College of North Atlantic, Doha,
State of Qatar, [12]Mediterranean Institute of Oncology, 95029 Viagrande, Italy, [13]Laboratory for Cell Genetics, Vrije Universiteit
Brussel, Brussels 1050, Belgium, [14]Department of Biomedical Science, Faculty of Medicine and Health Sciences, University
Putra, Serdang 43400, Selangor, Malaysia, [15]University of Copenhagen, Department of Public Health, Copenhagen 1353,
Denmark, [16]Institute of Molecular Genetics, National Research Council, Pavia 27100, Italy, [17]Medical Physics & Applied
Radiation Sciences, McMaster University, Hamilton, Ontario L8S4L8, Canada, [18]Department of Cardiac, Thoracic and Vascular
Sciences, Unit of Occupational Medicine, University of Padova, Padova 35128, Italy, [19]Toxicology Research Division, Bureau
of Chemical Safety Food Directorate, Health Products and Food Branch Health Canada, Ottawa, Ontario K1A0K9, Canada,
[20]Departamento de Medicina Genomica y Toxicologia Ambiental, Instituto de Investigaciones Biomedicas, Universidad
Nacional Autonoma de México, México CP 04510, México, [21]Lombardi Comprehensive Cancer Center, Georgetown University
Medical Center, Washington, DC 20057, USA, [22]Urology Department, kasr Al-Ainy School of Medicine, Cairo University, El
Manial, Cairo 12515, Egypt, [23]Centre for Advanced Research, King George's Medical University, Chowk, Lucknow 226003,
Uttar Pradesh, India, [24]Department of Toxicology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht
University, 6200MD, PO Box 61, Maastricht, The Netherlands, [25]Division of Environmental Health Sciences, School of Public
Health, University of California, Berkeley, CA 94720-7360, USA, [26]Laboratory for Analytical and Environmental Chemistry,

Vrije Universiteit Brussel, Brussels 1050, Belgium, [27]Study Centre for Carcinogenesis and Primary Prevention of Cancer, Ghent University, Ghent 9000, Belgium; [28]Department of Nutrition, University of Oslo, Oslo 0316, Norway

*To whom correspondence should be addressed. Tel: +32 14335165; Fax: +32 14580523 Email: gudrun.koppen@vito.be

Abstract

Genome instability is a prerequisite for the development of cancer. It occurs when genome maintenance systems fail to safeguard the genome's integrity, whether as a consequence of inherited defects or induced via exposure to environmental agents (chemicals, biological agents and radiation). Thus, genome instability can be defined as an enhanced tendency for the genome to acquire mutations; ranging from changes to the nucleotide sequence to chromosomal gain, rearrangements or loss. This review raises the hypothesis that in addition to known human carcinogens, exposure to low dose of other chemicals present in our modern society could contribute to carcinogenesis by indirectly affecting genome stability. The selected chemicals with their mechanisms of action proposed to indirectly contribute to genome instability are: heavy metals (DNA repair, epigenetic modification, DNA damage signaling, telomere length), acrylamide (DNA repair, chromosome segregation), bisphenol A (epigenetic modification, DNA damage signaling, mitochondrial function, chromosome segregation), benomyl (chromosome segregation), quinones (epigenetic modification) and nano-sized particles (epigenetic pathways, mitochondrial function, chromosome segregation, telomere length). The purpose of this review is to describe the crucial aspects of genome instability, to outline the ways in which environmental chemicals can affect this cancer hallmark and to identify candidate chemicals for further study. The overall aim is to make scientists aware of the increasing need to unravel the underlying mechanisms via which chemicals at low doses can induce genome instability and thus promote carcinogenesis.

Abbreviations

5hmC	5-hydroxymethylcytosine
5mC	5-methylcytosine
BC	black carbon
BER	base excision repair
BPA	bisphenol A
CNV	copy number variation
CYP	cytochrome P450
DNMT	DNA methyltransferase
HDAC	histone deacetylase
IARC	International Agency for Research on Cancer
miRNA	micro RNA
MMR	mismatch repair
	mRNA; messenger RNA
MSI	microsatellite instability
mtDNA	mitochondrial DNA
mtDNAcn	mtDNA copy number
NER	nucleotide excision repair
NF-κB	nuclear factor-kappaB
NP	nanoparticle
PAH	polycyclic aromatic hydrocarbons
ROS	reactive oxygen species
SNP	single-nucleotide polymorphism
TET	ten-eleven translocation
WC	tungsten carbide

Introduction

The understanding of cancer as a genetic disease has dramatically evolved during the last few decades with the knowledge that cancer cells acquire their characteristics at different times during cancer development, in diverse microenvironments, via various mechanisms (1,2). It is increasingly clear that the phenotypic variations underlying cancer result from multiple interactions among numerous environmental and genetic factors that occur over long periods of time (3). Molecular epidemiological studies (4–14) have shown interesting associations between certain single environmental exposures and early effects related to carcinogenesis. However, we know surprisingly little about the cancer risks that might be attributable to the combined effects of the many chemicals that we encounter in our everyday lives at low doses. Consequently, the non-governmental organization 'Getting to Know Cancer' (gettingtoknowcancer.org) invited scientists to prepare the current review, requesting them to examine the possibility that environmental chemicals that are not considered as class I carcinogens [according to the International Agency for Research on Cancer (IARC)] could still indirectly contribute to genome instability and carcinogenesis.

Genome instability is defined as an increased tendency of the genome to acquire mutations (15). It occurs when various processes involved in maintaining and replicating the genome are dysfunctional or when there is increasing exposure to carcinogens. Genome instability is an enabling characteristic that is causally associated with the acquisition of cancer hallmarks. The mechanisms leading to genome instability and enhanced mutation frequency include inherited or acquired defects in DNA repair, DNA replication, cell cycle control or chromosome segregation. Genome instability is indicated (and measured) by an elevated frequency of simple or complex mutations to the genome, namely changes in the nucleotide sequence (base substitutions, base loss, nucleotide deletion, insertion or amplification), DNA breaks, chromosomal translocations, inversions and deletions and abnormal numbers of chromosomes (aneuploidy). Altogether, this instability plays an essential role in carcinogenesis (16–18) (Figure 1). Exogenously induced DNA damage, caused by a variety of environmental chemicals, nanoparticles (NPs), radiation or biological agents, can cause loss of genome integrity, and also endogenously induced (metabolically caused) DNA damage is significant. It is estimated that DNA lesions of endogenous origin occur thousands of times daily in the genome of every human cell (19). In general, various DNA repair pathways prevent the persistence of such DNA lesions, maintaining genome integrity. Gene mutations, defined as irreversible
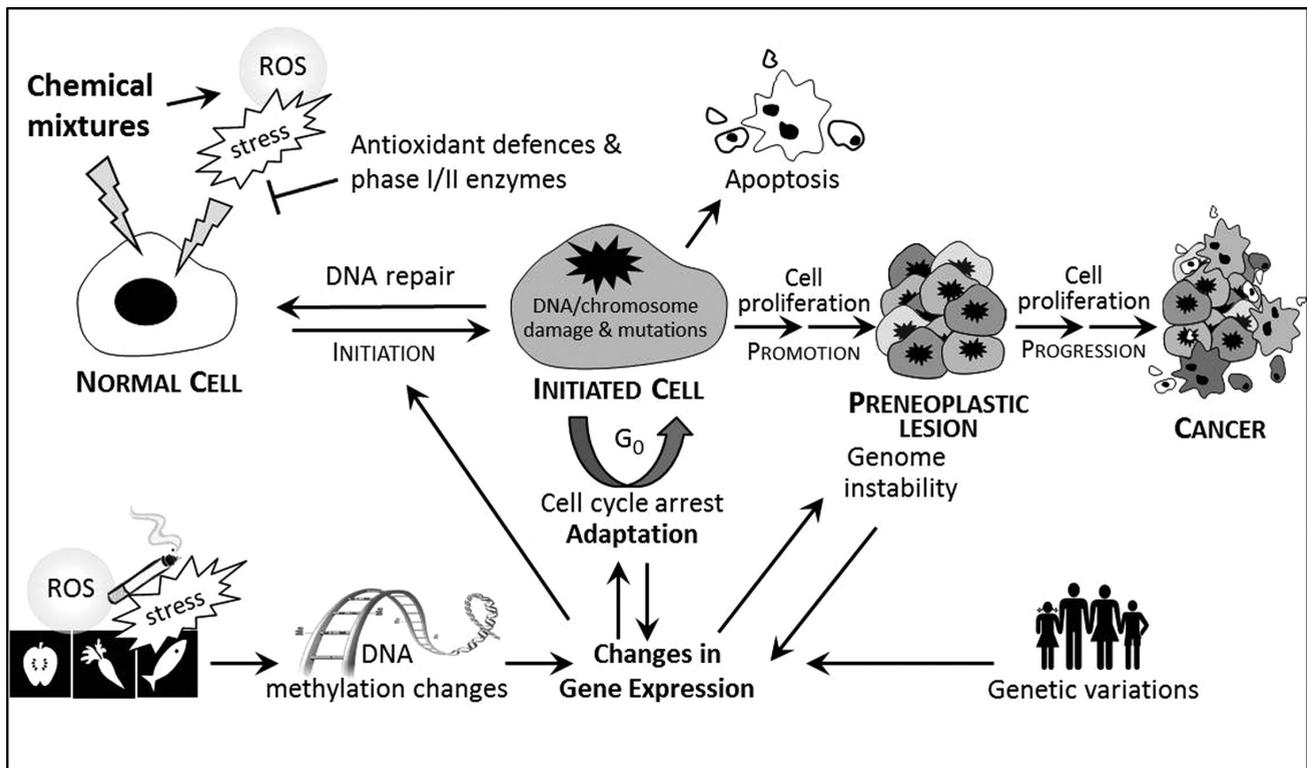
Figure 1. Cellular mechanisms linking exposures to chemical mixtures with cancer. Effects of chemical mixtures may be modulated by various pathways and mechanisms, including enzymic and non-enzymic antioxidants, phase I and II metabolizing enzymes, cell cycle arrest, DNA repair, apoptosis, and by epigenetic mechanisms (such as DNA methylation) that can regulate gene expression. Defense mechanisms limit the accumulation of DNA damage and reduce the risk of genome instability (mutations, chromosomal anomalies, telomere shortening etc.) and the progression to cancer. It should be noted, however, that phase I metabolism can result in the transient presence of activated carcinogens.

changes in the nucleotide sequence, arise much more rarely. They are a result of misrepair or erroneous replication of the nucleotide sequence containing the lesion. If mutations occur in certain genes that play essential roles in the finely tuned control of DNA integrity, altered expression (e.g. of oncogenes or tumor suppressor genes) may take place, with (among other things) genome instability as a consequence. Moreover, changes to the epigenome may also lead to genome instability in an indirect way. For example, epigenetic alterations can (i) affect DNA repair efficiency and fidelity by changing the expression of DNA repair genes (20–24); (ii) induce chromatin disruption (25,26) and (iii) deregulate enzymes involved in antioxidant defenses or phase I/phase II xenobiotic metabolism (27–29).

Here, we describe different aspects and causes of genome instability, referring to the various biological targets that maintain genome integrity. Furthermore, we discuss a selection of chemicals that can deregulate the genome maintenance systems, adding to the burden of genome instability and thus increasing cancer incidence.

Causes of genome instability and levels of dysfunction

Chemicals, radiations and biological agents (e.g. viruses, bacteria and parasites) can have direct effects on genome integrity, causing specific DNA lesions [e.g. 8-oxo-7,8-dihydroguanine (8-oxoG), cyclobutane pyrimidine dimers, bulky adducts], inducing gene mutations and chromosome aberrations. Environmental exposure can also cause genome instability via indirect mechanisms; these could involve single-nucleotide polymorphisms (e.g. SNPs

in chemical metabolism, DNA repair, cell cycle), effects on DNA repair enzyme activity, changes in nuclear and mitochondrial DNA copy number (mtDNAcn) or microsatellite instability (MSI), changes in epigenetic regulation of gene expression (e.g. differential promoter region methylation) or altered levels of specific proteins (30). Such indirect effects form the basis of our criteria for selecting the chemicals described in Chemical disruptors and their effect on biological target sites, but first we give an overview of the process of carcinogenesis insofar as it involves changes to or modifications of the genome.

Direct effects on genome integrity

When DNA damage is not repaired by the time a cell comes to replicates its DNA, it can give rise to gene mutations (base-pair alterations, deletions and insertions), and in turn chromosome aberrations (when, e.g., a double-strand break or large deletion is present at mitosis). These can all be regarded as direct effects on genome integrity.

DNA damage, gene mutations, oncogene activation and tumor suppressor inactivation

For decades, DNA damage has been considered as the most likely event to 'kick-start' the multistep carcinogenic process (31). Of all the chemicals classified as carcinogenic to humans by the IARC, a great proportion have been shown to exert their biological effects through binding of their DNA-reactive metabolites forming covalent DNA adducts or through base modifications (e.g. oxidation, alkylation). DNA adduct analyses reflect tissue-specific rates of adduct formation and removal, which depend on carcinogen uptake, metabolic activation, DNA repair,

adduct instability and tissue turnover and are thus useful markers of exposure to DNA-reactive chemicals and, to a certain extent, of cancer risk.

The various forms of DNA damage caused by radiation and exogenous or endogenous chemicals include single-strand breaks, double-strand breaks, apurinic/apyrimidinic sites, oxidation or alkylation of bases, bulky adducts (large chemical groups covalently bound to DNA bases), intra-strand cross-links (such as dimerization of adjacent pyrimidines), inter-strand cross-links (covalent links between the two strands of the double helix) and covalent bonds between DNA and protein. In addition, mismatches can occur through slipped alignment of microsatellite repeats and faulty replication, especially if an apurinic/apyrimidinic site or a base with altered base-pairing properties (caused by oxidation or alkylation, or a bulky adduct) is present when the DNA is replicated (32).

The development of cancers can be mediated through genetic (or epigenetic) alterations in oncogenes and tumor suppressor genes that regulate processes such as cell proliferation, cell death, cell differentiation and genome stability. Most oncogenes result from proto-oncogenes that are normal functional genes. When a proto-oncogene mutates at its critical DNA sequences or increases its expression, it becomes an oncogene, leading to cancer. This process is called oncogene activation. Examples of proto-oncogenes include *RAS* regulating growth signaling, and *MYC*, a gene coding for a regulatory transcription factor (33). Tumor suppressor genes, on the other hand, are normal genes that inhibit cell growth, stop cell division and promote DNA repair or apoptosis when a cell's DNA is damaged. When mutations occur in the tumor suppressor genes, cells can grow out of control, which can lead to cancer. Examples of tumor suppressor genes include DNA repair genes, *BRCA1* and *BRCA2*, and *TP53*, which is mutated in most human cancers (34).

Oncogenes are generally activated through mutations, gene amplification or chromosome rearrangements; only one of the two copies of a proto-oncogene needs to be activated since mutations are dominant. These three mechanisms result in either an alteration of proto-oncogene structure or an increase in proto-oncogene expression (35). Structural alterations in the encoded proteins often lead to the uncontrolled, continuous activity of the mutated protein. For example, *RAS* mutations induce uncontrolled cell division (36,37). Gene amplification occurs through replication of a DNA region containing an oncogene and can result in several hundred copies of the gene. Thus, the expression level of the oncogene increases, conferring a selective advantage for cell growth. About 20–30% of breast and ovarian cancers show c-*MYC* amplification (38). Chromosomal rearrangements consist of translocations and inversions. Chromosomal rearrangements can move a proto-oncogene to a site close to an immunoglobulin or T-cell receptor gene. Transcription of the proto-oncogene is then under control of regulatory elements from the immunoglobulin or T-cell receptor locus, leading to deregulation of the proto-oncogene expression. A well-known example is the *BCR–ABL* fusion gene, the Philadelphia chromosome, present in most cases of chronic myelogenous leukemia (39).

Since mutations in oncogenes generally affect other hallmarks of cancer (e.g. cell growth as described above), there are doubts as to whether oncogenes do induce genome instability. However, activation of oncogenes, and as a result growth signaling pathways, has been reported to induce loss of heterozygosity and genome instability in various *in vitro* and *in vivo* models, via a mechanism involving DNA replication stress [for review (40)].

In contrast with oncogene activation, tumor suppressor genes cause cancer when they are inactivated. Since there are normally two copies of a tumor suppressor gene per cell, loss-of-function mutations that occur in one copy of a tumor suppressor gene cannot inactivate the whole functions of the tumor suppressor gene because the other copy of the gene continues to produce functional proteins. Thus, mutations in tumor suppressor genes are considered recessive. Recent studies show that loss of a chromosomal segment harboring a haploinsufficient tumor suppressor gene can lead to reduced gene expression and is sufficient to contribute to tumorigenesis (41). Oncogene activation and tumor suppressor inactivation tend to enhance tumorigenesis cooperatively (42).

In addition to the genetic mechanisms, activation of oncogenes and inactivation of tumor suppressor genes can be instigated through epigenetic mechanisms as described below (Epigenetic regulation).

Structural and numerical chromosomal changes

Alterations to the chromosomes can be structural, including translocations, deletions, insertions, inversions, breaks, sister chromatid exchange, micronuclei, chromothripsis and changes in telomere length. Numerical changes in chromosome copy numbers can also occur as is the case in aneuploidy and polyploidy (43). Both structural and numerical aberrations are frequently observed in cancers. For example, the frequency of sister chromatid exchange (the process whereby, during DNA replication, two sister chromatids break and rejoin with one another, physically exchanging regions of the parental strands in the duplicated chromosomes) is almost 10-fold higher in Bloom syndrome patients with a predisposition to develop cancer, compared with healthy individuals (44).

Aneuploidy refers to an aberrant chromosome number that deviates from a multiple of the haploid set. Constitutional aneuploidy is present in ~0.3% of newborns. Mosaic aneuploidy (i.e. appearing in only a fraction of an individual's cells) is common in neurons of normal mice and humans and in mammalian hepatocytes. In these liver cells, an age-dependent increase in polyploidization occurs as aneuploid cells divide [for review (45)]. Several mechanisms are involved in mal-segregation of chromatids among both daughter cells during mitosis: cohesion defects of sister chromatids, merotelic attachment of chromosomes, hyperstabilization of kinetochore–microtubule interactions, tubulin depolymerization, dysfunctional telomeres, defects in mitotic checkpoints and induction of unstable tetraploid intermediates by mitotic slippage, cytokinesis failure or viral-induced cell fusion [for review (46–49)]. Mutagens that are able to induce aneuploidy are called aneugens. Aneuploidy can induce a 'mutator phenotype' that increases DNA damage and genome instability.

The major consequences of aneuploidy [reviewed in [45,50]] are (i) reduction of cellular fitness and the development of the organism by repression of cell proliferation; (ii) modification of the proteome leading to increased energy burden, alteration of metabolic capacities, increased drug sensitivity and increased likelihood of senescence; (iii) trading a reduction in proliferation rate for an increased ability of aneuploid cells to adapt and evolve, called the aneuploidy paradox and (iv) promotion of genome instability by creating imbalance in the levels of proteins required for DNA replication, repair and mitosis or by induction of chromosome breaks in the lagging chromosome trapped in the cleavage furrow during cytokinesis. In addition, lagging of chromosome(s) during the metaphase/anaphase transition may produce a micronucleus [for review (49)]. Micronuclei can

undergo rearrangements by two possible mechanisms [reviewed in (50)]: (i) chromosome shattering (chromothripsis) results from mitotic entry—before completion of DNA replication within the micronucleus—and a failure to disassemble the micronuclear envelope encapsulating the chromosomal fragments for random reassembly in the subsequent interphase or (ii) locally defective DNA replication initiates serial, microhomology-mediated template switching (called chromoanagenesis) that produces local rearrangements with altered gene copy numbers.

Boveri (51) was the first to postulate that misdistribution of chromosomes might be a cause of tumor development and birth defects. Whether aneuploidy is a cause or a consequence of carcinogenesis has been a matter of debate for many years, but today it can be stated that both are true. Constitutional aneuploidies show inhibition of cell proliferation with the potential for tumor suppression but, on the other hand, are associated with alterations in the risk of specific cancers and therefore support a causative role of aneuploidy in cancer [reviewed in (52)]. Aneuploidy is a remarkably common feature of human cancer, present in ~90% of solid tumors and >50% of hematopoietic cancers. Although the degree and spectrum of aneuploidy vary considerably among tumor types, many show recurrent whole-chromosome aneuploidies (53). The role of aneuploidy in tumorigenesis has been analyzed in several studies [reviewed in (45,54,55)]. Although aneuploidy correlates with transformation, empirical tests of the hypothesis that aneuploidy drives tumorigenesis have been hampered by the difficulty of generating aneuploidy without causing other cellular defects, particularly DNA damage. In the light of our present knowledge, it seems likely that aneuploidy can contribute to carcinogenesis, without being a sufficient condition for malignant tumoral transformation.

Telomere shortening has been associated with aging, and this process can be accelerated by increased oxidative stress and episodes of inflammation (56). Evidence is rapidly growing that telomere length may be affected by environmental chemicals that have frequently been associated with chronic diseases (57). Moreover, previous findings (58) showed a potential unifying mechanism connecting the nucleus and mitochondria in cellular aging. In that work, progressive nuclear telomere shortening—mediated by the activation of a p53-dependent pathway—was found to determine a reduction of mitochondrial function and mtDNAcn (58).

Accumulating evidence has revealed that telomere dysfunction makes a significant contribution to genome instability in human cancer (59,60). In general, continued proliferation of human cells requires maintenance of telomere length, usually accomplished by telomerase. Ninety percent of human tumors are telomerase-positive (61). In normal cells, extended proliferation leads to telomere erosion and eventual loss of telomere function, so-called telomere crisis. Most epithelial cells, lacking active telomerase, undergo telomere erosion, become genomically unstable and eventually die.

Caretakers of genome integrity

The integrity of the genome is crucial for cancer avoidance and for the propagation of genetic information to subsequent generations. The 'caretakers' of genome integrity consist of (i) phase I (hydrolysis, reduction, oxidation) and phase II (glucuronidation, sulfation, acetylation, methylation, conjugation with amino acids or with glutathione) metabolizing enzymes that can process, usually inactivate or intercept the mutagenic agents and thus prevent DNA damage; (ii) DNA repair pathways dealing with different classes of lesions and (iii) signaling molecules that detect DNA damage and activate defense checkpoints (Figure 1).

Antioxidant defense systems as a first line of defense
The main antioxidant defenses are: glutathione [a sulfhydryl-rich compound that binds reactive oxygen species (ROS) and free radical intermediates], enzymes linked to glutathione (such as glutathione peroxidase), superoxide dismutase (breaking down superoxide into H_2O_2 and oxygen) and catalase (breaking down H_2O_2). These 'caretakers' are generally effective, but if ROS are present in excess, they can overwhelm the cellular defenses and lead to 'oxidative stress' (62,63). Phase I and phase II metabolizing enzymes play a crucial role in eliminating toxic chemicals from the body. Phase I enzymes (P450 cytochromes, also known as mixed function oxidases) typically oxidize xenobiotics to a reactive form, which—with the help of phase II enzymes such as glutathione S-transferase—is then conjugated to a carrier molecule such as glutathione and eliminated (64). However, as a side effect, the phase I enzymes are also responsible for activating certain non-carcinogenic chemicals to form DNA-reactive molecules that can potentially induce mutations. Polymorphisms in genes coding for these enzymes are very common, and so individuals can vary significantly in their resistance to the effects of genotoxic chemicals.

DNA repair
DNA repair is the second line of defense in the prevention of chemical carcinogenesis, acting on DNA damage that occurs in spite of other cellular defenses. The amount of DNA damage induced by an agent is usually linear in relation to the dose (65,66), but the extent to which DNA damage leads to mutations differs as a function of the activity and fidelity of DNA repair mechanisms. Single-strand breaks are repaired by a process that involves mainly end-processing and DNA ligation; consequently, in most cell types, they have a short half-life (a few minutes) and are regarded as relatively harmless (67). Small base changes (oxidation or alkylation) are repaired by base excision repair (BER), in which more or less specific glycosylases cut out the altered base, leaving an apurinic/apyrimidinic site that is incised and converted to a small DNA gap, followed by DNA polymerization and ligation (68). A half-life of a few hours is typical for these small base changes. Bulky adducts, pyrimidine dimers and inter-strand cross-links are dealt with by nucleotide excision repair (NER), which involves dual incisions on either side of the lesion, leaving a gap of around 28 nucleotides, filled by a DNA polymerase and ligated—again, with a half-life of a few hours. Double-strand breaks can be repaired either by homologous recombination (occurring during S phase, using the sister chromatid for sequence matching) or by non-homologous end-joining, which carries a risk of loss of a DNA sequence from the broken ends and is therefore potentially mutagenic (69). Mutations in genes encoding mismatch repair enzymes such as MSH2 and MLH1 are known to be involved in colorectal cancer (70,71).

Despite active DNA repair enzymes and delays imposed by cell cycle checkpoints, DNA damage may still be present when the cell replicates its DNA. Mechanisms have evolved that deal with such situations by bypassing the damaged site, allowing synthesis of a nascent DNA strand opposite the blocking lesion (72), although at the price of a high risk of errors, leading to mutation.

Interactions between environmental, nutritional and genetic factors can influence, for good or ill, the efficiency or fidelity of the various DNA repair processes. Polymorphisms in genes that code for proteins involved in BER or NER have been shown to influence enzyme activity (73) and have been linked to cancer risk (see Single-nucleotide polymorphisms). They probably

account for a fraction of the inter-individual variation seen in repair capacity, and other factors such as induction or inhibition by dietary or environmental exposures need to be invoked to explain the bulk of the variation, which amounts to a range of several fold (74,75).

The importance of DNA repair for maintaining genome integrity and preventing the development of a neoplastic phenotype is underscored by the fact that defective DNA repair is linked to increased susceptibility of cells to toxic, mutagenic and carcinogenic effects of environmental exposures (76). This is, for example, illustrated by autosomal recessive disorders such as xeroderma pigmentosum photosensitive patients. Mutations in *XP* genes lead to defective NER and increased skin and thyroid cancer rates (76,77). Xeroderma pigmentosum is rare, but more frequent are patients with mutations in mismatch repair genes, which are responsible for hereditary and sporadic colon cancer (70,78).

Certain forms of DNA damage (such as those caused by ultraviolet radiation) occur only episodically, and the relevant DNA repair mechanisms appear to be inducible (directly or indirectly) by the corresponding types of damage (79–81). However, not all DNA repair mechanisms are inducible: some forms of DNA damage (notably oxidation) are omnipresent in mammalian or human cells (19), and the corresponding repair mechanisms are consequently permanently active.

The importance of removing DNA oxidation products is reflected in the redundancy of DNA repair enzymes for these lesions. Because of this redundancy, defining the role of ROS in cancer development and of the repair enzymes in preventing it is challenging. In any case, environmentally induced interference in the repair of such damage may contribute to cancer development. One example of a connection between ROS induction and cancer development is the increased incidence of cancers of the lung, skin, bladder and liver in humans who have been exposed to the ROS-inducing agent arsenic (82). In addition, reactive nitrogen species such as exogenous nitric oxide and peroxynitrite have been shown to inhibit the BER enzyme 8-oxoguanine DNA glycosylase (83) as well as DNA ligase (84). Moreover, it has been reported that NER can be inhibited by oxidative stress (85,86) and lipid peroxidation products (e.g. 4-hydroxynonenal, malondialdehyde) (87,88), most likely by direct oxidative attack and inactivation of NER proteins.

Although it is generally assumed that a high intrinsic ability to repair DNA will be protective against cancer, it is also possible that a measured high repair capacity reflects induction by exposure to DNA-damaging agents in the environment—in which case the precise link between repair capacity and cancer risk is less well understood.

DNA damage signaling
ROS, in addition to causing direct DNA damage, can also activate signal transduction pathways and induce transcription factors [e.g. *nuclear factor (erythroid-derived 2)-like 2 (Nrf2)*, *nuclear factor-kappaB (NF-κB), p53*] involved in regulation of various genes including DNA repair genes.

Activation of the p53 tumor suppressor will only occur after exposure to a certain dose of an exogenous agent, but not after exposure to very low doses. After activation of the p53 tumor suppressor, the 'global genomic repair' arm of NER is induced (80). However, there is no consensus on the amount of damage necessary for the activation of p53 (89–91).

Nrf2 is a master regulator of a battery of defensive and detoxification genes, through a series of signaling events, removing damaged proteins and promoting the overall survival of the cell. The precise role of Nrf2 in cancer remains controversial. Nrf2 acts as an anticancer protein that has been found to be both upregulated by tumor suppressor proteins and targeted for degradation by oncoproteins (92). Nrf2 also acts as a tumor promoter, as was concluded on the basis of various studies reviewed in Shelton *et al.* (92). Aberrant overexpression of Nrf2 in many cancers (produced by mutations), along with its ability to induce resistance to chemotherapeutic drugs, supports the notion that Nrf2 also acts as a tumor protein (93). Many chemopreventive agents are known to activate Nrf2 while repressing NF-κB activity. The publication of the Nrf2 interactome and regulatome highlights a vast array of potential proteins involved in the regulation of this pathway including NF-κB (94). The interplay between these two cellular defense pathways suggests that there is a coordinated protective response to cellular insults, but the exact mechanisms remain to be determined.

As the transcription factor NF-κB is inducible and transiently active downstream of a physiologically important and stress-induced pathway, it is not surprising that its deregulation is associated with promoting cancer. In addition, many viruses achieve their oncogenic effects via the NF-κB signaling cascade (95). A great variety of stimuli are able to induce the NF-κB pathway, among them pro-inflammatory cytokines tumor necrosis factor α and interleukin-1β, and also DNA-damaging agents such as ultraviolet light and some anticancer drugs. On the other hand, the NF-κB pathway drives the expression of over 100 genes including pro-inflammatory, anti-apoptotic and other important genes related with cancer development (vascular endothelial growth factor in angiogenesis, matrix metalloproteinase in metastasis and even important metabolism genes such as *γ-glutamyl-cysteine ligase (γ-GCL)*, *multidrug resistance 1 (MDR1)* gene and *superoxide dismutase (SOD2))* (95,96). NF-κB functions downstream of the tumor suppressor p53, suggesting that NF-κB, under certain conditions, also functions as a tumor suppressor.

In chronically inflamed tissues, the neutrophils and macrophages secrete large amounts of ROS/reactive nitrogen species, recruiting more activated immune cells, in a 'vicious cycle', exacerbating the oxidation of intracellular proteins, lipids and nucleic acids and resulting in possible genetic changes and/or epigenetic alterations, which can lead to gene deregulation and initiation of carcinogenesis (97,98).

Other modes of cell signaling and their aberrant functioning in tumorigenesis will be discussed in more detail in several other articles in this special issue.

Modifiers of the mechanisms maintaining genome integrity

Inter-individual differences in response to environmental agents can be due to genetic and phenotypic variations in the metabolism of carcinogens and DNA repair efficiency. In the past decade, much interest has been directed to the role of epigenetic mechanisms in the carcinogenic process. Epigenetic modifications (e.g. aberrant DNA methylation patterns) do not require mutation of the genome to silence the expression of cell cycle regulators or to reduce the efficiency of DNA repair processes, which may also initiate carcinogenesis. Epigenetic alterations are seen as indicators of susceptibility to environmental exposures and are increasingly being studied in association with disease outcomes (99).

Single-nucleotide polymorphisms
The human genome project revealed that ~99.9% of human DNA sequences are the same between individuals. Only the remaining small part of approximately 0.1% of the human genome can

vary in sequence between individuals (100). About 90% of these variations in the human genome consist of SNPs. DNA sequence variations are considered as SNPs when a single nucleotide (A, T, C or G) in the genome sequence is altered and the frequency of the variant allele in the population is at least 1%. SNPs that fall within coding sequences of genes can give rise to a protein that has an amino acid substitution or is truncated, leading to changes in activity, localization or stability (101,102). SNPs that do not occur in protein-coding regions may still have biological consequences. For instance, polymorphisms in promoter regions may affect the transcriptional regulation and level of expression of a protein, whereas SNPs in untranslated regions or near intron–exon junctions may disturb the messenger RNA (mRNA) structure and translational process or cause alterations in mRNA splicing, respectively (103). These genetic variations can affect an individual's phenotype and may predispose people to diseases such as obesity, cancer and cardiovascular disease. However, the accuracy with which these SNPs predict the phenotype is unknown in most cases (104,105). Moreover, the genetic profile of a person may affect their susceptibility toward exposure to chemical carcinogens. The volume of data available on genetic variations has increased considerably with the recent development of high-density SNP arrays. However, a number of issues are uncertain; for example, whether the alleles of several SNPs interact with one another, leading to a higher susceptibility to disease, or whether the individual risks associated with certain SNPs and environmental factors lead to more than additive risk profiles. Additionally, there is little information available on how the cancer risk due to these SNPs compares with the risk from environmental and occupational exposure to carcinogens.

Intrinsic variation as well as environmentally induced regulation of genes involved in xenobiotic metabolism can modulate the extent of exposure to reactive chemicals and damage at the target site and so can affect the risk of cancer. Exogenous substances are excreted following metabolic transformation by enzymes catalyzing oxidative activation (phase I) and inactivation by conjugation (phase II). Several of the 200 different known *cytochrome P450 (CYP)* genes code for proteins involved in phase I biotransformation processes. For each of the phase II enzymes, such as glutathione S-transferase, uridine 5′-diphospho-glucuronosyltransferase, *N*-acetyltransferase and sulphotransferases, several different isozyme forms are known. By 1998, ~10 polymorphisms were known to have an influence on the carcinogenic properties of exogenous substances (106). In addition to this list, Nebert (107) identified SNPs in *CYP1A2* and in the aryl hydrocarbon receptor that are linked with carcinogenesis. Hussain *et al.* (108) mention that the frequencies of alleles of biotransformation genes associated with increased risk vary between 2 and 50 per 100 births (depending on the type of detoxification gene). The increase in cancer risk associated with a risk allele amounts to a factor between 2 and 10. A combination of phase I and phase II polymorphisms can lead to a higher risk than a single polymorphism. These putative genetic biomarkers of susceptibility have severe limitations when we consider that a multiplicity of metabolic pathways is operating concurrently at different rates; it is therefore hard to predict the ultimate carcinogen-modulating effect by assessing just one or a few metabolic pathways (109).

Variation in expression and/or structure of enzymes involved in DNA repair pathways may influence the persistence of DNA damage. The majority of genes encoding for DNA repair proteins are polymorphic (110). Common SNPs in DNA repair genes have been associated with cancer risk (111–113). Several SNPs in NER and BER genes were shown to modulate the levels of chromosomal damage, measured as micronucleus frequencies (114–116). Moreover, the same SNPs that appear to influence cancer risk have been associated with changes in DNA repair activity (117,118). In general, however, studies regarding associations between SNPs and cancer risk or DNA repair are inconclusive (119). The diverse findings may be attributed to differences in study size and statistical power, as larger studies having greater power can detect smaller effects. It seems that either the ability of the candidate gene approach to identify genetic risk or the importance of DNA repair pathways may have been overestimated, considering that the risk conferred by single variants has been shown to be small in genome-wide association studies (120). However, environmental exposure is only now beginning to be considered as a covariate in genome-wide association studies, and so current findings should be regarded as provisional.

DNA copy number variations

DNA copy number variations (CNVs) are structurally variant regions in which copy number differences have been observed between two or more genomes. Defined as being larger than 1 kb in size, CNVs can involve gains or losses of genomic DNA, which may not be visible by standard G-banding karyotyping. These structural variants can alter the transcription of genes by altering dosage or by disrupting proximal or distant regulatory regions, as has been shown globally in healthy humans. Specific disease-associated CNV loci have also been identified, providing examples of how CNVs can alter cellular function (121). Genome-wide screening of populations affected by a specific disease could demonstrate the presence of CNVs related to disease incidence, clinical course and prognosis (122). Further refinement is required to assess CNVs as risk factors in complex diseases such as cancers. New technologies allow us to investigate CNVs in genome-wide scans and specific algorithms have been developed to determine CNV location and copy number (123).

Epigenetic regulation

Definitions of epigenetics vary in the literature, but as a minimum all include the concepts of molecular modifications to DNA and/or chromatin in the absence of any alteration to the underlying DNA sequence (124,125). Epigenetic alterations are increasingly being recognized for their roles in health and disease. The deregulation of epigenetic mechanisms is considered as a major cause of cancer, hereditary and neurodegenerative diseases.

DNA methylation patterns. DNA methylation of cytosine [5-methylcytosine (5mC)] is a normal epigenetic mechanism involved in controlling DNA structure, chromosome stability, the mobility of viral DNA-repeated elements (transposons, retrotransposons), gene imprinting and gene expression (126). The DNA methylation machinery includes families of methyl-binding proteins [*methyl-CpG binding domain protein (MBD)*, *steroid receptor RNA activator (SRA)* and zinc finger families (127)] conveying the biological signal of DNA methylation marks produced by families of DNA methyltransferases (DNMT1, -2, -3). The DNMTs catalyze the transfer of a methyl group from the universal methyl donor, S-adenosyl-L-methionine, mostly to the fifth position of cytosine in CpG dinucleotides. DNMTs often work cooperatively; expression of DNMT3B, usually low in somatic cells, tends to be increased in cancer and cooperates with DNMT1 in silencing tumor suppressor genes (128–130). The carcinogenic implications of genetic mutations or polymorphisms in DNMT

genes, or genes encoding the one-carbon metabolism pathway enzymes (glycine-*N*-methyltransferase) or chromatin remodeling proteins, were recently reviewed (131). The removal of 5mC involves, as an intermediate step, the oxidation of 5mC into 5-hydroxymethylcytosine (5hmC). This reaction is catalyzed by the ten-eleven translocation (TET) family of enzymes. The TET enzymes are mutated in several types of cancer, affecting their activity and likely altering genomic 5hmC and 5mC patterns. It is generally believed that 5hmC may have a more specific role in regulating transcription, whereas 5mC might have additional roles in maintaining genomic integrity and transposon stability (132). The abundance of 5hmC is low in cancers, but reciprocal changes in abundance of 5hmC and 5mC during liver development as well as in response to the non-genotoxic carcinogen phenobarbital have been reported (133).

An important feature of cancer development and progression is the change in DNA methylation patterns, characterized by the hypermethylation of specific genes concurrently with an overall decrease in the abundance of 5mC. In various cancers, CpG islands (DNA regions with high frequency of CpG dinucleotides) located in promoter regions or elsewhere are frequently hypermethylated, which repress expression of tumor suppressor genes such as cyclin-dependent kinase inhibitor *P16*, *TP53* and the DNA repair gene *MGMT* (134) and allow cells to grow and divide uncontrollably. DNA methylation, independently or in association with methyl-binding domain proteins or repressive histone marks, prevents binding of DNA polymerases (135,136) and transcription factors (135,137). Changes in DNA methylation occur not only in CpG islands but also throughout the genome where they also contribute to gene expression regulation. In addition to repressing tumor suppressor gene expression, DNA methylation contributes to genome instability given that 5mC is a hot spot for both germ line and somatic point mutations, since 5mC can undergo spontaneous or enzymically driven deamination to thymine creating C > T transversion mutations [reviewed in (138–140)].

In particular, hypomethylation can lead to overexpression of oncogenes. Ehrlich *et al.* (141) indicated that a major contributor toward the overall or global DNA hypomethylation seen in most cancers is the loss of methylation in tandem and interspersed DNA repeats, occurring as a result of demethylation and not a preexisting hypomethylation in a cancer stem cell. Repetitive DNA sequences account for approximately 40% of the genome (142) and methylation of these sequences is required to maintain chromosomal stability.

Histone modification. At all phases of the cell cycle, the interactions between chromatin and DNA are constantly being remodeled, ensuring the normal functioning of DNA replication, gene transcription and DNA repair. To achieve these cellular functions, a series of coordinated enzyme reactions are required to create new histone molecules and histone marks and to assemble, disassemble and position new and old nucleosomes onto the DNA through replication-coupled or replication-independent pathways (143). The dynamic interaction between the chromatin and DNA is associated with a series of histone posttranslational modifications. Histones are nuclear globular proteins that can be covalently modified by acetylation, methylation, phosphorylation, glycosylation, sumoylation, ubiquitination and adenosine diphosphate ribosylation. These epigenetic marks constitute the 'histone code' (144) and contribute to the various functions of the chromatin. These histone modifications are reversible and performed by families of enzymes. Histone acetyltransferases, using acetyl-coenzyme A as the donor,

add acetyl groups mainly to lysine residues of H3 and H4, which then lose a positive charge, reduce attraction to DNA and usually increase gene transcriptional activity. Histone acetylation is a marker of active genes. Acetyl groups are removed by histone deacetylases (HDACs), which then favor a contraction of the chromatin and gene silencing. Methyl groups can be added by histone methyltransferases, whereas histone demethylases remove methyl groups from arginine and lysine residues. Histone methylation can inhibit or increase gene expression depending on the amino acid position that is modified. Posttranslational modifications of histones have emerged as key regulators of genome integrity. Mutations in histone-modifying genes and in histone genes have been associated with tumorigenesis (131,145).

Epigenetic regulation by micro RNAs. Micro RNAs (miRNAs) comprise a large family of non-coding single-stranded RNA molecules of approximately 19–22 nucleotides in length. Recognizing the first 2–8 nucleotides of the 3′-untranslated region of their mRNA targets, miRNAs induce the target's degradation and downregulate gene expression at the posttranscriptional level (146). In mammals, miRNAs are predicted to control the activity of 30–50% of all protein-coding genes, which make their biogenesis and function a serious player in cell fate decisions and many critical biological events (147,148). It is generally believed that alterations in miRNA expression are the rule in human cancers. Several studies indicate that miRNAs can function as oncogenes or tumor suppressor genes (149), since they may be involved in the control of cell proliferation, inflammation, apoptosis, chromatin structure, genome instability (150), DNA damage response and DNA repair processes (151,152).

DNA methylation is known to regulate the expression of some miRNAs (153,154). Cell lines deficient in DNMTs, or treated with DNMT inhibitors alone or in combination with HDAC inhibitor, restored expressions of some miRNAs acting as tumor suppressor genes (miRNAs that are likely silencing oncogenic genes). Activation of miRNAs that are likely silencing tumor suppressor genes was also demonstrated (153), as well as miRNAs that target HDAC (SIRT1/HDACIII) and methyltransferase (EZH2) [reviewed in (155)]. Accumulating evidence in humans and mice shows an association between deregulation of miRNAs and exposure to environmental chemicals (156–158).

Other epigenetic influences on genome stability include several other classes of non-coding RNA molecules such as long non-coding RNAs and P-element-induced wimpy testis (PIWI)-interacting RNAs (159,160), as well as chromatin insulator DNA/protein complexes involved in transcription regulation, intra- and interchromosomal interactions (161).

Minisatellites

Micro- or minisatellites are simple tandem repeats that are scattered over the human genome. Because of DNA slippage events, the number of oligonucleotide repeats within these microsatellites can be changed leading to a phenomenon that is called MSI. This genetic unstable situation can disrupt other non-coding regulatory sequences or inactivate tumor suppressor genes, thereby driving the carcinogenic outcome. The MSI phenomenon may occur frequently in genomes of cancer cells when there is a defect in the DNA mismatch repair (MMR) system. Typically, DNA MMR enzymes are proofreaders of replicating DNA and restore replicative errors after exogenous and oxidative DNA-damaging insults (70,71,162). MMR is engaged in enhanced

apoptosis, p53 phosphorylation and cell cycle arrest. Obviously, impaired function of MMR enhances replicative errors and can be observed through the detection of MSI, and MSI is a hallmark of MMR dysfunction observed in colorectal and other malignancies (163–165). Although defective MMR genes are normally found in MSI-positive cancers, a puzzling observation was that several MSI-positive cancers do not display genetic or epigenetic defects in any known MMR genes. An epigenetic explanation for these cases was recently discovered that involved deficiencies in SET Domain Containing 2 (SETD2) activities resulting in less efficient MMR. SETD2 is the only histone methyltransferase that induces histone H3 trimethylation (H3K36me3) and this histone mark was found to be required to attract the MMR machinery to the chromatin (25). There is accumulating evidence to support the notion that the interrelationship between MSI and miRNA plays a key role in the pathogenesis of gastrointestinal cancer (166). Nowadays, high-throughput sequencing data will undoubtedly lead to detailed knowledge of MSI events in unstable cancer genomes and giving information of the evolutionary cancer process (167).

mtDNA content

An additional way to induce genome instability is at the level of mtDNA. Each human cell contains between several hundred and over a thousand mitochondria, each carrying 2–10 copies of mtDNA. mtDNA-encoded genes are involved in the production of proteins essential for cellular respiration and normal mitochondrial function. Mitochondria—which have no protective histones and diminished DNA repair capacity compared with nuclear DNA—are highly prone to damage (113). The damage is compensated for by replication of mtDNA molecules and an increase in the cellular mtDNAcn (114–116). The increase in mitochondrial mass and mtDNA content as a marker of mitochondrial damage and malfunctioning has been considered an early molecular event of human cells in response to endogenous or exogenous oxidative stress (117). mtDNAcn is correlated not only with the size and number of mitochondria, which have been shown to change under different energy demands, but also with different physiological or environmental conditions. Cells challenged with ROS have been shown to synthesize more copies of their mtDNA and to increase their mitochondrial abundance, compensating for damage and meeting the increased respiratory demand required for ROS clearance. mtDNAcn alterations have been associated with impaired apoptosis and subsequent increased cellular proliferation (118), as well as with nuclear DNA mutations due to aberrant mtDNA insertion into the nuclear genome (119). Evidence on environmental exposure and mtDNAcn has begun to accumulate, showing increased blood mtDNAcn within blood cells in relation to exposure to benzene (119,120), ambient particulate matter (121) and polycyclic aromatic hydrocarbons (PAHs) (122,123). Individuals with higher blood mtDNAcn at baseline have a higher risk of developing lung cancer (124).

Chronic low dose exposures to chemicals— some issues to consider

In the risk assessment procedure, low dose can refer to an estimated dose near the lower end of an observed dose–response curve (point of departure) from which a safe exposure level is calculated. This low dose (point of departure) can be based on various parameters of dose–response analyses, including (i) bench mark dose that involves dose–response modeling, (ii) no observed genotoxic effect levels or (iii) no observed effect level, the highest level of the chemical that does not induce any (toxic)

effect during continuous prolonged exposure (168,169). In terms of risk of human cancer and public concern, 'low dose' refers to concentrations to which workers or the general population are exposed or to the concentrations of chemicals that can be measured in human tissues or fluids (170,171). However, at present, it is impossible to define clearly when an exposure should be considered to involve a 'low dose' that has no adverse effect. As discussed in the following paragraphs many parameters intervene, and what is a low dose depends on the particular circumstances and conditions characterizing the exposure and the target.

Considerations of low dose and chronic versus acute exposures

In the general population, people are exposed to various chemicals and carcinogens in a cumulative manner over their lifetimes, while occupational exposure, or specific behavior or lifestyle, generates exposures that are more acute. Deriving an understanding of the impact of these various exposure scenarios (low dose, chronic, acute) on cancer risk is important but remains a scientific challenge.

Some observations suggest that chronic exposure to a mutagen is more likely to result in cancer than an acute exposure to a similar total dose. Experiments with N-nitrosodiethylamine or N-nitrosodimethylamine on a very large number of rats showed that duration of exposure contributes more to the risk of cancer than intensity of exposure (172,173). In humans, the amount of DNA adducts in white blood cells of persons occupationally exposed to high concentrations of PAHs was relatively (i.e. per unit of dose measured in air) lower than in persons exposed to lower concentrations (174,175). Also in humans, chronic exposures to benzene and styrene appeared to induce a relatively stronger genotoxic effect at low dose (176,177). These observations and the principle that carcinogenesis involves sequential mutations over a period of time in a clone of initially transformed cells provide support for the hypothesis that chronic exposures might be more mutagenic than acute exposure to mutagens.

With regard to low dose effects of genotoxic carcinogens and radiation, some researchers have found controversial hormetic or protective effects (178). This has led to the hypothesis that exposure to low doses of genotoxic agents could reduce the risk of cancer. Indeed, many DNA repair enzymes are inducible by DNA damage (179,180), but many DNA repair mechanisms act at maximal intensity only after maximal induction, meaning that low dose exposure might not be able to trigger DNA repair enzymes (80,89,90). Environmental exposures of the general population are usually at low doses—and lower than the doses reported to result in an adaptive response associated with induction of DNA repair. Although several research groups claim to have evidence for the existence of a hormetic effect implying that a limited exposure to some genotoxic agents might protect health, Crump *et al.* (541) found little evidence in a comprehensive animal radiation database to support the hormesis hypothesis. In addition, there is overwhelming evidence, mainly from experimental work and from molecular epidemiology and to a lesser extent even from epidemiology, that exposures of low intensity do have harmful effects (181–186). Druckrey *et al.* (187) found indeed that if a dose of the carcinogenic alkylating agent diethyl nitrosamine is reduced, carcinomas of the liver and esophagus in rodents still occurred but required a longer time to develop. Haber *et al.* made similar observations [reviewed in (188)].

Finally, the types of DNA damage induced by environmental contaminants differ from those occurring naturally and

thus can be more mutagenic than DNA damages induced endogenously, and this calls for improved environmental hygiene.

Susceptible (cell) populations

Different tissues and cell types exhibit varying DNA repair capacities and are therefore likely to differ in susceptibility to environmental exposures with respect to induction of mutations, changes in the epigenome and genome instability. There are distinct implications for cancer development as to whether genome instability or mutations are transmitted through the germ line and thus are present in all cells of the individual or are acquired later in life and thus are not omnipresent. Increased rates of congenital mutations or epigenetic dysregulation naturally lead to increased cancer risk later in life.

In stem cells, DNA damage that is not repaired can lead to mutation amplification or propagation through the processes of self-renewal and differentiation, respectively, whereas damage to postmitotic cells can affect mostly tissue homeostasis.

Germ cells

Germ line mutations can be inherited via the mother or the father, and any exposure or disruption of biological functions that leads to increased mutation rates in either of the parents may influence the susceptibility of the child to cancer. A dysregulated epigenome in offspring originating via the paternal or the maternal genome through reproduction will potentially influence genetic instability and cancer proneness of the offspring. There are indications that parental lifestyle can be associated with increased risk of childhood cancer, and the significance of the father's exposure may be particularly important (189–191). Increased minisatellite mutations in offspring were found to be associated with paternal lifestyle factors (192). Male germ cell types exhibit different repair characteristics compared with most somatic cell types (193–197). Unrepaired DNA adducts in sperm are transferred to the mouse zygote, and epigenetic mechanisms may be involved (198,199). It has been reported that new mutations arising in the germ line (*de novo* mutations) lead to a significant portion (~20%) of the genetic disorders occurring in infants (200,201). *De novo* mutations can arise both in the mother and in the father, but the types of mutations inherited from the mother are different from those from the father. This indicates that the kind of stress put on the parents is likely to give different outcomes with respect to genome instability and mutations in their offspring.

Stem cells

Stem cells differ markedly from somatic cells in how they cycle and cope with genotoxic insults.

Stem cells have the unique properties of self-renewal and potential to differentiate into various cell types. Embryonic stem cells, derived from the inner cell mass of a blastocyst stage embryo, are able to differentiate into any cell type, showing the hallmarks of pluripotency. Tissue-specific or adult stem cells are responsible for maintaining homeostasis by cell replacement or repair after tissue damage. Tissue-specific stem cells have been found in both regenerative (blood, skin, digestive tract) as well as in non-regenerative organs such as muscle or brain. Cancer stem cells are functionally similar to tissue-specific stem cells but with an aberrant self-renewal and differentiation capacity. They are found in a series of cancer types (leukemia, glioblastoma, breast and skin cancers) as highly clonogenic cells.

The importance of the maintenance of genomic integrity in stem cells, however, is higher compared with non-stem cells for different reasons. From a developmental perspective, it is clear

that genetic damage generated and not repaired in stem cells could be transmitted to the progeny with severe consequences for the developing embryo or regenerating tissue. Chromosomal abnormalities, such as aneuploidy, can function as a diversifying agent. For example, 33% of mitotic neural progenitor cells are characterized by aneuploidy, and some of these are able to generate mature aneuploid neurons. It is thought that this aneuploidy leads to a higher degree of variability and to uniqueness (202,203).

Mutation frequencies are generally much lower in stem cells compared with somatic cells, for example, 100–1000 times lower in mouse embryonic stem cells compared with embryonic fibroblasts (204). This more stringent maintenance of genomic integrity in stem cells is the consequence of differences in cell cycle regulation and increased DNA repair capacity (205). Besides differences in cell cycle checkpoints and repair, two other ways to deal with DNA damage for embryonic stem cells are the induction of apoptosis or the process of differentiation in order to avoid passing mutations to their progeny.

In utero exposure

Defined point of departures should be interpreted with care, since exposures that had virtually no detrimental effect on a mature organism have been shown to cause very serious adverse effects on the developing fetus [reviewed in (206)]. Moreover, environmental chemical studies showed that exposures during development at low doses did not cause any 'acute' teratogenic end points, although dysfunctions and diseases showed up later in life. Interestingly, for certain tissues and organs (e.g. brain, lungs and immune system), the critical 'windows' of developmental vulnerability may continue beyond the *in utero* stage through the neonatal period and perhaps even into puberty, thereby extending the period of increased vulnerability to adverse effects from environmental chemical exposures. Exposure to chemicals *in utero* can have direct effects on the genome integrity (5,207–209) though epigenetics, as a modifier of the mechanisms maintaining genome integrity, has become the cornerstone of the 'Developmental Origins of Health and Disease' hypothesis, which points to epigenetic regulation as the likely mechanism behind the environment-driven epidemic of non-communicable disease such as many cancers (210–212). Epigenetics may thus provide a new tool for understanding mechanisms underlying well-recognized gene–environment interactions and their role in carcinogenesis.

Chemical disruptors and their effect on biological target sites

The term 'chemical disruptor' in this section refers to a chemical within the environment that is able to affect the integrity of the genome. For example, with regard to carcinogenesis, a chemical might be selective for its chemical reactivity with DNA, as opposed to another chemical that might be selective for interference with microtubule polymerization and therefore disrupt the separation of replicated chromosomes during cell division. In Table 1, we summarize chemicals present in the environment that can selectively affect a specific pathway that when disrupted can induce genome instability. The selection of chemicals was based on criteria preestablished by the non-governmental organization Getting to Know Cancer (gettingtoknowcancer.org), which expressed interest in fostering a better understanding of the potential carcinogenicity of environmental chemicals and invited scientists to prepare this review. The guiding criteria for chemical selection were (i) to limit the number of chemicals to 10; (ii) to select, rather than chemicals

that directly attack the DNA or cause mutations (which have been studied thoroughly for decades), chemicals that create indiscriminate damage by affecting, for example, DNA repair pathways, epigenetic pathways or mitochondrial function (indirect effects that have only recently received attention); (iii) to focus on chemicals that are not currently known as carcinogenic to humans (class 1; according to IARC), but which have properties that place them into areas of concern; (iv) the selected chemicals should be ubiquitous in the environment. It has not been our aim in this review to give a full toxicological evaluation of the selected chemicals (Table 1), but only to highlight the pathways (or biological targets) through which they can affect genome stability. For each of the biological target sites, one chemical was selected (identified in bold characters in Table 1) that could be regarded as a 'prototypical' chemical to act via this pathway to promote genome instability.

Heavy metals

Toxic metals are important environmental hazards because of their wide distribution and long persistence leading to accumulation in biological systems. Mercury (inorganic, IARC group 3), lead (inorganic, IARC 2A), nickel (IARC 1 for Ni compounds and alloys and 2B for metallic nickel) and cobalt (metal with or without tungsten carbide (WC), respectively, IARC 2A and 2B)—as well as the carcinogenic compounds cadmium and arsenic—have been reported to inhibit DNA repair. Even though their DNA-damaging potentials are rather weak, they interfere with the nucleotide and BER at low, non-cytotoxic concentrations (213–215). Various steps of the repair process can be affected. A mechanism of action (studied *in vitro* in PM2 bacteriophage DNA) is alteration of the binding activity of zinc finger proteins through displacement of Zn(II) by those heavy metals at levels just above 1 mM for lead, nickel and cobalt, but at doses as low as 50 nM for mercury (213–215). DNA repair can also be inhibited by the production of ROS (247). Toxic metals have been shown to affect DNA methylation and DNMTs and therefore influence gene transcription in animal and human studies (248). Prenatal arsenic exposure was recently shown to be related to 5mC alterations in human cord blood (249). In workers, nickel (alongside chromium and arsenic) was also shown to be capable of inducing posttranslational histone modifications by affecting the enzymes that modulate them (223–225). Changes in miRNA expression levels were associated with exposures to epidemiologically relevant concentrations of an arsenic, cadmium and lead mixture [2 μM NaAsO$_2$, 2.4 μM CdCl$_2$ and 4.8 μM Pb(Pb(C$_2$H$_3$O$_2$)$_2$·3H$_2$O] in a mouse fibroblast cell line (250).

Metal alloy dusts

Combinations of WC and cobalt or nickel or iron are used to improve the robustness of hard metals. Cobalt with WC is probably carcinogenic to humans (group 2A), whereas without WC it is classified as possibly carcinogenic (group 2B). Exposure to hard metal alloy dusts has been associated with lung cancer (251,252). Also tungsten metal alloys were found to transform a human osteoblast-like cell line, and this was in part considered to be due to direct DNA damage (229). Intratracheal instillation of these alloys (92% tungsten/5% nickel/3% cobalt and 92% tungsten/5% nickel/3% iron) has been linked to increased ROS production, induction of genes associated with oxidative stress and metabolic stress in rats, which contribute to lung injury through increased inflammation and oxidative stress (230). In type II rat pneumocytes, single intratracheal instillation of WC-Co (6.3% cobalt, 84% tungsten and 5.4% carbon) induced single-strand breaks and chromosome mutations (micronuclei) (253). Interestingly, Lombaert *et al.* (231) described a possible

hypoxia-inducible factor 1 signaling cascade after *in vitro* exposure to the alloy WC-Co mixture (94% tungsten and 6% cobalt), in human peripheral blood mononucleated cells, whereas individually WC and cobalt chloride did not induce the cascade. The authors discussed the possibility that the effect on hypoxia-inducible factor 1 responsive genes could increase the carcinogenic properties of the mixture (231).

Acrylamide

Acrylamide can be ingested, inhaled (e.g. in tobacco smoke) or absorbed through the skin. Fried, starchy foods are the most prominent sources of exposure. The reaction between asparagine and fructose typically produces the most acrylamide in foods from plant sources. Hemoglobin adducts present a reliable short-term measurement of acrylamide and glycidamide (CYP2E1-mediated DNA-reactive metabolite of acrylamide) exposure (235,254). It is well established that the glycidamide metabolism product reacts readily with DNA, which has been shown to be a major route for its genotoxicity. Already in the 1990s, acrylamide was shown to be positive in the Muta Mouse transgenic mutation assay (255). Clastogenic effects were noted in a number of tests for genotoxicity and assays for germ cell damage. In 1994, the compound was classified as a probable human carcinogen (IARC 2A). The US National Centre for Toxicology Research has conducted a lot of work on the toxicity and carcinogenicity of the compound and recently showed clear evidence of carcinogenicity in a 2 year study in rats and mice (256). There are epidemiological indications that common dietary acrylamide concentrations might cause postmenopausal endometrial and ovarian cancers, but epidemiological studies are not conclusive as they might be confounded by the fact that the exposure is population-wide (236). Acrylamide was included in Table 1 since (apart from DNA adduct formation), alternative mechanisms causing indirect acrylamide carcinogenicity are described. Indeed, effects on kinesin proteins (expressed in bacteria using recombinant DNA techniques) could explain some of the genotoxic effects of acrylamide. These proteins form the spindle fibers in the nucleus that function in the separation of chromosomes during cell division (216,237). Other mechanisms underlying acrylamide-induced carcinogenesis or nerve toxicity are related to an affinity for sulfhydryl groups on proteins. Binding of the sulfhydryl groups could inactive proteins/enzymes involved in DNA repair and other critical cell functions (216).

Bisphenol A

Bisphenol A (BPA) is used to produce polycarbonate plastics which, due to their properties of transparency and hardness, are often used in food and drink packaging. The compound has been detected in body tissues and urine in most western populations. United States Environmental Protection Agency, the US Food and Drug Administration, the European Food Safety Authority and the Japanese Institute of Advanced Industrial Science and Technology have concluded that human exposure to BPA is below safe exposure levels (257–259). BPA is not classified as a human carcinogen (IARC group 3). However, there is much evidence of BPA being able to transform cells *in vitro* and acting as an aneugen by interfering with microtubule assembly and therefore with the function of the spindle apparatus during mitosis in human fibroblasts *in vitro* (260). Although apparently high concentrations of BPA (250 μM and more) were required in the culture medium, it was indicated that it was unknown how much BPA in the medium was protein-bound and how much reached the cells (cytotoxicity was only observed above 400 μM). BPA has been found to have a threshold effect with regard to its action as an aneugen (261). BPA can also

Table 1. Selected pathways through which chemical disruptors can affect genome stability

Biological target site	Affected part of pathway	Mode of action	Chemical disruptor[a] (IARC group)	Human exposure	References
DNA repair pathways	Repair enzymes	Binding of repair enzymes (zinc finger proteins) resulting in dysfunctional DNA repair	Metals: **Lead** (2A), nickel (metallic: 2B, compounds + alloys: 1), cobalt (2B, 2A with WC), mercury (3)	Ingestion for contaminated crops and water	(213–215)
		Binding of the sulfhydryl groups could inactivate proteins/enzymes involved in DNA repair and other critical cell functions	**Acrylamide** (2A)	Ingestion of heated, fried and baked food	(216)
Epigenetic pathways	DNA methylation	Disruption of DNA methylation patterns via affecting DNMTs	Bisphenol A (3)	Leaking from plastics into food and water	(217,218)
			SiO_2-NP (not evaluated by IARC)	Leaking from, e.g., rubber, plastics, paints, glass, steel, batteries, adhesives as well as in cosmetics	(219)
		Possibly react with thiol functional groups of free cysteine residues in catalytic center of DNMTs	Quinones (3)	Drinking water disinfection by-products	(220)
	Histone modifications	Disruption of histone acetylation; affect histone acetylases and deacetylases	Bisphenol A (3)	Leaking from plastics into food and water	(221)
			Quantum dot-NP (not evaluated by IARC)	Used for optical (e.g. light emission diode [LED] displays), electronic and computational applications	(222)
		Affecting enzymes that modulate post-translational histone modification	**Nickel** (metallic 2B, compounds + alloys: 1)	Primarily via oral intake, as a contaminant in drinking water or as either a constituent or contaminant of foods, including chocolate, nuts and grains	(223–225)
	miRNA	Disturbed binding to mRNA	**Bisphenol A** (3)	Leaking from plastics into food and water	(226)
		Changes in miRNA expression	Metals: nickel (metallic 2B, compounds + alloys: 1), titanium (not evaluated by IARC)	Ingestion for contaminated crops and water	(227)
			Gold (Au) NPs (not classified)	Used in electronics, paint, as sensors in food and as an antibiotic, antifungal and antimicrobial in plastics, coating and textile	(228)
DNA damage signaling	Redox signaling	Disruption of redox signaling involving Nrf, NF-κB, *early growth response (EGR)*, etc.	**Alloy particles**: tungsten/nickel/cobalt (2A, 2B)	Inhalation	(229–231)
			Bisphenol A (3)	Leaking from plastics into food and water	(232)
Mitochondrial function	Mitochondrial respiration	Decreased Nicotinamide adenine dinucleotide (NADH) levels and impairs mitochondrial membrane potential and mitochondrial respiration accompanied by ROS generation	**Titanium dioxide NPs** (2B)	Used as additives in many food products and cosmetics; also present in paints, plastics (e.g. toys and food packages), paper, clothes, etc.	(233)
Cell cycle/cell division	Spindle defects	Activation of the mitochondrial germ cell apoptotic pathway: B-cell CLL/*lymphoma 2 (Bcl-2) family and caspases in testis*	Bisphenol A (3)	Leaking from plastics into food and water	(234)
		Spindle defects leading to formation of micronuclei	Acrylamide (2A)	Ingestion of heated, fried and baked food	(235–237)
			Benomyl (+ metabolite Carbendazim) (2B)	Ingestion from residues in crops	(238–240)
			Bisphenol A (3)	Leaking from plastics into food and water	(241)
			Carbon nanotubes (to be evaluated by IARC)	Used in many consumer and industrial products	(242–244)
Telomeres	Telomere loss	Defect in telomere maintenance	**Lead** (2A)	Ingestion for contaminated crops and water	(245,246)
			Carbon black (2B)	Inhalation	(246)

[a]Chemicals in bold are the once that could be regarded as 'prototypical' chemical to act via this pathway to induce genome instability.

bind the estrogen receptor and elicit unwanted effects such as induced growth of MCF-7 human breast cancer cells. When the estrogen receptor is the selective target, there is evidence that BPA can induce non-monotonic dose–response curves. The endocrine system is primed to detect and respond to low levels of hormones. Moderate changes within the low dose concentrations of estrogen in women can have large effects because of the availability of estrogen receptors (262,263). It was predicted via *in vitro* human cell models that an estrogenic endocrine disruptor such as BPA would be biologically active in, for example, the fetus if the estrogenic activity of the free chemical in blood was equivalent to an increase in free estradiol of only 0.1 pg/ml (255).

In utero and neonatal exposure in rodents to low doses of BPA and/or phthalates di (2-ethylhexyl) phthalate (DEHP)/monoethylhexyl phthalate (MEHP) and butyl benzyl phthalate (BBP)/dibutyl phthalate (DBP)/ monobutyl phthalate (MBP)) may cause aberrant changes in DNA methylation at CpG islands near gene promoter regions (217,218), histone modifications (acetylation, methylation, phosphorylation, ubiquitination, sumoylation and adenosine diphosphate ribosylation) (221) and expression of non-coding RNAs, including miRNAs in human placental cell lines *in vitro* (226). Such epigenetic marks can induce up/down alterations in gene expression that may persist throughout a lifetime. These permanent changes can result in adverse health effects such as neural and immune disorders, infertility and late-onset complex diseases (cancers and diabetes). The transient exposure of gestating female rats to BPA and phthalates (1% of lethal dose 50% (LD50)) was further shown to cause a transgenerational differential DNA methylation in the F3 generation sperm epigenome (264,265).

Quinones

Halobenzoquinones—such as 2,6-dichloro-1,4-benzoquinone, 2,6-dichloro-3-methyl-1,4-benzoquinone and 2,6-dibromo-1,4-benzoquinone (among other quinones)—have recently been reported as disinfection by-products in chlorinated drinking water (266–268). Quinones are electrophilic compounds, known to react with proteins and DNA to form adducts (269). Animal studies provided inadequate evidence of cancer (IARC group 3). More recently, Wang *et al.* (220) showed, via an *in vitro* inhibition reaction, reduced DNA methylation by quinones (some of them starting already at 0.1 µM concentration) probably due to inhibition of DNMT. These electrophilic chemicals most probably interact with functional thiol groups via Michael-type addition, causing free cysteine residues of DNMTs to be modified (220). In this context, another interesting target that could explain active demethylation involves the TET family of Fe^{2+}- and α-ketoglutarate-dependent 5mC deoxygenases. That mechanism was discussed for benzene and its metabolite hydroquinone as a possible pathway for decreased methylation (besides inhibition of the DNMTs) in an HEK293 cell line (at a concentration of 60 µM, with cytotoxicity occurring at 100 µM hydroquinone). It was suggested that an increased conversion of 5mC to 5hmC catalyzed by TET1, followed by deamination to 5hmU and subsequent removal by BER, could result in an unmethylated cytosine (270). This mechanism might be shared by other xenobiotics that increase ROS.

Benomyl

The fungicide benomyl is metabolized to carbendazim; both are classed as possible human carcinogens (IARC group 2B). The route of exposure is most likely ingestion via residues in crops. Benomyl has an aneugenic mechanism of action, disrupting the microtubules involved in the function of the spindle apparatus during cell division, leading to production of micronuclei.

Benomyl and its metabolite have both been associated with hepatocellular tumors in male and female rodents (238,239). Also threshold concentrations (of 3.2–4.1 mM) have been identified based on *in vitro* and animal studies for these compounds, with regard to non-disjunction and chromosome loss (271). Considering non-disjunction in the human chromosome 17, after exposure *in vitro*, there is evidence of significant response only above an exposure of 1.1 µg/ml. However, it was found to be among seven chemicals that, when combined at concentrations below their individual threshold, showed a response *in vitro* (272). Induction of micronuclei was observed, which could be explained by the additive effect of chemicals with a similar mechanism of action.

Nano-sized particles

During the past decade, industries related with cosmetics, biomedical compounds, textiles, food, plastics and paints, among others, have been taking advantage of the unique characteristics of nano-sized materials. Consequently, human exposure to these types of materials has increased not only in a conscious way but also passively by the leakage of nanomaterials from different objects. Their physicochemical and biological characteristics cause them potentially to disrupt the normal function of mammalian cells and increase the toxicity and genotoxicity of some materials. Available literature about nanomaterial genotoxicity illustrates the complexity of identifying and understanding the hazard of NP in relation to human health. Not only is the chemical composition of nanomaterials responsible for their genotoxicity but also shape, specific surface area, size, size distribution and zeta potential determine the effects of these materials on the genome. Moreover, there is still a debate about the suitability of standard genotoxicity assays for studying the effects of nanomaterials (273,274).

Nanoparticles.
In addition to affecting mitochondrial respiration, NPs can induce genome instability via different mechanisms of action: (i) $ZnFe_2O_4$-NP (275), SiO_2-NP (276,277), CuO-NP (278) and TiO_2-NP (233) were shown to impair mitochondrial function *in vitro*; (ii) Ag-NP (279,280), ZnO-NP (281) and carbon black-NP (282) induced mitochondrial-related apoptosis *in vitro*; (iii) decreased DNA repair was observed due to exposure to TiO_2-NP (283), Ag-NP (280), SiO_2-NP (219) and Au-NP (284) *in vitro*; (iv) many NPs induce micronuclei *in vitro* and *in vivo* [e.g. CuO-, Fe_3O_4-, Fe_2O_3-, TiO_2-, as well as Ag-NP *in vivo* (285), and SiO_2-NP (286) *in vitro*]; (v) exposure to quantum dot-NP in mammalian cell lines can lead to hypoacetylation of histones (222); (vi) DNA methylation can be disrupted by SiO_2-NP in mammalian cell lines (219) and (vii) miRNA can be upregulated due to Au-NP, in the fetus of administered mice (228). Other mechanisms can also be responsible for the indirect genotoxicity of nanomaterials; they produce inflammation and alteration of the antioxidant defenses that can also lead to genome instability. Synergistic genotoxicity between NP and other chemical compounds has also been described in a mammalian cell line (287).

The majority of the studies are performed after an acute exposure and in *in vitro* systems. Their material diversity, and the lack of chronic exposure studies and *in vivo* studies using relevant concentrations of NP, makes it difficult to assess the real adverse effect of NP on human health, including their effect on the genome. Adaptive responses *in vitro* (288) as well as induction of genome instability *in vitro* (289) and *in vivo* (290) have been described in long-term studies.

Carbon nanotubes.

Carbon nanotubes are a specific type of nano-sized particles, which are used in many consumer and industrial products, including electronic and drug-delivery products, protective clothing, sports equipment and space exploration (242). Preliminary information indicates that carbon nanotubes may have a similar carcinogenic potential to other durable natural or man-made fibers. That is one of the reasons why IARC has placed carbon nanotubes on the list of compounds that need evaluation with high priority during 2015–19. Muller *et al.* (243) showed for the first time the genotoxic and mutagenic potential of carbon nanotubes in lung cells, both *in vivo* and *in vitro* at (sub)cytotoxic concentrations. The aneugenic effect induced in the MCF-7 human breast cancer carcinoma cell line was speculated to be due to physical interaction with components of the mitotic spindle during cell division or to interaction with proteins directly or indirectly involved in chromosome segregation (e.g. tubulin, actin) (243). Indeed, the size and physical properties of carbon nanotubes are strikingly similar to cellular microtubules. Recent publications describe mitotic spindle aberrations in cultured primary and immortalized human airway epithelial cells exposed to high and workplace relevant concentrations (i.e. at doses equivalent to 20 weeks of exposure at the permissible exposure limit for particulates not otherwise regulated). Sargent *et al.* (242) demonstrated fragmented centrosomes, disrupted mitotic spindles and aneuploidy chromosome number following 24–72 h exposure to concentrations of carbon nanotubes that could be anticipated during workplace exposure. Interaction of the mitotic motors with carbon nanotubes or carbon nanotube/microtubule hybrids may result in incorporation into the mitotic spindle, which is highly associated with carcinogenesis (242,244).

Carbon black.

IARC classifies carbon black particles as possibly carcinogenic to humans (2B). According to the IARC carbon black is a generic term for a particulate form of elemental carbon manufactured by the vapor-phase pyrolysis and partial combustion of hydrocarbons. It is mainly used as reinforcing filler in tires and other rubber products. In plastics, paints and inks, carbon black is used as a color pigment. Carbon black is widely used as a model compound for assessment of the impact of pollutant diesel soot (black carbon, BC). The latter particles are a good indicator of adverse health effects from urban air pollution and are ubiquitous in the environment, alongside other air pollution particles (291). Oxidative stress induction is one of the plausible mechanisms leading to these particles' potential as a genome-destabilizing agent. Indeed, ROS formation has been shown to reduce nuclear as well as mitochondrial telomerase activity (292). Büchner *et al.* (292) showed a lower telomerase activity in endothelial and lung epithelial cells *in vitro* exposed to ultrafine carbon black using concentrations the vessels (1 µg/cm^2) and lung (10 µg/cm^2) are daily exposed to. McCracken *et al.* (293) reported in elderly men an association between long-term ambient BC concentrations (interquartile increase of 0.25 µg/m^3) at their residences and shorter telomeres. Environmental and occupational exposures to BC, and other traffic-related air pollutants, such as particulate matter, benzene and toluene, are associated with shorter telomere length (57). Reduction of telomere length by BC may be due to both: (i) an increased rate of hematopoetic stem cell replication for replenishing leukocytes needed in the inflammation process following BC exposure (accelerated senescing) and (ii) telomere loss per replication, caused by oxidative stress (57,293).

Cross talk between genomic instability and other hallmarks of cancer

Carcinogenicity of low dose exposures to chemical mixtures in any given tissue will likely depend upon simultaneous instigation of several important tumor promotion mechanisms and the disruption of several important defense mechanisms. Accordingly, we undertook a cross-validation activity to illustrate the effect the target pathways and/or the chemical disruptors discussed have on other cancer hallmarks (Tables 2 and 3). The literature search was performed within PubMed and Google using the following key words along with the compound/chemical of interest: genomic instability, mutation, genotoxicity, clastogenic, etc. Some of the prototype examples were included in the tables.

For example, mutation of tumor suppressor p53, an important guardian gene, not only promotes genomic instability but has also been shown to play a role in promoting chronic inflammation via sustained NF-κB activation and participation in tumor-promoting inflammation (524). Telomerase activity prevents telomere loss that can lead to genomic instability (see Caretakers of genome integrity). However, high telomerase activity is also associated with increased invasiveness and metastatic capability (another cancer hallmark) of colon, breast, gastric and liver cancers (407,408,525,526). It is also interesting to note that certain mechanisms that maintain genome stability can be pro-carcinogenic in some cases. The cell's primary defense mechanisms against mutagenic DNA damage are numerous DNA repair pathways. In the presence of DNA damage, the cell has two fates. Either damage will be repaired by repair pathways or the cell will undergo damage-induced apoptosis. Therefore, in a paradoxical manner, the same DNA repair pathways that are charged with preventing damage from being fixed to carcinogenic mutations may promote the survival of an initiated but damaged cell (297).

It is also useful to understand the cross talk that potential chemical disruptors of genomic stability processes have with other cancer hallmarks (Table 3). Interestingly, this has both pro- and anti-apoptotic effects on cells, depending on cell type. In promyelocytic leukemia and ovarian granulosa cells, BPA induced apoptosis (461,462) while it promoted survival and proliferation in breast epithelial cells (459,463). It is noteworthy that, although many of the compounds discussed in this review are pro-carcinogenic in their ability to promote genomic instability, they are simultaneously anticarcinogenic in their ability to promote apoptosis; for example, the metals lead, nickel, cobalt and mercury act in this way (411,420,430). Apoptosis is often independent of the genotoxic effects of the metal as is the case for nickel and mercury (430,439). However, most of them can also lead to sustained proliferation, another hallmark of cancer, by a wide variety of mechanisms, including induction of oncogenes, modification of miRNA signaling and hypoxia (414,424,432). The literature review performed in the preparation of these tables (although not exhaustive) suggests knowledge gaps particularly related to the possibility that chemical disruptors (Table 3) contribute to immune system evasion as well as tissue invasion and metastasis.

Overall, the cross-validation exercise demonstrated that many chemicals with documented effects on genomic stability simultaneously affect other cancer hallmark pathways, but a large portion of cross talk remains to be studied, which the cross-validation highlighted (Table 3). Additionally, the cross-validation of genomic instability target pathways demonstrated that there is some cross talk between the genomic

instability targets and other cancer hallmark pathways (Table 2). Further study is required to determine the involvement of genomic instability target pathways in a few areas, including the tumor microenvironment and angiogenesis. Finally, we believe the cross-validation results have provided a valuable update concerning progress toward understanding the connections among these cancer pathways and environmental chemical disruptors.

Discussion and conclusion

Genome instability is an enabling condition that can lead to cancer development (1) and is defined as an increased tendency of the genome to acquire mutations. This review raised the hypothesis that in addition to known human carcinogens, exposure to low doses of other chemicals in our environment could contribute to carcinogenesis by indirectly affecting genome stability. The chemicals discussed here (Table 1) can promote genome instability by interfering with pathways such as DNA damage signaling (heavy metals, BPA), DNA repair (heavy metals, acrylamide), epigenetics (nano-sized particles, BPA, quinones, heavy metals), mitochondrial function (NPs, BPA), spindle apparatus during cell division (acrylamide, benomyl, BPA, NPs) or telomere integrity (heavy metals, carbon black).

Cancer evolves as the long-term result of multiple causal interactions between environmental and genetic/epigenetic factors (3). Cancer cell types acquire their characteristics with different strategies, timeframes and microenvironments (1). Assessing the relevance of an internal dose of genome-disrupting chemicals should be done in the context of the exposome, being the life-course environmental exposures from the prenatal period onward (527). In this context, it is relevant to point out that the impact of genome instability varies throughout the life span; in particular, germ cells as well as the fetus show increased sensitivities to genotoxic agents and moderate (*in utero*) exposures can be associated with significantly increased mutation rates or changes to the epigenome of the human offspring (528). Individual variations in genotype, phenotype and exposome history are critically important factors determining the effect of genetic disruptors. Furthermore, populations are also experiencing temporal changes in chemical exposure. The abundance of most of the classical persistent organic pollutants has been steadily declining for many years while some flame retardants and PAHs are emerging or leveling off in human biological biomatrices such as breast milk and blood (529), and in the environment (530). In the past, a proportion of the working population in industrialized countries was undoubtedly exposed to high concentrations of (mixtures of) well-characterized carcinogenic substances. At present, due to increasing awareness of health risks and usually with improved worker protections, a great majority of the population in modern western countries have never been exposed to such substances at the high doses of the past. In some industries and/or regions, however, exposure is still substantial. The modern public health problem associated with carcinogenic or tumor-promoting substances is getting even more complex considering potential low dose effects of chemicals present in our daily life.

Special attention should be paid to the effect of combined exposure that can, through co-carcinogenic effects, lead to a rise in cancer risk (531,532). An interesting epidemiological study showed that individuals with multiple types of DNA adducts can have a 10-fold greater risk of cancer (532), thus implying that exposure to a mixture of genotoxins might

more likely induce cancer than single chemicals. Interactions between (metabolites of) chemicals can and do occur. Metals such as lead, arsenic, cadmium and chromium constitute a frequently occurring quaternary mixture at hazardous waste sites. This mixture was found in soil at 219 out of 1608 sites examined by US Agency for Toxic Substances and Disease Registry. No pertinent health effects are known, nor do physiologically based pharmacokinetic models exist for such a mixture. However, intermediate-duration dietary studies of binary and trinary mixtures of lead, arsenic and cadmium in rats indicated that subthreshold doses (below the Lowest Observable Effect Levels (LOELs) for the individual metals, i.e. 5–25 p.p.m.)—when administered in combination—resulted in effects not observed when exposed individually (211,212). Other examples of mixtures include metals and PAHs that are frequently encountered as co-contaminants, such as in airborne particulates. PAHs, such as benzo[a]pyrene, are oxidized by CYP families (most importantly in this case by CYP1 families) to become DNA reactive and mutagenic. Numerous metals (arsenic, mercury, lead, cadmium, chromium, copper, vanadium) exert toxicities through various mechanisms. However, these metals were shown to modulate *CYP* activities (through changes in mRNA, or protein abundance, or catalytic activity) in tissue and species-specific manner but generally reduced *CYP* catalytic activities in human cells leading to a reduction in PAH-induced DNA damage [reviewed in (533)]. Altogether these examples demonstrate that the toxicity of a mixture differs from the toxicity of its individual components, which creates scientific difficulties in the risk assessment of mixtures.

In the 20th century, cancer incidence (after correction for age) has increased worldwide (534–536) in parallel with the spread of western technology, pollution and consumer products (181,182,537) and some cancers can be regarded as diseases of affluence. Lifestyle factors including diet, smoking and lack of exercise probably contribute importantly to the risk of cancer in a large part of the population of the more developed countries, but exposure to carcinogens or co-carcinogens present in polluted air and drinking water, as well as in food, is also thought to contribute significantly. However, it is not easy to test for links between cancer outcomes and exposure to chemicals or chemical mixtures at low doses. A recent review of investigations into causes of geographical cancer clusters in the USA (538) found that out of over 400 clusters, only one was unequivocally attributed to an environmental cause; a pleural cancer cluster linked to asbestos-exposed shipyard workers (538). It is difficult to detect the carcinogenic effect on humans of a single low-dose chemical through classical epidemiology, as a relative risk of <1.5 or 2.0 can rarely be shown to be statistically significant. Furthermore, with the exception of some cancer-prone conditions such as leukoplakia or colon polyps, presently no early markers for the whole of the carcinogenesis process are available. As yet we have no means to assess the extent to which a process of carcinogenesis has advanced in an individual.

Nevertheless, the more sensitive approach of molecular epidemiology (6,8,9,11–14,185,539) has shown interesting associations between certain environmental exposures and early biomarkers related to carcinogenesis. Several biomarker assays monitoring genome instability (e.g. microsatellite mutations, DNA damage/repair assessment, miRNA, DNA methylation changes in promotor regions, mtDNAcn, telomere length) are used in biomonitoring of individuals exposed to carcinogens. However, in most (but not all) cases, these intermediate biomarkers—though they may show up as significant in case–control

Table 2. Cross-validation of target pathways

Genome instability priority targets	Deregulated metabolism	Evasion of anti-growth signaling	Angiogenesis	Resistance to cell death	Immune system evasion	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor-promoting inflammation	Tumor microenvironment
DNA repair pathways	+ (294)	+ (295)	– (296)	+ (297)	+ (298)	+ (299–301)	+ (302)	+/– (303–306)	– (307)	0
Epigenetic pathways: DNA methylation	+ (308–310)	+ (311)	0	+/– (312–314)	+ (315)	+ (316)	+ (317)	+ (318–321)	+ (322)	0
Epigenetic pathways: histone acetylation	+ (323–325)	+ (326)	0	– (327–329)	+ (330)	+ (331)	+ (317)	Acetylases: – (332,333); Deacetylases: + (332,334–337)	(338)	0
Epigenetic pathways: disturbed miRNA binding	+ (339,340)	+ent (341)	0	+/– (342–344)	+ (345)	+ (346,347)	+ (348)	+/– (349–354)	+ (322)	0
DNA damage signaling: disturbed by redox signaling (NF-κB, Nrf, early growth response (EGR))	+ (355,356)	+ (357)	+ (358)	– (297)	+ (359)	0	+ (360)	+ (361–367)	+ (368)	+ (369)
Mitochondrial function	+ (370,371)	+ (372)	– (373)	– (374)	+ (375,376)	+/– (377–379)	+ (380)	Respiration: – (381–383); Bcl-2: + (384–389)	+ (390)	0
Cell cycle/cell division: spindle defect	+/–; + (391,392)	+ (393)	0	+ (394,395)	+ (396)	+ (397)	+ (398)	0	+ (399)	0
Telomere loss	+ (400)	– (401)	0	– (402–404)	+ (405)	– (299)	– (406)	+ (407–410)	+ (399)	0

Target pathways for genome instability were cross-validated for effects in other cancer hallmark pathways. Targets that were found to have opposing actions in a particular hallmark (i.e. anticarcinogenic) were indicated with '–', whereas targets that were found to have promoting actions in a particular hallmark (i.e. carcinogenic) were indicated with '+'. In instances where reports on relevant actions in other hallmarks were mixed (i.e. reports showing both pro-carcinogenic potential and anticarcinogenic potential), the symbol '+/–' was used. Finally, in instances where no literature support was found to document the relevance of a target in a particular aspect of cancer's biology, we documented this as '0'.

Table 3. Cross-validation of disruptors

Genetic instability prototypical disruptors	Deregulated metabolism	Evasion of anti-growth signaling	Angiogenesis	Immune system evasion	Resistance to cell death	Replicative immortality	Sustained proliferative signaling	Tissue invasion and metastasis	Tumor-promoting inflammation	Tumor micro-environment
Lead	0	0	0	0	– (411–413)	+ (57, 245)	+ (414)	0	+ (415,416)	0
Nickel	0	+ (417)	+ (418)	0	+/– (419,420)	– (421,422)	+ (423)	+ (424)	+ (420,425)	+ PMID: (426)
Cobalt	+ (427)	0	+ (428)	0	– (429,430)	0	+ (431)	+ (432)	+ (433)	– (434)
Mercury	+ (435,436)	0	+/– (437)	0	– (438–440)	0	+ (441)	0	+ (442)	– (443)
Acrylamide	+/– (216,444–446)	0	+ (447)	0	– (448,449); – or no effect (450)	0	+ (451)	0	+ (452,453)	0
Bisphenol A	+ (454–457)	+ (458)	+ (459)	0	+/– (458,460–462)	+ (463)	+ (232)	0	+ (465)	0
Quinones	+/– (466,467)	– (468)	– (469)	0	– (470–472)	– (473–478)	– (479,480)	– (481,482)	+ (269,483)	0
Tungsten	+/– (466,484)	0	0	0	– (485–487)	0	+ (229)	0	+ (230)	0
Paraquat	+ (488–490)	0	0	0	– (491–493)	0	– (494)	0	+ (494,495)	+ (496)
Titanium dioxide NPs	+/– (497–499)	0	+ (500)	0	– (282,501)	0	+ (502)	0	+ (503,504)	0
Benomyl	– (505)	0	– (506)	0	0	0	– (507)	0	+/– +/– (508,509)	0
Carbendazim	– (505)	0	0	0	0	0	– (507)	0	+/– +/– (510)	0
Triclosan	+/– (511,512,540)	0	– (515)	0	– (514)	0	+ (515)	0	+ (516,517)	0
Carbon black	+ (518)	0	+ (519)	0	– (282)	+ (57)	+ (520)	0	+ (521)	0

Disruptors of genomic stability were cross-validated for effects in other cancer hallmark pathways. Disruptors that were found to have opposing actions in a particular hallmark (i.e. anticarcinogenic) were indicated with '–', whereas disruptors that were found to have promoting actions in a particular hallmark (i.e. carcinogenic) were indicated with '+'. In instances where reports on relevant actions in other hallmarks were mixed (i.e. reports showing both pro-carcinogenic potential and anticarcinogenic potential), the symbol '+/–' was used. Finally, in instances where no literature support was found to document the relevance of a chemical in a particular aspect of cancer's biology, we documented this as '0'.

studies—have yet to be tested in prospective trials with clinical end points, to validate them as indicators of cancer risk.

Although epidemiological links between exposure to environmental chemicals and carcinogenesis are difficult to disclose, it is accepted that exposure to chemical mixtures and lifestyle factors can contribute to genome instability (530,538). A complex mixture of hundreds of environmental chemicals are present in the human body. Indeed, the Fourth National Report on Human Exposure-2009 provides blood or urinary exposure data for 212 environmental chemicals in the US population, with updated tables in 2013 for 151 chemicals (http://www.cdc.gov/exposurereport). Together with physical and biological agents, these chemicals might disturb the biological processes described in this special issue and contribute to the risk of developing cancers. Cancer can be viewed as resulting from an increase in entropy in the complex biological systems of the human body. Therefore, the implementation of a new form of hygiene, the physical chemical hygiene, comprising a reduction of exposure to chemical mixtures, among other genome-destabilizing agents, might well be a necessary condition for an effective prevention of cancer.

Funding

Acknowledgements

References

1. Hanahan, D. et al. (2011) Hallmarks of cancer: the next generation. Cell, 144, 646–674.
2. Vogelstein, B. et al. (2013) Cancer genome landscapes. Science, 339, 1546–1558.
3. Thomas, D. (2010) Gene–environment-wide association studies: emerging approaches. Nat. Rev. Genet., 11, 259–272.
4. De Coster, S. et al. (2008) Pollutant effects on genotoxic parameters and tumor-associated protein levels in adults: a cross sectional study. Environ. Health, 7, 26.
5. Perera, F. et al. (2002) *In utero* DNA damage from environmental pollution is associated with somatic gene mutation in newborns. Cancer Epidemiol. Biomarkers Prev., 11(10 Pt 1), 1134–1137.
6. Perera, F.P. et al. (2005) Relationships among polycyclic aromatic hydrocarbon-DNA adducts, proximity to the World Trade Center, and effects on fetal growth. Environ. Health Perspect., 113, 1062–1067.
7. Schoeters, G. et al. (2012) Concept of the Flemish human biomonitoring programme. Int. J. Hyg. Environ. Health, 215, 102–108.
8. Sram, R.J. et al. (2007) Environmental exposure to carcinogenic polycyclic aromatic hydrocarbons–the interpretation of cytogenetic analysis by FISH. Toxicol. Lett., 172, 12–20.
9. Sram, R.J. et al. (2011) Biomarkers of exposure and effect-interpretation in human risk assessment. Air Qual. Atmos. Health, 4, 161–167.
10. van Larebeke, N.A. et al. (2006) Differences in tumor-associated protein levels among middle-age Flemish women in association with area of residence and exposure to pollutants. Environ. Health Perspect., 114, 887–892.
11. Van Larebeke, N. et al. (2004) Differences in HPRT mutant frequency among middle-aged Flemish women in association with area of residence and blood lead levels. Biomarkers, 9, 71–84.
12. Pedersen, M. et al. (2013) Bulky DNA adducts in cord blood, maternal fruit-and-vegetable consumption, and birth weight in a European mother-child study (NewGeneris). Environ. Health Perspect., 121, 1200–1206.
13. Hochstenbach, K. et al. (2012) Global gene expression analysis in cord blood reveals gender-specific differences in response to carcinogenic exposure *in utero*. Cancer Epidemiol. Biomarkers Prev., 21, 1756–1767.
14. Vande Loock, K. et al. (2011) Maternal and gestational factors and micronucleus frequencies in umbilical blood: the NewGeneris Rhea cohort in Crete. Environ. Health Perspect., 119, 1460–1465.
15. Shen, Z. (2011) Genomic instability and cancer: an introduction. J. Mol. Cell Biol., 3, 1–3.
16. Deman, J. et al. (2001) Carcinogenesis: mutations and mutagens. Tumour Biol., 22, 191–202.
17. Kinzler, K.W. et al. (1997) Cancer-susceptibility genes. Gatekeepers and caretakers. Nature, 386, 761, 763.
18. Loeb, L.A. (1994) Microsatellite instability: marker of a mutator phenotype in cancer. Cancer Res., 54, 5059–5063.
19. De Bont, R. et al. (2004) Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis, 19, 169–185.
20. Langie, S.A. et al. (2013) Maternal folate depletion and high-fat feeding from weaning affects DNA methylation and DNA repair in brain of adult offspring. FASEB J., 27, 3323–3334.
21. Langie, S.A. et al. (2014) Redox and epigenetic regulation of the APE1 gene in the hippocampus of piglets: the effect of early life exposures. DNA Repair (Amst)., 18, 52–62.
22. Fang, M.Z. et al. (2003) Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. Cancer Res., 63, 7563–7570.
23. Fang, M.Z. et al. (2005) Reversal of hypermethylation and reactivation of p16INK4a, RARbeta, and MGMT genes by genistein and other isoflavones from soy. Clin. Cancer Res., 11(19 Pt 1), 7033–7041.
24. Langie, S.A.C. et al. (2013) The ageing brain; effects on DNA repair and DNA methylation in mice. 37th Congress of IUPS, Proc. 37th IUPS, SA58, Birmingham, UK.
25. Li, F. et al. (2013) The histone mark H3K36me3 regulates human DNA mismatch repair through its interaction with MutSα. Cell, 153, 590–600.
26. Miller, K.M. et al. (2012) Histone marks: repairing DNA breaks within the context of chromatin. Biochem. Soc. Trans., 40, 370–376.
27. Chen, R. et al. (2013) Impact of glutathione-S-transferases (GST) polymorphisms and hypermethylation of relevant genes on risk of prostate cancer biochemical recurrence: a meta-analysis. PLoS One, 8, e74775.
28. Schnekenburger, M. et al. (2014) Regulation of epigenetic traits of the glutathione S-transferase P1 gene: from detoxification toward cancer prevention and diagnosis. Front. Pharmacol., 5, 170.
29. Lertratanangkoon, K. et al. (1997) Alterations of DNA methylation by glutathione depletion. Cancer Lett., 120, 149–156.
30. Wogan, G.N. (1992) Molecular epidemiology in cancer risk assessment and prevention: recent progress and avenues for future research. Environ. Health Perspect., 98, 167–178.
31. Santella, R.M. et al. (2005) DNA adducts, DNA repair genotype/phenotype and cancer risk. Mutat. Res., 592, 29–35.
32. Friedberg, E.C. et al. (2006) DNA damage. In Friedberg, E.C. et al. (eds) DNA Repair and Mutagenisis. ASM Press, Washington, DC, pp. 9–70.

33. Jang, J.W. et al. (2006) Isoform-specific ras activation and oncogene dependence during MYC- and Wnt-induced mammary tumorigenesis. Mol. Cell. Biol., 26, 8109–8121.

34. Hollstein, M. et al. (1991) p53 mutations in human cancers. Science, 253, 49–53.

35. Pierotti, M.A. et al. (2003) Mechanisms of oncogene activation, Chapter 6. In Kufe, D.W. et al. (eds) Holland-Frei Cancer Medicine. 6th edn. BC Decker, Hamilton, Ontario, Canada.

36. Oudejans, J.J. et al. (1991) Differential activation of ras genes by point mutation in human colon cancer with metastases to either lung or liver. Int. J. Cancer, 49, 875–879.

37. Goodsell, D.S. (1999) The molecular perspective: the ras oncogene. Stem Cells, 17, 235–236.

38. Brison, O. (1993) Gene amplification and tumor progression. Biochim. Biophys. Acta, 1155, 25–41.

39. Kurzrock, R. et al. (2003) Philadelphia chromosome-positive leukemias: from basic mechanisms to molecular therapeutics. Ann. Intern. Med., 138, 819–830.

40. Negrini, S. et al. (2010) Genomic instability–an evolving hallmark of cancer. Nat. Rev. Mol. Cell Biol., 11, 220–228.

41. Cook, W.D. et al. (2000) Accommodating haploinsufficient tumor suppressor genes in Knudson's model. Oncogene, 19, 3434–3438.

42. Muñoz, D.M. et al. (2013) Loss of p53 cooperates with K-ras activation to induce glioma formation in a region-independent manner. Glia, 61, 1862–1872.

43. International Atomic Energy Agency (2011) Cytogenetic Dosimetry: Applications in Preparedness for and Response to Radiation Emergencies. IAEA, Vienna, Austria.

44. Honma, M. et al. (2002) Chromosomal instability in B-lymphoblastoid cell lines from Werner and Bloom syndrome patients. Mutat. Res., 520, 15–24.

45. Holland, A.J. et al. (2012) Losing balance: the origin and impact of aneuploidy in cancer. EMBO Rep., 13, 501–514.

46. Ganem, N.J. et al. (2007) Tetraploidy, aneuploidy and cancer. Curr. Opin. Genet. Dev., 17, 157–162.

47. Gordon, D.J. et al. (2012) Causes and consequences of aneuploidy in cancer. Nat. Rev. Genet., 13, 189–203.

48. Kirsch-Volders, M. et al. (2002) Importance of detecting numerical versus structural chromosome aberrations. Mutat. Res., 504, 137–148.

49. Kirsch-Volders, M. et al. (2011) The *in vitro* MN assay in 2011: origin and fate, biological significance, protocols, high throughput methodologies and toxicological relevance. Arch. Toxicol., 85, 873–899.

50. Holland, A.J. et al. (2012) Chromoanagenesis and cancer: mechanisms and consequences of localized, complex chromosomal rearrangements. Nat. Med., 18, 1630–1638.

51. Boveri, T. (1914) Zur Frage der Enstehung maligner tumoren. Gustav Fischer Verlag, Jena, Germany.

52. Ganmore, I. et al. (2009) Constitutional aneuploidy and cancer predisposition. Hum. Mol. Genet., 18, R84–R93.

53. Mitelman, F. et al. (2012) Mitelman Database of Chromosome Aberrations and Gene Fusion in Cancer. http://cgap.nci.nih.gov/Chromosomes/Mitelman.

54. Kops, G.J. et al. (2005) On the road to cancer: aneuploidy and the mitotic checkpoint. Nat. Rev. Cancer, 5, 773–785.

55. Weaver, B.A. et al. (2006) Does aneuploidy cause cancer? Curr. Opin. Cell Biol., 18, 658–667.

56. Houben, J.M. et al. (2008) Telomere length assessment: biomarker of chronic oxidative stress? Free Radic. Biol. Med., 44, 235–246.

57. Zhang, X. et al. (2013) Environmental and occupational exposure to chemicals and telomere length in human studies. Occup. Environ. Med., 70, 743–749.

58. Sahin, E. et al. (2011) Telomere dysfunction induces metabolic and mitochondrial compromise. Nature, 470, 359–365.

59. De, L.T. (2005) Telomere-related genome instability in cancer. Cold Spring Harb. Symp. Quant. Biol., 70, 197–204.

60. Frias, C. et al. (2012) Telomere dysfunction and genome instability. Front. Biosci. (Landmark Ed)., 17, 2181–2196.

61. Nakashima, M. et al. (2013) Inhibition of telomerase recruitment and cancer cell death. J. Biol. Chem., 288, 33171–33180.

62. Collins, A.R. et al. (2009) Antioxidants and cancer: fact and fiction. In Knasmüller, S. et al. (eds) Chemoprevention of Cancer and DNA Damage by Dietary Factors. Wiley-VCH, Weinheim, Germany, 73–92.

63. Hayes, J.D. et al. (2005) Glutathione transferases. Annu. Rev. Pharmacol. Toxicol., 45, 51–88.

64. Guengerich, F.P. (2001) Common and uncommon cytochrome P450 reactions related to metabolism and chemical toxicity. Chem. Res. Toxicol., 14, 611–650.

65. Phillips, D.H. et al. (1988) Correlation of DNA adduct levels in human lung with cigarette smoking. Nature, 336, 790–792.

66. Lutz, W.K. (1990) Dose-response relationship and low dose extrapolation in chemical carcinogenesis. Carcinogenesis, 11, 1243–1247.

67. Collins, A.R. et al. (2001) Oxidative DNA damage, antioxidants and DNA repair: applications of the comet assay. Biochem. Soc. Trans., 29(Pt 2), 337–341.

68. Friedberg, E.C. et al. (2006) Correcting altered bases in DNA: DNA repair. In Friedberg, E.C. et al. (eds) DNA Repair and Mutagenisis. ASM Press, Washington, DC, pp. 107–460.

69. Lieber, M.R. (2010) The mechanism of double-strand DNA break repair by the nonhomologous DNA end-joining pathway. Annu. Rev. Biochem., 79, 181–211.

70. Müller, A. et al. (2002) Mismatch repair and the hereditary non-polyposis colorectal cancer syndrome (HNPCC). Cancer Invest., 20, 102–109.

71. Kunkel, T.A. et al. (2005) DNA mismatch repair. Annu. Rev. Biochem., 74, 681–710.

72. Friedberg, E.C. (2003) DNA damage and repair. Nature, 421, 436–440.

73. Langie, S.A. et al. (2010) Modulation of nucleotide excision repair in human lymphocytes by genetic and dietary factors. Br. J. Nutr., 103, 490–501.

74. Berwick, M. et al. (2005) Measuring DNA repair capacity: small steps. J. Natl Cancer Inst., 97, 84–85.

75. Collins, A.R. et al. (2012) Effects of micronutrients on DNA repair. Eur. J. Nutr., 51, 261–279.

76. Sancar, A. (1995) Excision repair in mammalian cells. J. Biol. Chem., 270, 15915–15918.

77. Boyer, J.C. et al. (1990) Defective postreplication repair in xeroderma pigmentosum variant fibroblasts. Cancer Res., 50, 2593–2598.

78. Mazzei, F. et al. (2013) Role of MUTYH in human cancer. Mutat. Res., 743–744, 33–43.

79. Walker, G.C. (1985) Inducible DNA repair systems. Annu. Rev. Biochem., 54, 425–457.

80. Hanawalt, P.C. (2002) Subpathways of nucleotide excision repair and their regulation. Oncogene, 21, 8949–8956.

81. Li, Q. et al. (1998) Cisplatin and phorbol ester independently induce ERCC-1 protein in human ovarian carcinoma cells. Int. J. Oncol., 13, 987–992.

82. Wang, X. et al. (2012) Arsenic and chromium in drinking water promote tumorigenesis in a mouse colitis-associated colorectal cancer model and the potential mechanism is ROS-mediated Wnt/β-catenin signaling pathway. Toxicol. Appl. Pharmacol., 262, 11–21.

83. Jaiswal, M. et al. (2001) Human Ogg1, a protein involved in the repair of 8-oxoguanine, is inhibited by nitric oxide. Cancer Res., 61, 6388–6393.

84. Graziewicz, M. et al. (1996) Nitric oxide inhibits DNA ligase activity: potential mechanisms for NO-mediated DNA damage. Carcinogenesis, 17, 2501–2505.

85. Langie, S.A. et al. (2010) The effect of oxidative stress on nucleotide-excision repair in colon tissue of newborn piglets. Mutat. Res., 695, 75–80.

86. Langie, S.A. et al. (2007) The role of glutathione in the regulation of nucleotide excision repair during oxidative stress. Toxicol. Lett., 168, 302–309.

87. Feng, Z. et al. (2004) Trans-4-hydroxy-2-nonenal inhibits nucleotide excision repair in human cells: a possible mechanism for lipid peroxidation-induced carcinogenesis. Proc. Natl Acad. Sci. USA, 101, 8598–8602.

88. Feng, Z. et al. (2006) Malondialdehyde, a major endogenous lipid peroxidation product, sensitizes human cells to UV- and BPDE-induced killing and mutagenesis through inhibition of nucleotide excision repair. Mutat. Res., 601, 125–136.

89. Lloyd, D.R. et al. (2000) p53-dependent global genomic repair of benzo[a]pyrene-7,8-diol-9,10-epoxide adducts in human cells. Cancer Res., 60, 517–521.

90. Binková, B. et al. (2000) The effect of dibenzo[a,1]pyrene and benzo[a]pyrene on human diploid lung fibroblasts: the induction of DNA adducts, expression of p53 and p21(WAF1) proteins and cell cycle distribution. Mutat. Res., 471, 57–70.

91. Topinka, J. et al. (2007) Biomarkers of air pollution exposure–a study of policemen in Prague. Mutat. Res., 624, 9–17.

92. Shelton, P. et al. (2013) The transcription factor NF-E2-related factor 2 (Nrf2): a protooncogene? FASEB J., 27, 414–423.

93. Mitsuishi, Y. et al. (2012) The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism. Front. Oncol., 2, 200.

94. Papp, D. et al. (2012) The NRF2-related interactome and regulome contain multifunctional proteins and fine-tuned autoregulatory loops. FEBS Lett., 586, 1795–1802.

95. Loaiza-Ruiz, B. et al. (2011) Understanding cancer stem cell: role of NF-KB in the chemotherapy resistance. In Pandalai, S.G. (ed.) In Recent Research Developments in Cancer. Vol 9. Transworld Research Network, Kerala, India, pp. 25–50.

96. Gilmore, T.D. et al. (2004) RELevant gene amplification in B-cell lymphomas? Blood, 103, 3243–3244.

97. Knaapen, A.M. et al. (2006) Neutrophils and respiratory tract DNA damage and mutagenesis: a review. Mutagenesis, 21, 225–236.

98. Borm, P.J. et al. (1997) Neutrophils amplify the formation of DNA adducts by benzo[a]pyrene in lung target cells. Environ. Health Perspect., 105(suppl. 5), 1089–1093.

99. Mathers, J.C. et al. (2010) Induction of epigenetic alterations by dietary and other environmental factors. Adv. Genet., 71, 3–39.

100. Orphanides, G. et al. (2003) Toxicogenetics: applications and opportunities. Toxicol. Sci., 75, 1–6.

101. Iida, A. et al. (2001) Catalog of 46 single-nucleotide polymorphisms (SNPs) in the microsomal glutathione S-transferase 1 (MGST1) gene. J. Hum. Genet., 46, 590–594.

102. Marez, D. et al. (1997) Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. Pharmacogenetics, 7, 193–202.

103. Kuehl, P. et al. (2001) Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat. Genet., 27, 383–391.

104. Deitz, A.C. et al. (2004) Impact of misclassification in genotype-exposure interaction studies: example of N-acetyltransferase 2 (NAT2), smoking, and bladder cancer. Cancer Epidemiol. Biomarkers Prev., 13, 1543–1546.

105. Hein, D.W. et al. (2010) Relationship between N-acetyltransferase 2 single-nucleotide polymorphisms and phenotype. Carcinogenesis, 31, 326–327.

106. Hengstler, J.G. et al. (1998) Polymorphisms of N-acetyltransferases, glutathione S-transferases, microsomal epoxide hydrolase and sulfotransferases: influence on cancer susceptibility. In Schwab, M. et al. (eds) Genes and Environment in Cancer. Springer-Verlag, Berlin/Heidelberg, Germany, pp. 47–85.

107. Nebert, D.W. (1999) Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? Clin. Genet., 56, 247–258.

108. Hussain, S.P. et al. (1998) Molecular epidemiology of human cancer. In Schwab, M. et al. (eds) Genes and Environment in Cancer. Springer-Verlag, Berlin/Heidelberg, Germany, pp. 22–36.

109. Garte, S. (2001) Metabolic susceptibility genes as cancer risk factors: time for a reassessment? Cancer Epidemiol. Biomarkers Prev., 10, 1233–1237.

110. Mohrenweiser, H.W. et al. (2002) Identification of 127 amino acid substitution variants in screening 37 DNA repair genes in humans. Cancer Epidemiol. Biomarkers Prev., 11(10 Pt 1), 1054–1064.

111. Kiyohara, C. et al. (2006) Association of genetic polymorphisms in the base excision repair pathway with lung cancer risk: a meta-analysis. Lung Cancer, 54, 267–283.

112. Kiyohara, C. et al. (2007) Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. Int. J. Med. Sci., 4, 59–71.

113. Manuguerra, M. et al. (2006) XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. Am. J. Epidemiol., 164, 297–302.

114. Cheng, J. et al. (2007) Association between nucleotide excision repair gene polymorphisms and chromosomal damage in coke-oven workers. Biomarkers, 12, 76–86.

115. Mateuca, R. et al. (2005) Influence of hOGG1, XRCC1 and XRCC3 genotypes on biomarkers of genotoxicity in workers exposed to cobalt or hard metal dusts. Toxicol. Lett., 156, 277–288.

116. Mateuca, R.A. et al. (2008) hOGG1(326), XRCC1(399) and XRCC3(241) polymorphisms influence micronucleus frequencies in human lymphocytes *in vivo*. Mutagenesis, 23, 35–41.

117. Hou, S.M. et al. (2002) The XPD variant alleles are associated with increased aromatic DNA adduct level and lung cancer risk. Carcinogenesis, 23, 599–603.

118. Wu, X. et al. (2003) XPA polymorphism associated with reduced lung cancer risk and a modulating effect on nucleotide excision repair capacity. Carcinogenesis, 24, 505–509.

119. Vineis, P. et al. (2009) A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. J. Natl Cancer Inst., 101, 24–36.

120. Manolio, T.A. et al. (2009) Finding the missing heritability of complex diseases. Nature, 461, 747–753.

121. Stranger, B.E. et al. (2007) Relative impact of nucleotide and copy number variation on gene expression phenotypes. Science, 315, 848–853.

122. Magri, C. et al. (2010) New copy number variations in schizophrenia. PLoS One, 5, e13422.

123. Marenne, G. et al. (2011) Assessment of copy number variation using the Illumina Infinium 1M SNP-array: a comparison of methodological approaches in the Spanish Bladder Cancer/EPICURO study. Hum. Mutat., 32, 240–248.

124. Bohacek, J. et al. (2013) Epigenetic inheritance of disease and disease risk. Neuropsychopharmacology, 38, 220–236.

125. Anderson, O.S. et al. (2012) Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. J. Nutr. Biochem., 23, 853–859.

126. Berman, B.P. et al. (2012) Regions of focal DNA hypermethylation and long-range hypomethylation in colorectal cancer coincide with nuclear lamina-associated domains. Nat. Genet., 44, 40–46.

127. Buck-Koehntop, B.A. et al. (2013) On how mammalian transcription factors recognize methylated DNA. Epigenetics, 8, 131–137.

128. Ko, Y.G. et al. (2005) Stage-by-stage change in DNA methylation status of Dnmt1 locus during mouse early development. J. Biol. Chem., 280, 9627–9634.

129. Rhee, I. et al. (2002) DNMT1 and DNMT3b cooperate to silence genes in human cancer cells. Nature, 416, 552–556.

130. Egger, G. et al. (2004) Epigenetics in human disease and prospects for epigenetic therapy. Nature, 429, 457–463.

131. Huidobro, C. et al. (2013) The role of genetics in the establishment and maintenance of the epigenome. Cell. Mol. Life Sci., 70, 1543–1573.

132. Kinney, S.R. et al. (2013) Ten eleven translocation enzymes and 5-hydroxymethylation in mammalian development and cancer. Adv. Exp. Med. Biol., 754, 57–79.

133. Thomson, J.P. et al. (2013) Dynamic changes in 5-hydroxymethylation signatures underpin early and late events in drug exposed liver. Nucleic Acids Res., 41, 5639–5654.

134. Esteller, M. (2007) Cancer epigenomics: DNA methylomes and histone-modification maps. Nat. Rev. Genet., 8, 286–298.

135. Medvedeva, Y.A. et al. (2014) Effects of cytosine methylation on transcription factor binding sites. BMC Genomics, 15, 119.

136. Casadesús, J. et al. (2006) Epigenetic gene regulation in the bacterial world. Microbiol. Mol. Biol. Rev., 70, 830–856.

137. Watt, F. et al. (1988) Cytosine methylation prevents binding to DNA of a HeLa cell transcription factor required for optimal expression of the adenovirus major late promoter. Genes Dev., 2, 1136–1143.

138. Holliday, R. et al. (1993) DNA methylation and mutation. Mutat. Res., 285, 61–67.

139. Chahwan, R. et al. (2010) Crosstalk between genetic and epigenetic information through cytosine deamination. Trends Genet., 26, 443–448.

140. Sassa, A. et al. (2012) DNA sequence context effects on the glycosylase activity of human 8-oxoguanine DNA glycosylase. J. Biol. Chem., 287, 36702–36710.

141. Ehrlich, M. et al. (2013) DNA hypomethylation and hemimethylation in cancer. Adv. Exp. Med. Biol., 754, 31–56.

142. Lander, E.S. et al. (2001) Initial sequencing and analysis of the human genome. Nature, 409, 860–921.

143. Burgess, R.J. et al. (2013) Histone chaperones in nucleosome assembly and human disease. Nat. Struct. Mol. Biol., 20, 14–22.

144. Turner, B.M. (2002) Cellular memory and the histone code. Cell, 111, 285–291.

145. Lewis, P.W. et al. (2013) Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma. Science, 340, 857–861.

146. Huntzinger, E. et al. (2011) Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat. Rev. Genet., 12, 99–110.

147. Choudhuri, S. (2010) Small noncoding RNAs: biogenesis, function, and emerging significance in toxicology. J. Biochem. Mol. Toxicol., 24, 195–216.

148. Huang, Y. et al. (2011) Biological functions of microRNAs: a review. J. Physiol. Biochem., 67, 129–139.

149. Croce, C.M. (2009) Causes and consequences of microRNA dysregulation in cancer. Nat. Rev. Genet., 10, 704–714.

150. Caffarelli, E. et al. (2011) Epigenetic regulation in cancer development. Front. Biosci. (Landmark Ed)., 16, 2682–2694.

151. Chowdhury, D. et al. (2013) Charity begins at home: non-coding RNA functions in DNA repair. Nat. Rev. Mol. Cell Biol., 14, 181–189.

152. Wang, Y. et al. (2013) MicroRNAs and DNA damage response: implications for cancer therapy. Cell Cycle, 12, 32–42.

153. Baer, C. et al. (2013) Genome-wide epigenetic regulation of miRNAs in cancer. Cancer Res., 73, 473–477.

154. Li, X.Q. et al. (2012) DNA methylation and microRNAs in cancer. World J. Gastroenterol., 18, 882–888.

155. Kala, R. et al. (2013) MicroRNAs: an emerging science in cancer epigenetics. J. Clin. Bioinforma., 3, 6.

156. Motta, V. et al. (2013) Integrative Analysis of miRNA and inflammatory gene expression after acute particulate matter exposure. Toxicol. Sci., 132, 307–316.

157. Guida, M. et al. (2013) Association between exposure to dioxin-like polychlorinated biphenyls and miR-191 expression in human peripheral blood mononuclear cells. Mutat. Res., 753, 36–41.

158. Halappanavar, S. et al. (2011) Pulmonary gene and microRNA expression changes in mice exposed to benzo(a)pyrene by oral gavage. Toxicology, 285, 133–141.

159. Kim, T. et al. (2013) Non-coding RNAs: functional aspects and diagnostic utility in oncology. Int. J. Mol. Sci., 14, 4934–4968.

160. Lee, J.T. (2012) Epigenetic regulation by long noncoding RNAs. Science, 338, 1435–1439.

161. Yang, J. et al. (2012) Chromatin insulators and epigenetic inheritance in health and disease. In Sahu, S.C.J. (ed.) Toxicology and Epigenetics. Wiley, New Jersey, pp. 539–567.

162. Brierley, D.J. et al. (2013) Oxidative stress and the DNA mismatch repair pathway. Antioxid. Redox Signal., 18, 2420–2428.

163. Chiaravalli, A.M. et al. (2001) Immunohistochemical pattern of hMSH2/hMLH1 in familial and sporadic colorectal, gastric, endometrial and ovarian carcinomas with instability in microsatellite sequences. Virchows Arch., 438, 39–48.

164. Murata, H. et al. (2005) Roles of mismatch repair proteins hMSH2 and hMLH1 in the development of sporadic breast cancer. Cancer Lett., 223, 143–150.

165. Popat, S. et al. (2005) Systematic review of microsatellite instability and colorectal cancer prognosis. J. Clin. Oncol., 23, 609–618.

166. Yamamoto, H. et al. (2012) Interrelationship between microsatellite instability and microRNA in gastrointestinal cancer. World J. Gastroenterol., 18, 2745–2755.

167. Kim, T.M. et al. (2014) A genome-wide view of microsatellite instability: old stories of cancer mutations revisited with new sequencing technologies. Cancer Res., 74, 6377–6382.

168. US EPA (2005) Guidelines for Carcinogen Risk Assessment. National Center for Environmental Assessment, Washington, DC, EPA/630/P-03/0001b, NCEA-F-0644b.

169. Johnson, G.E. et al. (2014) Derivation of point of departure (PoD) estimates in genetic toxicology studies and their potential applications in risk assessment. Environ. Mol. Mutagen., 55, 609–623.

170. Hernández, A.F. et al. (2013) Toxic effects of pesticide mixtures at a molecular level: their relevance to human health. Toxicology, 307, 136–145.

171. Ukpebor, J. et al. (2011) Sublethal genotoxicity and cell alterations by organophosphorus pesticides in MCF-7 cells: implications for environmentally relevant concentrations. Environ. Toxicol. Chem., 30, 632–639.

172. Peto, R. et al. (1991) Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study. Cancer Res., 51(23 Pt 2), 6415–6451.

173. Peto, R. et al. (1991) Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine. Cancer Res., 51(23 Pt 2), 6452–6469.

174. Lewtas, J. et al. (1997) Air pollution exposure-DNA adduct dosimetry in humans and rodents: evidence for non-linearity at high doses. Mutat. Res., 378, 51–63.

175. Van Schooten, F.J. et al. (1997) 32P-postlabelling of aromatic DNA adducts in white blood cells and alveolar macrophages of smokers: saturation at high exposures. Mutat. Res., 378, 65–75.

176. Carere, A. et al. (1995) Genetic effects of petroleum fuels: cytogenetic monitoring of gasoline station attendants. Mutat. Res., 332, 17–26.

177. Bastlová, T. et al. (1995) Styrene oxide-induced HPRT mutations, DNA adducts and DNA strand breaks in cultured human lymphocytes. Carcinogenesis, 16, 2357–2362.

178. Calabrese, E.J. et al. (2003) Toxicology rethinks its central belief. Nature, 421, 691–692.

179. Bercht, M. et al. (2007) Is the repair of oxidative DNA base modifications inducible by a preceding DNA damage induction? DNA Repair (Amst)., 6, 367–373.

180. Grösch, S. et al. (1998) Apurinic endonuclease (Ref-1) is induced in mammalian cells by oxidative stress and involved in clastogenic adaptation. Cancer Res., 58, 4410–4416.

181. Belpomme, D. et al. (2007) The multitude and diversity of environmental carcinogens. Environ. Res., 105, 414–429.

182. Clapp, R.W. et al. (2006) Environmental and occupational causes of cancer re-visited. J. Public Health Policy, 27, 61–76.

183. Perera, F. et al. (2005) DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center Area, Poland, and China. Cancer Epidemiol. Biomarkers Prev., 14, 709–714.

184. Perera, F.P. et al. (2005) A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. Neurotoxicology, 26, 573–587.

185. Staessen, J.A. et al. (2001) Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. Lancet, 357, 1660–1669.

186. Tang, D. et al. (2006) PAH-DNA adducts in cord blood and fetal and child development in a Chinese cohort. Environ. Health Perspect., 114, 1297–1300.

187. Druckrey, H. et al. (1963) [Quantitative analysis of the carcinogenic effect of diethylnitrosamine]. Arzneimittelforschung., 13, 841–851.

188. Schramm, K.W. et al. (2002) From more to less than Haber's law. Environ. Toxicol. Pharmacol., 11, 227–232.

189. Grufferman, S. et al. (1983) Parents' cigarette smoking and childhood cancer. Med. Hypotheses, 12, 17–20.

190. Ji, B.T. et al. (1997) Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. J. Natl Cancer Inst., 89, 238–244.

191. MacArthur, A.C. et al. (2008) Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. Cancer Causes Control, 19, 283–295.

192. Linschooten, J.O. et al. (2013) Paternal lifestyle as a potential source of germline mutations transmitted to offspring. FASEB J., 27, 2873–2879.

193. Jansen, J. et al. (2001) Nucleotide excision repair in rat male germ cells: low level of repair in intact cells contrasts with high dual incision activity in vitro. Nucleic Acids Res., 29, 1791–1800.

194. Olsen, A.K. et al. (2005) How do male germ cells handle DNA damage? Toxicol. Appl. Pharmacol., 207, 521–531.

195. Xu, G. et al. (2005) Nucleotide excision repair activity varies among murine spermatogenic cell types. Biol. Reprod., 73, 123–130.

196. Verhofstad, N. et al. (2010) DNA adduct kinetics in reproductive tissues of DNA repair proficient and deficient male mice after oral exposure to benzo(a)pyrene. Environ. Mol. Mutagen., 51, 123–129.

197. Olsen, A.K. et al. (2003) Limited repair of 8-hydroxy-7,8-dihydroguanine residues in human testicular cells. Nucleic Acids Res., 31, 1351–1363.

198. Brevik, A. et al. (2012) Paternal benzo[a]pyrene exposure modulates microRNA expression patterns in the developing mouse embryo. Int. J. Cell Biol., 2012, 407431.

199. Brevik, A. et al. (2012) Paternal benzo[a]pyrene exposure affects gene expression in the early developing mouse embryo. Toxicol. Sci., 129, 157–165.

200. Crow, J.F. et al. (1981) The mutation component of genetic damage. Science, 212, 888–893.

201. Nelson, K. et al. (1989) Malformations due to presumed spontaneous mutations in newborn infants. N. Engl. J. Med., 320, 19–23.

202. Devalle, S. et al. (2012) Implications of aneuploidy for stem cell biology and brain therapeutics. Front. Cell. Neurosci., 6, 36.

203. Rehen, S.K. et al. (2001) Chromosomal variation in neurons of the developing and adult mammalian nervous system. Proc. Natl Acad. Sci. USA, 98, 13361–13366.

204. Cervantes, R.B. et al. (2002) Embryonic stem cells and somatic cells differ in mutation frequency and type. Proc. Natl Acad. Sci. USA, 99, 3586–3590.

205. Leyns, L. et al. (2012) Genomic integrity of mouse embryonic stem cells, Chapter 15. In Sato,KI. (ed.) *Embryogenesis*. InTech, Rijeka, pp. 335–358. ISBN:978-953-51-0466-7.

206. Barouki, R. et al. (2012) Developmental origins of non-communicable disease: implications for research and public health. Environ. Health, 11, 42.

207. El-Zein, R. et al. (2007) Reduction in telomere length in individuals exposed *in utero* to glycol ether. Arch. Environ. Occup. Health, 62, 161–163.

208. Laubenthal, J. et al. (2012) Cigarette smoke-induced transgenerational alterations in genome stability in cord blood of human F1 offspring. FASEB J., 26, 3946–3956.

209. Perera, F. (2011) Molecular epidemiology, prenatal exposure and prevention of cancer. Environ. Health, 10(suppl. 1), S5.

210. McKay, J.A. et al. (2011) Diet induced epigenetic changes and their implications for health. Acta Physiol. (Oxf)., 202, 103–118.

211. Vanhees, K. et al. (2014) You are what you eat, and so are your children: the impact of micronutrients on the epigenetic programming of offspring. Cell. Mol. Life Sci, 71, 271–285.

212. Hou, L. et al. (2012) Environmental chemical exposures and human epigenetics. Int. J. Epidemiol., 41, 79–105.

213. Asmuss, M. et al. (2000) Differential effects of toxic metal compounds on the activities of Fpg and XPA, two zinc finger proteins involved in DNA repair. Carcinogenesis, 21, 2097–2104.

214. Blessing, H. et al. (2004) Interaction of selenium compounds with zinc finger proteins involved in DNA repair. Eur. J. Biochem., 271, 3190–3199.

215. Hartwig, A. et al. (2002) Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. Environ. Health Perspect., 110(suppl. 5), 797–799.

216. Exon, J.H. (2006) A review of the toxicology of acrylamide. J. Toxicol. Environ. Health B Crit. Rev., 9, 397–412.

217. Doshi, T. et al. (2011) Hypermethylation of estrogen receptor promoter region in adult testis of rats exposed neonatally to bisphenol A. Toxicology, 289, 74–82.

218. Kundakovic, M. et al. (2013) Sex-specific epigenetic disruption and behavioral changes following low-dose *in utero* bisphenol A exposure. Proc. Natl Acad. Sci. USA, 110, 9956–9961.

219. Gong, C. et al. (2012) Methylation of PARP-1 promoter involved in the regulation of nano-SiO2-induced decrease of PARP-1 mRNA expression. Toxicol. Lett., 209, 264–269.

220. Wang, X. et al. (2013) Epigenotoxicity of environmental pollutants evaluated by a combination of DNA methylation inhibition and capillary electrophoresis-laser-induced fluorescence immunoassay. Anal. Bioanal. Chem., 405, 2435–2442.

221. Doherty, L.F. et al. (2010) *In utero* exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: an epigenetic mechanism linking endocrine disruptors to breast cancer. Horm. Cancer, 1, 146–155.

222. Choi, A.O. et al. (2008) Quantum dot-induced epigenetic and genotoxic changes in human breast cancer cells. J. Mol. Med. (Berl)., 86, 291–302.

223. Arita, A. et al. (2012) Global levels of histone modifications in peripheral blood mononuclear cells of subjects with exposure to nickel. Environ. Health Perspect., 120, 198–203.

224. Cantone, L. et al. (2011) Inhalable metal-rich air particles and histone H3K4 dimethylation and H3K9 acetylation in a cross-sectional study of steel workers. Environ. Health Perspect., 119, 964–969.

225. Chervona, Y. et al. (2012) Carcinogenic metals and the epigenome: understanding the effect of nickel, arsenic, and chromium. Metallomics, 4, 619–627.

226. Avissar-Whiting, M. et al. (2010) Bisphenol A exposure leads to specific microRNA alterations in placental cells. Reprod. Toxicol., 29, 401–406.

227. Palmieri, A. et al. (2008) Short-period effects of zirconia and titanium on osteoblast microRNAs. Clin. Implant Dent. Relat. Res., 10, 200–205.

228. Balansky, R. et al. (2013) Transplacental clastogenic and epigenetic effects of gold nanoparticles in mice. Mutat. Res, 751–752, 42–48.

229. Miller, A.C. et al. (2001) Neoplastic transformation of human osteoblast cells to the tumorigenic phenotype by heavy metal-tungsten alloy particles: induction of genotoxic effects. Carcinogenesis, 22, 115–125.

230. Roedel, E.Q. et al. (2012) Pulmonary toxicity after exposure to military-relevant heavy metal tungsten alloy particles. Toxicol. Appl. Pharmacol., 259, 74–86.

231. Lombaert, N. et al. (2013) Hard-metal (WC-Co) particles trigger a signaling cascade involving p38 MAPK, HIF-1α, HMOX1, and p53 activation in human PBMC. Arch. Toxicol., 87, 259–268.

232. 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.

233. Freyre-Fonseca, V. et al. (2011) Titanium dioxide nanoparticles impair lung mitochondrial function. Toxicol. Lett., 202, 111–119.

234. Wang, Q. et al. (2010) Mitochondrial signaling pathway is also involved in bisphenol A induced germ cell apoptosis in testes. Toxicol. Lett., 199, 129–135.

235. Pruser, K.N. et al. (2011) Acrylamide in health and disease. Front. Biosci. (Schol. Ed.), 3, 41–51.

236. Hogervorst, J.G. et al. (2010) The carcinogenicity of dietary acrylamide intake: a comparative discussion of epidemiological and experimental animal research. Crit. Rev. Toxicol., 40, 485–512.

237. Sickles, D.W. et al. (2007) Acrylamide effects on kinesin-related proteins of the mitotic/meiotic spindle. Toxicol. Appl. Pharmacol., 222, 111–121.

238. Frame, S.R. et al. (1990) Oncogenicity Studies with Benomyl and MBC in Mice (Supplemental Peer Review). Final report; study nos. 3194: 3207:20-82. Unpublished report by Haskell Laboratory, MRID no. 41607904 reviewed in HED document no. 010723.

239. Schneider, P.W. et al. (1982) Long-term Feeding Study with 2-Benzimidazolecarbamic Acid, Methyl Ester in Mice. Final report; report no. 70-82. Unpublished report by Haskell Laboratory, MRID no. 00096513 reviewed in HED document nos. 004678, 004679.

240. Marshall, H. (2002) Fact sheet: carbendazim. Pesticides News, 57, 20–21.

241. Ribeiro-Varandas, E. et al. (2013) Bisphenol A at concentrations found in human serum induces aneugenic effects in endothelial cells. Mutat. Res., 751, 27–33.

242. Sargent, L.M. et al. (2012) Single-walled carbon nanotube-induced mitotic disruption. Mutat. Res., 745, 28–37.

243. Muller, J. et al. (2008) Clastogenic and aneugenic effects of multi-wall carbon nanotubes in epithelial cells. Carcinogenesis, 29, 427–433.

244. Liu, Y. et al. (2013) Understanding the toxicity of carbon nanotubes. Acc. Chem. Res., 46, 702–713.

245. Pottier, G. et al. (2013) Lead exposure induces telomere instability in human cells. PLoS One, 8, e67501.

246. Zhang, X. et al. (2013) Environmental and occupational exposure to chemicals and telomere length in human studies. Occup. Environ. Med., 70, 743–749.

247. Galaris, D. et al. (2002) The role of oxidative stress in mechanisms of metal-induced carcinogenesis. Crit. Rev. Oncol. Hematol., 42, 93–103.

248. Zawia, N.H. et al. (2009) Epigenetics, oxidative stress, and Alzheimer disease. Free Radic. Biol. Med., 46, 1241–1249.

249. Rojas, D. et al. (2015) Prenatal arsenic exposure and the epigenome: identifying sites of 5-methylcytosine alterations that predict functional changes in gene expression in newborn cord blood and subsequent birth outcomes. Toxicol. Sci., 143, 97–106.

250. Martínez-Pacheco, M. et al. (2014) MRNA and miRNA expression patterns associated to pathways linked to metal mixture health effects. Gene, 533, 508–514.

251. Cugell, D.W. et al. (1990) The respiratory effects of cobalt. Arch. Intern. Med., 150, 177–183.

252. Lauwerys, R. et al. (1994) Health risks associated with cobalt exposure–an overview. Sci. Total Environ., 150, 1–6.

253. De Boeck, M. et al. (2003) *In vivo* genotoxicity of hard metal dust: induction of micronuclei in rat type II epithelial lung cells. Carcinogenesis, 24, 1793–1800.

254. Duale, N. et al. (2009) Biomarkers of human exposure to acrylamide and relation to polymorphisms in metabolizing genes. Toxicol. Sci., 108, 90–99.

255. Myhr, B.C. (1991) Validation studies with Muta Mouse: a transgenic mouse model for detecting mutations *in vivo*. Environ. Mol. Mutagen., 18, 308–315.

256. National Toxicology Program (2012) Toxicology and carcinogenesis studies of acrylamide (CASRN 79-06-1) in F344/N rats and B6C3F1 mice (feed and drinking water studies). Natl. Toxicol. Program Tech. Rep. Ser., 1–234.

257. European Food Safety Association (2006) Opinion of the scientific panel on food additives, flavourings, processing aids and materials in contact with food on a request from the commission related to 2,2-BIS(4-HYDROXYPHENYL)PROPANE (bisphenol A). EFSA J., 428, 1–75.

258. US Food and Drug Administration (2009) Exposure to Bisphenol A (BPA) for Infants, Toddlers and Adults from the Consumption of Infant Formula, Toddler Food and Adult (Canned) Food. Food and Drug Administration, Washington, DC

259. Japanese National Institute of Advanced Industrial Science and Technology (2011) Bisphenol A (BPA) Risk Assessment Report.

260. Lehmann, L. et al. (2004) Bisphenol A and its methylated congeners inhibit growth and interfere with microtubules in human fibroblasts *in vitro*. Chem. Biol. Interact., 147, 273–285.

261. Johnson, G.E. et al. (2008) Mechanistic investigations of low dose exposures to the genotoxic compounds bisphenol-A and rotenone. Mutat. Res., 651, 56–63.

262. Welshons, W.V. et al. (2006) Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology, 147, S56–S69.

263. Vandenberg, L.N. et al. (2006) The mammary gland response to estradiol: monotonic at the cellular level, non-monotonic at the tissue-level of organization? J. Steroid Biochem. Mol. Biol., 101, 263–274.

264. Manikkam, M. et al. (2012) Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. PLoS One, 7, e31901.

265. Manikkam, M. et al. (2013) Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS One, 8, e55387.

266. Zhao, Y. et al. (2012) Occurrence and formation of chloro- and bromo-benzoquinones during drinking water disinfection. Water Res., 46, 4351–4360.

267. Qin, F. et al. (2010) A toxic disinfection by-product, 2,6-dichloro-1,4-benzoquinone, identified in drinking water. Angew. Chem. Int. Ed. Engl., 49, 790–792.

268. Zhao, Y. et al. (2010) Characterization and determination of chloro- and bromo-benzoquinones as new chlorination disinfection byproducts in drinking water. Anal. Chem., 82, 4599–4605.

269. Bolton, J.L. et al. (2000) Role of quinones in toxicology. Chem. Res. Toxicol., 13, 135–160.

270. Coulter, J.B. et al. (2013) Hydroquinone increases 5-hydroxymethylcytosine formation through ten eleven translocation 1 (TET1) 5-methylcytosine dioxygenase. J. Biol. Chem., 288, 28792–28800.

271. Elhajouji, A. et al. (2011) Potential thresholds for genotoxic effects by micronucleus scoring. Mutagenesis, 26, 199–204.

272. Ermler, S. et al. (2013) Seven benzimidazole pesticides combined at sub-threshold levels induce micronuclei *in vitro*. Mutagenesis, 28, 417–426.

273. Magdolenova, Z. et al. (2014) Mechanisms of genotoxicity. A review of *in vitro* and *in vivo* studies with engineered nanoparticles. Nanotoxicology, 8, 233–278.

274. Magdolenova, Z. et al. (2012) Can standard genotoxicity tests be applied to nanoparticles? J. Toxicol. Environ. Health A, 75, 800–806.

275. Saquib, Q. et al. (2013) Zinc ferrite nanoparticles activate IL-1b, NFKB1, CCL21 and NOS2 signaling to induce mitochondrial dependent intrinsic apoptotic pathway in WISH cells. Toxicol. Appl. Pharmacol., 273, 289–297.

276. Bhattacharya, K. et al. (2012) Reactive oxygen species mediated DNA damage in human lung alveolar epithelial (A549) cells from exposure to non-cytotoxic MFI-type zeolite nanoparticles. Toxicol. Lett., 215, 151–160.

277. Duan, J. et al. (2013) Toxic effect of silica nanoparticles on endothelial cells through DNA damage response via Chk1-dependent G2/M checkpoint. PLoS One, 8, e62087.

278. Wang, Z. et al. (2012) CuO nanoparticle interaction with human epithelial cells: cellular uptake, location, export, and genotoxicity. Chem. Res. Toxicol., 25, 1512–1521.

279. Govender, R. et al. (2013) Silver nanoparticles of Albizia adianthifolia: the induction of apoptosis in human lung carcinoma cell line. J. Nanobiotechnol., 11, 5.

280. Piao, M.J. et al. (2011) Silver nanoparticles induce oxidative cell damage in human liver cells through inhibition of reduced glutathione and induction of mitochondria-involved apoptosis. Toxicol. Lett., 201, 92–100.

281. Sharma, V. et al. (2012) Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2). Apoptosis, 17, 852–870.

282. Hussain, S. et al. (2010) Carbon black and titanium dioxide nanoparticles elicit distinct apoptotic pathways in bronchial epithelial cells. Part. Fibre Toxicol., 7, 10.

283. Jugan, M.L. et al. (2012) Titanium dioxide nanoparticles exhibit genotoxicity and impair DNA repair activity in A549 cells. Nanotoxicology, 6, 501–513.

284. Li, J.J. et al. (2011) Genomic instability of gold nanoparticle treated human lung fibroblast cells. Biomaterials, 32, 5515–5523.

285. Song, M.F. et al. (2012) Metal nanoparticle-induced micronuclei and oxidative DNA damage in mice. J. Clin. Biochem. Nutr., 50, 211–216.

286. Gonzalez, L. et al. (2014) Co-assessment of cell cycle and micronucleus frequencies demonstrates the influence of serum on the *in vitro* genotoxic response to amorphous monodisperse silica nanoparticles of varying sizes. Nanotoxicology, 8, 876–884.

287. Shi, Y. et al. (2010) Synergistic genotoxicity caused by low concentration of titanium dioxide nanoparticles and p,p'-DDT in human hepatocytes. Environ. Mol. Mutagen., 51, 192–204.

288. Wang, S. et al. (2011) Chronic exposure to nanosized, anatase titanium dioxide is not cyto- or genotoxic to Chinese hamster ovary cells. Environ. Mol. Mutagen., 52, 614–622.

289. Huang, S. et al. (2009) Disturbed mitotic progression and genome segregation are involved in cell transformation mediated by nano-TiO2 long-term exposure. Toxicol. Appl. Pharmacol., 241, 182–194.

290. Griffitt, R.J. et al. (2013) Chronic nanoparticulate silver exposure results in tissue accumulation and transcriptomic changes in zebrafish. Aquat. Toxicol., 130-131, 192–200.

291. Janssen, N.A. et al. (2011) Black carbon as an additional indicator of the adverse health effects of airborne particles compared with PM10 and PM2.5. Environ. Health Perspect., 119, 1691–1699.

292. Büchner, N. et al. (2013) Unhealthy diet and ultrafine carbon black particles induce senescence and disease associated phenotypic changes. Exp. Gerontol., 48, 8–16.

293. McCracken, J. et al. (2010) Annual ambient black carbon associated with shorter telomeres in elderly men: Veterans Affairs Normative Aging Study. Environ. Health Perspect., 118, 1564–1570.

294. Di, L.J. et al. (2013) Genome-wide profiles of CtBP link metabolism with genome stability and epithelial reprogramming in breast cancer. Nat. Commun., 4, 1449.

295. Wang, X.W. et al. (1996) The XPB and XPD DNA helicases are components of the p53-mediated apoptosis pathway. Genes Dev., 10, 1219–1232.

296. Chavakis, T. et al. (2009) A possible crosstalk between DNA repair pathways and angiogenesis. Cell Cycle, 8, 3438–3439.

297. Rich, T. et al. (2000) Defying death after DNA damage. Nature, 407, 777–783.

298. Kloor, M. et al. (2010) Immune evasion of microsatellite unstable colorectal cancers. Int. J. Cancer, 127, 1001–1010.

299. Pinto, A.R. et al. (2011) Telomere protein complexes and interactions with telomerase in telomere maintenance. Front. Biosci. (Landmark Ed)., 16, 187–207.

300. Slijepcevic, P. (2006) The role of DNA damage response proteins at telomeres–an "integrative" model. DNA Repair (Amst)., 5, 1299–1306.

301. Gocha, A.R. et al. (2013) Alternative mechanisms of telomere lengthening: permissive mutations, DNA repair proteins and tumorigenic progression. Mutat. Res., 743–744, 142–150.

302. Kim, Y.S. et al. (2013) Low production of reactive oxygen species and high DNA repair: mechanism of radioresistance of prostate cancer stem cells. Anticancer Res., 33, 4469–4474.

303. Nagathihalli, N.S. et al. (2011) RAD51 as a potential biomarker and therapeutic target for pancreatic cancer. Biochim. Biophys. Acta, 1816, 209–218.

304. Wierstra, I. (2013) FOXM1 (Forkhead box M1) in tumorigenesis: overexpression in human cancer, implication in tumorigenesis, oncogenic functions, tumor-suppressive properties, and target of anticancer therapy. Adv. Cancer Res., 119, 191–419.

305. Giannonatti, C. et al. (1987) Glioarchitectonics of the cerebellum of the lizard (Lacerta lepida Daudin). Ultrastructural study. J. Hirnforsch., 28, 701–705.

306. Yang, M.H. et al. (2007) Overexpression of NBS1 induces epithelial-mesenchymal transition and co-expression of NBS1 and Snail predicts metastasis of head and neck cancer. Oncogene, 26, 1459–1467.

307. Jaiswal, M. et al. (2000) Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res., 60, 184–190.

308. Volkmar, M. et al. (2012) DNA methylation profiling identifies epigenetic dysregulation in pancreatic islets from type 2 diabetic patients. EMBO J., 31, 1405–1426.

309. Silviera, M.L. et al. (2012) Epigenetic differences in normal colon mucosa of cancer patients suggest altered dietary metabolic pathways. Cancer Prev. Res. (Phila)., 5, 374–384.

310. Nan, H. et al. (2013) Pre-diagnostic leukocyte genomic DNA methylation and the risk of colorectal cancer in women. PLoS One, 8, e59455.

311. Nabilsi, N.H. et al. (2009) DNA methylation inhibits p53-mediated survivin repression. Oncogene, 28, 2046–2050.

312. Gopisetty, G. et al. (2006) DNA methylation and apoptosis. Mol. Immunol., 43, 1729–1740.

313. Murphy, T.M. et al. (2008) The emergence of DNA methylation as a key modulator of aberrant cell death in prostate cancer. Endocr. Relat. Cancer, 15, 11–25.

314. Lettini, A.A. et al. (2007) Epigenetic remodelling of DNA in cancer. Histol. Histopathol., 22, 1413–1424.

315. Sehouli, J. et al. (2011) Epigenetic quantification of tumor-infiltrating T-lymphocytes. Epigenetics, 6, 236–246.

316. Blasco, M.A. (2007) The epigenetic regulation of mammalian telomeres. Nat. Rev. Genet., 8, 299–309.

317. Itoh, Y. et al. (2013) Small-molecular modulators of cancer-associated epigenetic mechanisms. Mol. Biosyst., 9, 873–896.

318. Chen, M.F. et al. (2010) Role of DNA methyltransferase 1 in hormone-resistant prostate cancer. J. Mol. Med. (Berl)., 88, 953–962.

319. Wu, C.T. et al. (2011) Expression and function role of DNA methyltransferase 1 in human bladder cancer. Cancer, 117, 5221–5233.

320. Fadić, R. et al. (1988) Changes in contralateral synaptic acetylcholinesterase following motor nerve section in rats. Neurosci. Lett., 90, 229–233.

321. Sultanov, M.I.u. et al. (1987) [Modification of the fenestrated ophthalmic forceps for operations on the lacrimal points and canaliculi]. Vestn. Oftalmol., 103, 69–70.

322. Schetter, A.J. et al. (2010) Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. Carcinogenesis, 31, 37–49.

323. Kaelin, W.G Jr et al. (2013) Influence of metabolism on epigenetics and disease. Cell, 153, 56–69.

324. Lin, R. et al. (2014) Acetylation control of cancer cell metabolism. Curr Pharm Des, 20, 2627–2633.

325. Gupta, V. et al. (2014) Interplay between epigenetics & cancer metabolism. Curr Pharm Des, 20, 1706–1713.

326. Legube, G. et al. (2004) Role of the histone acetyl transferase Tip60 in the p53 pathway. J. Biol. Chem., 279, 44825–44833.

327. Wojciechowski, J. et al. (2003) Rapid onset of nucleolar disintegration preceding cell cycle arrest in roscovitine-induced apoptosis of human MCF-7 breast cancer cells. Int. J. Cancer, 106, 486–495.

328. Boix-Chornet, M. et al. (2006) Release of hypoacetylated and trimethylated histone H4 is an epigenetic marker of early apoptosis. J. Biol. Chem., 281, 13540–13547.

329. Allera, C. et al. (1997) The condensation of chromatin in apoptotic thymocytes shows a specific structural change. J. Biol. Chem., 272, 10817–10822.

330. Villagra, A. et al. (2010) Histone deacetylases and the immunological network: implications in cancer and inflammation. Oncogene, 29, 157–173.

331. Schoeftner, S. et al. (2010) Chromatin regulation and non-coding RNAs at mammalian telomeres. Semin. Cell Dev. Biol., 21, 186–193.

332. Toh, Y. et al. (2003) Histone H4 acetylation and histone deacetylase 1 expression in esophageal squamous cell carcinoma. Oncol. Rep., 10, 333–338.

333. Zhao, W. et al. (2011) Suppression of lung cancer cell invasion and metastasis by connexin43 involves the secretion of follistatin-like 1 mediated via histone acetylation. Int. J. Biochem. Cell Biol., 43, 1459–1468.

334. Taylor, M.D. et al. (2010) Combined proteasome and histone deacetylase inhibition attenuates epithelial-mesenchymal transition through E-cadherin in esophageal cancer cells. J. Thorac. Cardiovasc. Surg., 139, 1224–1232, 1232.e1.

335. Catalano, M.G. et al. (2012) Histone deacetylase inhibition modulates E-cadherin expression and suppresses migration and invasion of anaplastic thyroid cancer cells. J. Clin. Endocrinol. Metab., 97, E1150–E1159.

336. Byles, V. et al. (2012) SIRT1 induces EMT by cooperating with EMT transcription factors and enhances prostate cancer cell migration and metastasis. Oncogene, 31, 4619–4629.

337. Chen, J. et al. (2013) SIRT2 overexpression in hepatocellular carcinoma mediates epithelial to mesenchymal transition by protein kinase B/glycogen synthase kinase-3β/β-catenin signaling. Hepatology, 57, 2287–2298.

338. Rahman, I. et al. (2002) Oxidative stress and TNF-alpha induce histone acetylation and NF-kappaB/AP-1 activation in alveolar epithelial cells: potential mechanism in gene transcription in lung inflammation. Mol. Cell. Biochem., 234-235, 239–248.

339. Chen, B. et al. (2012) Roles of microRNA on cancer cell metabolism. J. Transl. Med., 10, 228.

340. Gao, P. et al. (2012) MicroRNAs and the Warburg Effect: new players in an old arena. Curr. Gene Ther., 12, 285–291.

341. Suh, S.O. et al. (2011) MicroRNA-145 is regulated by DNA methylation and p53 gene mutation in prostate cancer. Carcinogenesis, 32, 772–778.

342. Song, S.J. et al. (2013) The oncogenic microRNA miR-22 targets the TET2 tumor suppressor to promote hematopoietic stem cell self-renewal and transformation. Cell Stem Cell, 13, 87–101.

343. Subramanian, S. et al. (2010) MicroRNAs as gatekeepers of apoptosis. J. Cell. Physiol., 223, 289–298.

344. Li, C. et al. (2012) Apoptosis and microRNA aberrations in cancer. Clin. Exp. Pharmacol. Physiol., 39, 739–746.

345. Wang, W. et al. (2012) A frequent somatic mutation in CD274 3'-UTR leads to protein over-expression in gastric cancer by disrupting miR-570 binding. Hum. Mutat., 33, 480–484.

346. Koziel, J.E. et al. (2011) Medical genetics and epigenetics of telomerase. J. Cell. Mol. Med., 15, 457–467.

347. Sachdeva, M. et al. (2009) p53 represses c-Myc through induction of the tumor suppressor miR-145. Proc. Natl Acad. Sci. USA, 106, 3207–3212.

348. Manikandan, M. et al. (2014) Single nucleotide polymorphisms in microRNA binding sites of oncogenes: implications in cancer and pharmacogenomics. OMICS, 18, 142–154.

349. Goldschmidt, H. et al. (1986) [Sequelae of splenectomy]. Z. Arztl. Fortbild. (Jena), 80, 607–609.

350. Yan, J. et al. (2013) Regulation of mesenchymal phenotype by microRNAs in cancer. Curr. Cancer Drug Targets, 13, 930–934.

351. Bullock, M.D. et al. (2012) MicroRNAs: critical regulators of epithelial to mesenchymal (EMT) and mesenchymal to epithelial transition (MET) in cancer progression. Biol. Cell, 104, 3–12.

352. Mongroo, P.S. et al. (2010) The role of the miR-200 family in epithelial-mesenchymal transition. Cancer Biol. Ther., 10, 219–222.

353. Hurst, D.R. et al. (2009) Metastamir: the field of metastasis-regulatory microRNA is spreading. Cancer Res., 69, 7495–7498.

354. Verdoodt, B. et al. (2013) MicroRNA-205, a novel regulator of the anti-apoptotic protein Bcl2, is downregulated in prostate cancer. Int. J. Oncol., 43, 307–314.

355. Alexander, A. et al. (2010) ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. Proc. Natl Acad. Sci. USA, 107, 4153–4158.

356. Kim, H.R. et al. (2013) p53 regulates glucose metabolism by miR-34a. Biochem. Biophys. Res. Commun., 437, 225–231.

357. Méplan, C. et al. (2000) Redox signalling and transition metals in the control of the p53 pathway. Biochem. Pharmacol., 59, 25–33.

358. Nagini, S. et al. (2009) Of humans and hamsters: a comparative evaluation of carcinogen activation, DNA damage, cell proliferation, apoptosis, invasion, and angiogenesis in oral cancer patients and hamster buccal pouch carcinomas. Oral Oncol., 45, e31–e37.

359. Levy, L.S. et al. (1996) Mechanisms that contribute to the development of lymphoid malignancies: roles for genetic alterations and cytokine production. Crit. Rev. Immunol., 16, 31–57.

360. Hu, Z. et al. (2014) Induction of DNA damage and p21-dependent senescence by Riccardin D is a novel mechanism contributing to its growth suppression in prostate cancer cells in vitro and in vivo. Cancer Chemother Pharmacol, 73, 397–407.

361. Vanstapel, F. et al. (1986) Assay of mannose-6-phosphatase in untreated and detergent-disrupted rat-liver microsomes for assessment of integrity of microsomal preparations. Eur. J. Biochem., 156, 73–77.

362. Kuo, P.L. et al. (2011) CXCL5/ENA78 increased cell migration and epithelial-to-mesenchymal transition of hormone-independent prostate cancer by early growth response-1/snail signaling pathway. J. Cell. Physiol., 226, 1224–1231.

363. Salah, Z. et al. (2007) Transcriptional regulation of human protease-activated receptor 1: a role for the early growth response-1 protein in prostate cancer. Cancer Res., 67, 9835–9843.

364. Egerod, F.L. et al. (2009) High frequency of tumor cells with nuclear Egr-1 protein expression in human bladder cancer is associated with disease progression. BMC Cancer, 9, 385.

365. Li, Q. et al. (2011) Monocytes induce proximal tubular epithelial-mesenchymal transition through NF-kappa B dependent upregulation of ICAM-1. J. Cell. Biochem., 112, 1585–1592.

366. White, M. (1979) A new effect of pattern on perceived lightness. Perception, 8, 413–416.

367. Chua, H.L. et al. (2007) NF-kappaB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: potential involvement of ZEB-1 and ZEB-2. Oncogene, 26, 711–724.

368. Wiseman, H. et al. (1996) Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer. Biochem. J., 313(Pt 1), 17–29.

369. Sun, Y. et al. (2012) Molecular pathways: involving microenvironment damage responses in cancer therapy resistance. Clin. Cancer Res., 18, 4019–4025.

370. Giang, A.H. et al. (2013) Mitochondrial dysfunction and permeability transition in osteosarcoma cells showing the Warburg effect. J. Biol. Chem., 288, 33303–33311.

371. Guha, M. et al. (2013) Mitochondrial retrograde signaling at the crossroads of tumor bioenergetics, genetics and epigenetics. Mitochondrion, 13, 577–591.

372. Yoshida, S. et al. (2013) Molecular chaperone TRAP1 regulates a metabolic switch between mitochondrial respiration and aerobic glycolysis. Proc. Natl Acad. Sci. USA, 110, E1604–E1612.

373. Sutendra, G. et al. (2013) Mitochondrial activation by inhibition of PDKII suppresses HIF1a signaling and angiogenesis in cancer. Oncogene, 32, 1638–1650.

374. Wang, X. (2001) The expanding role of mitochondria in apoptosis. Genes Dev., 15, 2922–2933.

375. Villalba, M. et al. (2013) From tumor cell metabolism to tumor immune escape. Int. J. Biochem. Cell Biol., 45, 106–113.

376. Spanoudakis, E. et al. (2009) Regulation of multiple myeloma survival and progression by CD1d. Blood, 113, 2498–2507.

377. Passos, J.F. et al. (2007) Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence. PLoS Biol., 5, e110.

378. Deeb, D. et al. (2013) Inhibition of telomerase activity by oleanane triterpenoid CDDO-Me in pancreatic cancer cells is ROS-dependent. Molecules, 18, 3250–3265.

379. Romilda, C. et al. (2012) Oxidative DNA damage correlates with cell immortalization and mir-92 expression in hepatocellular carcinoma. BMC Cancer, 12, 177.

380. Boland, M.L. et al. (2013) Mitochondrial dysfunction in cancer. Front. Oncol., 3, 292.

381. Lee, S.Y. et al. (2012) Wnt/Snail signaling regulates cytochrome C oxidase and glucose metabolism. Cancer Res., 72, 3607–3617.

382. Meyrick Thomas, J. et al. (1987) Dyspepsia: the dilemma. Lancet, 2, 1151–1152.

383. Diers, A.R. et al. (2013) Mitochondrial bioenergetics of metastatic breast cancer cells in response to dynamic changes in oxygen tension: effects of HIF-1α. PLoS One, 8, e68348.

384. Srivastava, M. et al. (1990) Genomic organization and chromosomal localization of the human nucleolin gene. J. Biol. Chem., 265, 14922–14931.

385. Fleischmann, A. et al. (2012) Prognostic relevance of Bcl-2 overexpression in surgically treated prostate cancer is not caused by increased copy number or translocation of the gene. Prostate, 72, 991–997.

386. Choi, J. et al. (2005) Bcl-2 promotes invasion and lung metastasis by inducing matrix metalloproteinase-2. Cancer Res., 65, 5554–5560.

387. Kumar, P. et al. (2008) Endothelial cells expressing Bcl-2 promotes tumor metastasis by enhancing tumor angiogenesis, blood vessel leakiness and tumor invasion. Lab. Invest., 88, 740–749.

388. Zuo, J. et al. (2010) Bcl-2 overexpression induces a partial epithelial to mesenchymal transition and promotes squamous carcinoma cell invasion and metastasis. Mol. Cancer Res., 8, 170–182.

389. Koehler, B.C. et al. (2013) Beyond cell death - antiapoptotic Bcl-2 proteins regulate migration and invasion of colorectal cancer cells in vitro. PLoS One, 8, e76446.

390. Kamp, D.W. et al. (2011) Chronic inflammation and cancer: the role of the mitochondria. Oncology (Williston Park), 25, 400–10, 413.

391. Capparelli, C. et al. (2012) CTGF drives autophagy, glycolysis and senescence in cancer-associated fibroblasts via HIF1 activation, metabolically promoting tumor growth. Cell Cycle, 11, 2272–2284.

392. Amoedo, N.D. et al. (2011) Cell cycle and energy metabolism in tumor cells: strategies for drug therapy. Recent Pat. Anticancer Drug Discov., 6, 15–25.

393. Gjoerup, O.V. et al. (2007) Surveillance mechanism linking Bub1 loss to the p53 pathway. Proc. Natl Acad. Sci. USA, 104, 8334–8339.

394. King, K.L. et al. (1995) Cell cycle and apoptosis: common pathways to life and death. J. Cell. Biochem., 58, 175–180.

395. Pucci, B. et al. (2000) Cell cycle and apoptosis. Neoplasia, 2, 291–299.

396. Noh, K.H. et al. (2012) Nanog signaling in cancer promotes stem-like phenotype and immune evasion. J. Clin. Invest., 122, 4077–4093.

397. Ha, G.H. et al. (2012) Tankyrase-1 function at telomeres and during mitosis is regulated by Polo-like kinase-1-mediated phosphorylation. Cell Death Differ., 19, 321–332.

398. Aarts, M. et al. (2013) Tumour selective targeting of cell cycle kinases for cancer treatment. Curr. Opin. Pharmacol., 13, 529–535.

399. Hanahan, D. et al. (2000) The hallmarks of cancer. Cell, 100, 57–70.

400. Low, K.C. et al. (2013) Telomerase: central regulator of all of the hall-marks of cancer. Trends Biochem. Sci., 38, 426–434.

401. Artandi, S.E. et al. (2005) Pathways connecting telomeres and p53 in senescence, apoptosis, and cancer. Biochem. Biophys. Res. Commun., 331, 881–890.

402. Zhang, X. et al. (1999) Telomere shortening and apoptosis in telomerase-inhibited human tumor cells. Genes Dev., 13, 2388–2399.

403. Ishibashi, T. et al. (1998) Telomere loss in cells treated with cisplatin. Proc. Natl Acad. Sci. USA, 95, 4219–4223.

404. Lowe, S.W. et al. (2000) Apoptosis in cancer. Carcinogenesis, 21, 485–495.

405. Montes, C.L. et al. (2008) Tumor-induced senescent T cells with suppressor function: a potential form of tumor immune evasion. Cancer Res., 68, 870–879.

406. Liu, J.Y. et al. (2013) PinX1 suppresses bladder urothelial carcinoma cell proliferation via the inhibition of telomerase activity and p16/cyclin D1 pathway. Mol. Cancer, 12, 148.

407. Mokbel, K.M. et al. (2000) Telomerase activity and lymphovascular invasion in breast cancer. Eur. J. Surg. Oncol., 26, 30–33.

408. Kakeji, Y. et al. (2001) Gastric cancer with high telomerase activity shows rapid development and invasiveness. Oncol. Rep., 8, 107–110.

409. Bagheri, S. et al. (2006) Genes and pathways downstream of telomerase in melanoma metastasis. Proc. Natl Acad. Sci. USA, 103, 11306–11311.

410. Russell, J.C. (1992) Insulin resistance and atherosclerosis. CMAJ, 146, 951.

411. Ma, Y. et al. (2012) Effect of lead on apoptosis in cultured rat primary osteoblasts. Toxicol. Ind. Health, 28, 136–146.

412. Liu, J. et al. (2010) Lead affects apoptosis and related gene XIAP and Smac expression in the hippocampus of developing rats. Neurochem. Res., 35, 473–479.

413. Dribben, W.H. et al. (2011) Low-level lead exposure triggers neuronal apoptosis in the developing mouse brain. Neurotoxicol. Teratol., 33, 473–480.

414. Tchounwou, P.B. et al. (2004) Lead-induced cytotoxicity and transcriptional activation of stress genes in human liver carcinoma (HepG2) cells. Mol. Cell. Biochem., 255, 161–170.

415. Liu, C.M. et al. (2012) Protective role of quercetin against lead-induced inflammatory response in rat kidney through the ROS-mediated MAPKs and NF-κB pathway. Biochim. Biophys. Acta, 1820, 1693–1703.

416. Liu, C.M. et al. (2013) Protective effect of quercetin on lead-induced oxidative stress and endoplasmic reticulum stress in rat liver via the IRE1/JNK and PI3K/Akt pathway. Free Radic. Res., 47, 192–201.

417. Pan, J.J. et al. (2011) Activation of Akt/GSK3β and Akt/Bcl-2 signaling pathways in nickel-transformed BEAS-2B cells. Int. J. Oncol., 39, 1285–1294.

418. Azuma, K. et al. (2012) NDRG1/Cap43/Drg-1 may predict tumor angiogenesis and poor outcome in patients with lung cancer. J. Thorac. Oncol., 7, 779–789.

419. Freitas, M. et al. (2013) Nickel induces apoptosis in human neutrophils. Biometals, 26, 13–21.

420. Ding, J. et al. (2006) Nickel compounds render anti-apoptotic effect to human bronchial epithelial Beas-2B cells by induction of cyclooxygenase-2 through an IKKbeta/p65-dependent and IKKalpha- and p50-independent pathway. J. Biol. Chem., 281, 39022–39032.

421. Campbell, N.H. et al. (2012) Molecular basis of structure-activity relationships between salphen metal complexes and human telomeric DNA quadruplexes. J. Med. Chem., 55, 209–222.

422. Reed, J.E. et al. (2006) Stabilization of G-quadruplex DNA and inhibition of telomerase activity by square-planar nickel(II) complexes. J. Am. Chem. Soc., 128, 5992–5993.

423. Zhang, J. et al. (2013) The alteration of miR-222 and its target genes in nickel-induced tumor. Biol. Trace Elem. Res., 152, 267–274.

424. Dubois, F. et al. (1988) [A sure method of treatment of the pancreatic stump after cephalic duodenopancreatectomy: pancreaticogastric anastomosis]. Ann. Chir., 42, 319–321.

425. Ding, J. et al. (2009) TNF-alpha induction by nickel compounds is specific through ERKs/AP-1-dependent pathway in human bronchial epithelial cells. Curr. Cancer Drug Targets, 9, 81–90.

426. 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.

427. Xiao, L. et al. (2012) Induction of gastrin expression in gastrointestinal cells by hypoxia or cobalt is independent of hypoxia-inducible factor (HIF). Endocrinology, 153, 3006–3016.

428. Tanaka, T. et al. (2005) Cobalt promotes angiogenesis via hypoxia-inducible factor and protects tubulointerstitium in the remnant kidney model. Lab. Invest., 85, 1292–1307.

429. Chong, R. et al. (2009) Induction of germline apoptosis by cobalt and relevant signal transduction pathways in Caenorhabditis elegans. Toxicol. Mech. Methods, 19, 541–546.

430. Cai, G. et al. (2012) The effects of cobalt on the development, oxidative stress, and apoptosis in zebrafish embryos. Biol. Trace Elem. Res., 150, 200–207.

431. Dai, Z.J. et al. (2012) Up-regulation of hypoxia inducible factor-1α by cobalt chloride correlates with proliferation and apoptosis in PC-2 cells. J. Exp. Clin. Cancer Res., 31, 28.

432. 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.

433. Potnis, P.A. et al. (2013) Toll-like receptor 4 signaling pathway mediates proinflammatory immune response to cobalt-alloy particles. Cell. Immunol., 282, 53–65.

434. Zhang, B. et al. (2013) Cobalt chloride inhibits tumor formation in osteosarcoma cells through upregulation of HIF-1α. Oncol. Lett., 5, 911–916.

435. Barcia-Sanjurjo, I. et al. (2013) Sensitivity of the kinase activity of human vaccinia-related kinase proteins to toxic metals. J. Biol. Inorg. Chem., 18, 473–482.

436. Hou, L. et al. (2013) Induction of miR-21-PDCD4 signaling by tungsten carbide-cobalt nanoparticles in JB6 cells involves ROS-mediated MAPK pathways. J. Environ. Pathol. Toxicol. Oncol., 32, 41–51.

437. Sherwani, S.I. et al. (2013) Eicosanoid signaling and vascular dysfunction: methylmercury-induced phospholipase D activation in vascular endothelial cells. Cell Biochem. Biophys., 67, 317–329.

438. Shenker, B.J. et al. (1999) Induction of apoptosis in human T-cells by methyl mercury: temporal relationship between mitochondrial dysfunction and loss of reductive reserve. Toxicol. Appl. Pharmacol., 157, 23–35.

439. Shenker, B.J. et al. (2000) Mercury-induced apoptosis in human lymphoid cells: evidence that the apoptotic pathway is mercurial species dependent. Environ. Res., 84, 89–99.

440. Shenker, B.J. et al. (2002) Mercury-induced apoptosis in human lymphocytes: caspase activation is linked to redox status. Antioxid. Redox Signal., 4, 379–389.

441. Zefferino, R. et al. (2006) Role of tumour necrosis factor alpha and interleukin 1 beta in promoter effect induced by mercury in human keratinocytes. Int. J. Immunopathol. Pharmacol., 19(4 suppl), 15–20.

442. Kim, S.H. et al. (2002) Mercury inhibits nitric oxide production but activates proinflammatory cytokine expression in murine macrophage: differential modulation of NF-kappaB and p38 MAPK signaling pathways. Nitric Oxide, 7, 67–74.

443. Zefferino, R. et al. (2008) Mercury modulates interplay between IL-1beta, TNF-alpha, and gap junctional intercellular communication in keratinocytes: mitigation by lycopene. J. Immunotoxicol., 5, 353–360.

444. Santidrian, A.F. et al. (2013) Mitochondrial complex I activity and NAD+/NADH balance regulate breast cancer progression. J. Clin. Invest., 123, 1068–1081.

445. Ehlers, A. et al. (2013) Dose dependent molecular effects of acrylamide and glycidamide in human cancer cell lines and human primary hepatocytes. Toxicol. Lett., 217, 111–120.

446. Raju, J. et al. (2011) Dietary acrylamide does not increase colon aberrant crypt foci formation in male F344 rats. Food Chem. Toxicol., 49, 1373–1380.

447. Zhang, P. et al. (2014) Telomerase activity-independent function of telomerase reverse transcriptase is involved in acrylamide-induced neuron damage. Biotech Histochem, 89, 327–335.

448. Li, S.X. et al. (2006) Effect of subchronic exposure to acrylamide induced on the expression of bcl-2, bax and caspase-3 in the rat nervous system. Toxicology, 217, 46–53.

449. Sumizawa, T. et al. (2007) Apoptosis induced by acrylamide in SH-SY5Y cells. Arch. Toxicol., 81, 279–282.

450. Lafferty, J.S. et al. (2004) Subchronic acrylamide treatment induces a tissue-specific increase in DNA synthesis in the rat. Toxicol. Lett., 154, 95–103.

451. Klaunig, J.E. et al. (2005) Mechanisms of acrylamide induced rodent carcinogenesis. Adv. Exp. Med. Biol., 561, 49–62.

452. Chen, J.H. et al. (2013) Acrylamide-induced mitochondria collapse and apoptosis in human astrocytoma cells. Food Chem. Toxicol., 51, 446–452.

453. Song, J. et al. (2013) Protection of cyanidin-3-glucoside against oxidative stress induced by acrylamide in human MDA-MB-231 cells. Food Chem. Toxicol., 58, 306–310.

454. Jiang, Y. et al. (2014) Prenatal exposure to bisphenol A at the reference dose impairs mitochondria in the heart of neonatal rats. J Appl Toxicol, 34(9), 1012–1022.

455. 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.

456. 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.

457. Fillon, M. (2012) Getting it right: BPA and the difficulty proving environmental cancer risks. J. Natl Cancer Inst., 104, 652–655.

458. 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.

459. 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.

460. Terasaka, H. et al. (2005) Cytotoxicity and apoptosis-inducing activity of bisphenol A and hydroquinone in HL-60 cells. Anticancer Res., 25, 2241–2247.

461. 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.

462. Goodson, W.H. III 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.

463. Takahashi, A. et al. (2004) Bisphenol A from dental polycarbonate crown upregulates the expression of hTERT. J. Biomed. Mater. Res. B Appl. Biomater., 71, 214–221.

464. Hassan, Z.K. et al. (2012) Bisphenol A induces hepatotoxicity through oxidative stress in rat model. Oxid. Med. Cell. Longev., 2012, 194829.

465. Nocito, L. et al. (2012) Tungstate reduces the expression of gluconeogenic enzymes in STZ rats. PLoS One, 7, e42305.

466. Siegel, D. et al. (2012) NAD(P)H:quinone oxidoreductase 1 (NQO1) localizes to the mitotic spindle in human cells. PLoS One, 7, e44861.

467. Qiu, X.B. et al. (1998) Anticancer quinones induce pRb-preventable G2/M cell cycle arrest and apoptosis. Free Radic. Biol. Med., 24, 848–854.

468. Kogan, N.M. et al. (2006) A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. Mol. Pharmacol., 70, 51–59.

469. Shoieb, A.M. et al. (2003) *In vitro* inhibition of growth and induction of apoptosis in cancer cell lines by thymoquinone. Int. J. Oncol., 22, 107–113.

470. Xia, T. et al. (2004) Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. Environ. Health Perspect., 112, 1347–1358.

471. Emdadul Haque, M. et al. (2003) Apoptosis-inducing neurotoxicity of dopamine and its metabolites via reactive quinone generation in neuroblastoma cells. Biochim. Biophys. Acta, 1619, 39–52.

472. Lee, C.C. et al. (2012) Design, synthesis and evaluation of telomerase inhibitory, hTERT repressing, and anti-proliferation activities of symmetrical 1,8-disubstituted amidoanthraquinones. Eur. J. Med. Chem., 50, 102–112.

473. Lee, C.C. et al. (2012) Synthesis, antiproliferative activities and telomerase inhibition evaluation of novel asymmetrical 1,2-disubstituted amidoanthraquinone derivatives. Eur. J. Med. Chem., 47, 323–336.

474. Soares, J. et al. (2011) ortho-Quinone tanshinones directly inhibit telomerase through an oxidative mechanism mediated by hydrogen peroxide. Bioorg. Med. Chem. Lett., 21, 7474–7478.

475. Huang, F.C. et al. (2012) Synthesis, telomerase evaluation and anti-proliferative studies on various series of diaminoanthraquinone-linked aminoacyl residue derivatives. Arch. Pharm. (Weinheim), 345, 101–111.

476. Gurung, R.L. et al. (2010) Thymoquinone induces telomere shortening, DNA damage and apoptosis in human glioblastoma cells. PLoS One, 5, e12124.

477. Liu, X.D. et al. (2010) Down-regulation of telomerase activity and activation of caspase-3 are responsible for Tanshinone I-induced apoptosis in monocyte leukemia cells *in vitro*. Int. J. Mol. Sci., 11, 2267–2280.

478. Rajput, S. et al. (2013) Targeted apoptotic effects of thymoquinone and tamoxifen on XIAP mediated Akt regulation in breast cancer. PLoS One, 8, e61342.

479. Deng, R. et al. (2010) SYUNZ-16, a newly synthesized alkannin derivative, induces tumor cells apoptosis and suppresses tumor growth through inhibition of PKB/AKT kinase activity and blockade of AKT/FOXO signal pathway. Int. J. Cancer, 127, 220–229.

480. Sanderson, S. et al. (2006) Benzoquinone ansamycin heat shock protein 90 inhibitors modulate multiple functions required for tumor angiogenesis. Mol. Cancer Ther., 5, 522–532.

481. Koga, F. et al. (2007) Low dose geldanamycin inhibits hepatocyte growth factor and hypoxia-stimulated invasion of cancer cells. Cell Cycle, 6, 1393–1402.

482. Cavalieri, E.L. et al. (1997) Molecular origin of cancer: catechol estrogen-3,4-quinones as endogenous tumor initiators. Proc. Natl Acad. Sci. USA, 94, 10937–10942.

483. Lombaert, N. et al. (2013) Hard-metal (WC-Co) particles trigger a signaling cascade involving p38 MAPK, HIF-1α, HMOX1, and p53 activation in human PBMC. Arch. Toxicol., 87, 259–268.

484. Guilbert, C. et al. (2011) Exposure to tungsten induces DNA damage and apoptosis in developing B lymphocytes. Leukemia, 25, 1900–1904.

485. Lombaert, N. et al. (2004) Evaluation of the apoptogenic potential of hard metal dust (WC-Co), tungsten carbide and metallic cobalt. Toxicol. Lett., 154, 23–34.

486. Kelly, A.D. et al. (2013) *In vivo* tungsten exposure alters B-cell development and increases DNA damage in murine bone marrow. Toxicol. Sci., 131, 434–446.

487. Podder, B. et al. (2012) Antioxidant effect of silymarin on paraquat-induced human lung adenocarcinoma A549 cell line. Food Chem. Toxicol., 50, 3206–3214.

488. Lee, T.B. et al. (2003) Differential induction of Mn-containing superoxide dismutase by paraquat in peripheral lymphocytes of normal subjects and gastric cancer patients. Mol. Cells, 16, 13–18.

489. Spiegelman, B.M. (2007) Transcriptional control of mitochondrial energy metabolism through the PGC1 coactivators. Novartis Found. Symp., 287, 60–63; discussion 63.

490. Yang, W. et al. (2008) Paraquat-induced apoptosis in human neuroblastoma SH-SY5Y cells: involvement of p53 and mitochondria. J. Toxicol. Environ. Health A, 71, 289–299.

491. Rio, M.J. et al. (2008) Paraquat induces apoptosis in human lymphocytes: protective and rescue effects of glucose, cannabinoids and insulin-like growth factor-1. Growth Factors, 26, 49–60.

492. González-Polo, R.A. et al. (2004) Paraquat-induced apoptotic cell death in cerebellar granule cells. Brain Res., 1011, 170–176.

493. Chang, X. et al. (2013) Paraquat inhibits cell viability via enhanced oxidative stress and apoptosis in human neural progenitor cells. Chem. Biol. Interact., 206, 248–255.

494. Paolillo, N. et al. (2011) Effects of paraquat and capsaicin on the expression of genes related to inflammatory, immune responses and cell death in immortalized human HaCat keratinocytes. Int. J. Immunopathol. Pharmacol., 24, 861–868.

495. 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.

496. Sha, B. et al. (2013) Potential application of titanium dioxide nanoparticles in the prevention of osteosarcoma and chondrosarcoma recurrence. J. Nanosci. Nanotechnol., 13, 1208–1211.

497. Fröhlich, E. (2013) Cellular targets and mechanisms in the cytotoxic action of non-biodegradable engineered nanoparticles. Curr. Drug Metab., 14, 976–988.

498. Shi, H. et al. (2013) Titanium dioxide nanoparticles: a review of current toxicological data. Part. Fibre Toxicol., 10, 15.

499. Gui, S. et al. (2013) Intragastric exposure to titanium dioxide nanoparticles induced nephrotoxicity in mice, assessed by physiological and gene expression modifications. Part. Fibre Toxicol., 10, 4.

500. Shukla, R.K. et al. (2011) Titanium dioxide nanoparticles induce oxidative stress-mediated apoptosis in human keratinocyte cells. J. Biomed. Nanotechnol., 7, 100–101.

501. Botelho, M.C. et al. (2014) Effects of titanium dioxide nanoparticles in human gastric epithelial cells in vitro. Biomed. Pharmacother, 68, 59–64.

502. Hiroike, M. et al. (2013) Acicular, but not globular, titanium dioxide nanoparticles stimulate keratinocytes to produce pro-inflammatory cytokines. J. Dermatol., 40, 357–362.

503. Cui, Y. et al. (2011) Signaling pathway of inflammatory responses in the mouse liver caused by TiO2 nanoparticles. J. Biomed. Mater. Res. A, 96, 221–229.

504. Staub, R.E. et al. (1998) Mechanism for benomyl action as a mitochondrial aldehyde dehydrogenase inhibitor in mice. Chem. Res. Toxicol., 11, 535–543.

505. Ehteda, A. et al. (2013) Combination of albendazole and 2-methoxyestradiol significantly improves the survival of HCT-116 tumor-bearing nude mice. BMC Cancer, 13, 86.

506. Rathinasamy, K. et al. (2008) Kinetic stabilization of microtubule dynamic instability by benomyl increases the nuclear transport of p53. Biochem. Pharmacol., 76, 1669–1680.

507. Sakr, S.A. et al. (2014) Carbendazim-induced testicular damage and oxidative stress in albino rats: ameliorative effect of licorice aqueous extract. Toxicol. Ind. Health, 30, 259–267.

508. Morinaga, H. et al. (2004) A benzimidazole fungicide, benomyl, and its metabolite, carbendazim, induce aromatase activity in a human ovarian granulose-like tumor cell line (KGN). Endocrinology, 145, 1860–1869.

509. Jia, L. et al. (2003) Carbendazim: disposition, cellular permeability, metabolite identification, and pharmacokinetic comparison with its nanoparticle. J. Pharm. Sci., 92, 161–172.

510. Vandhana, S. et al. (2010) Evaluation of suitable solvents for testing the anti-proliferative activity of triclosan - a hydrophobic drug in cell culture. Indian J. Biochem. Biophys., 47, 166–171.

511. Deepa, P.R. et al. (2010) Chemical inhibition of fatty acid synthase: molecular docking analysis and biochemical validation in ocular cancer cells. J. Ocul. Biol. Dis. Infor., 3, 117–128.

512. Stratul, S.I. et al. (2009) Antimicrobial agents in periodontal disease therapy: rationale and use of the triclosan-PVM/MA copolymer in the management of gingivitis. Data from a consensus report. Part I. Timisoara Med. J., 95, 105–108.

513. 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(2 Pt 1), 628–636.

514. Gee, R.H. et al. (2008) Oestrogenic and androgenic activity of triclosan in breast cancer cells. J. Appl. Toxicol., 28, 78–91.

515. Tamura, I. et al. (2012) Triclosan, an antibacterial agent, increases intracellular Zn(2+) concentration in rat thymocytes: its relation to oxidative stress. Chemosphere, 86, 70–75.

516. Cullinan, M.P. et al. (2012) Long term use of triclosan toothpaste and thyroid function. Sci. Total Environ., 416, 75–79.

517. Schreiber, N. et al. (2013) Lung alterations following single or multiple low-dose carbon black nanoparticle aspirations in mice. J. Toxicol. Environ. Health A, 76, 1317–1332.

518. Chang, C.C. et al. (2005) The induction of vascular endothelial growth factor by ultrafine carbon black contributes to the increase of alveolar-capillary permeability. Environ. Health Perspect., 113, 454–460.

519. Driscoll, K.E. et al. (1996) Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. Toxicol. Appl. Pharmacol., 136, 372–380.

520. Knaapen, A.M. et al. (2004) Inhaled particles and lung cancer. Part A: mechanisms. Int. J. Cancer, 109, 799–809.

521. Saunders, M.J. (1990) Pharmacotherapeutic management of geriatric patients. Tex. Dent. J., 107, 11–14.

522. Shoji, Y. et al. (2000) Quantification of telomerase activity in sporadic colorectal carcinoma: association with tumor growth and venous invasion. Cancer, 88, 1304–1309.

523. Kanamaru, T. et al. (1999) Clinical implications of telomerase activity in resected hepatocellular carcinoma. Int. J. Mol. Med., 4, 267–271.

524. Wild, C.P. (2005) Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol. Biomarkers Prev., 14, 1847–1850.

525. Linschooten, J.O. et al. (2013) Paternal lifestyle as a potential source of germline mutations transmitted to offspring. FASEB J., 27, 2873–2879.

526. Donaldson, S.G. et al. (2010) Environmental contaminants and human health in the Canadian Arctic. Sci. Total Environ., 408, 5165–5234.

527. Laender, F.D. et al. (2011) Combining monitoring data and modeling identifies PAHs as emerging contaminants in the arctic. Environ. Sci. Technol., 45, 9024–9029.

528. Kortenkamp, A. et al. (2007) Low-level exposure to multiple chemicals: reason for human health concerns? Environ. Health Perspect., 115(suppl. 1), 106–114.

529. Poirier, M.C. (2012) Chemical-induced DNA damage and human cancer risk. Discov. Med., 14, 283–288.

530. Anwar-Mohamed, A. et al. (2009) Regulation of CYP1A1 by heavy metals and consequences for drug metabolism. Expert Opin. Drug Metab. Toxicol., 5, 501–521.

531. Adami, H.O. et al. (1993) Increasing cancer risk in younger birth cohorts in Sweden. Lancet, 341, 773–777.

532. Ries, L.A.G. et al. (1999) SEER Cancer Statistics Review, 1977–1996. National Cancer Institute, Bethesda, MD.

533. Sasco, A. (2008) Cancer and globalization. Biomed. Pharmacother, 62, 110–121.

534. Clapp, R.W. et al. (2007) Environmental and occupational causes of cancer: a call to act on what we know. Biomed. Pharmacother., 61, 631–639.

535. Goodman, M. et al. (2012) Cancer clusters in the USA: what do the last twenty years of state and federal investigations tell us? Crit. Rev. Toxicol., 42, 474–490.

536. Perera, F. et al. (2002) In utero DNA damage from environmental pollution is associated with somatic gene mutation in newborns. Cancer Epidemiol. Biomarkers Prev., 11(10 Pt 1), 1134–1137.

537. Kotova, N. et al. (2014) Differences in micronucleus frequency and acrylamide adduct levels with hemoglobin between vegetarians and non-vegetarians. Eur J Nutr. [Epub ahead of print].

538. Crump, K.S. (2012) Meta-analysis of evidence for hormesis in animal radiation carcinogenesis, including a discussion of potential pitfalls in statistical analyses to detect hormesis. J Toxicol Environ Health B Crit Rev., 15(3):210–231.

539. Quak, S.H. (1991) Pre-liver transplantation management of children. Ann. Acad. Med. Singapore, 20, 534–539.