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Unravelling the molecular mechanism of mutagenic factors impacting human health

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Abstract

Environmental mutagens are chemical and physical substances in the environment that has a potential to induce a wide range of mutations and generate multiple physiological, biochemical, and genetic modifications in humans. Most mutagens are having genotoxic effects on the following generation through germ cells. The influence of germinal mutations on health will be determined by their frequency, nature, and the mechanisms that keep a specific mutation in the population. Early prenatal lethal mutations have less public health consequences than genetic illnesses linked with long-term medical and social difficulties. Physical and chemical mutagens are common mutagens found in the environment. These two environmental mutagens have been associated with multiple neurological disorders and carcinogenesis in humans. Thus in this study, we aim to unravel the molecular mechanism of physical mutagens (UV rays, X-rays, gamma rays), chemical mutagens (dimethyl sulfate (DMS), bisphenol A (BPA), polycyclic aromatic hydrocarbons (PAHs), 5-chlorocytosine (5ClC)), and several heavy metals (Ar, Pb, Al, Hg, Cd, Cr) implicated in DNA damage, carcinogenesis, chromosomal abnormalities, and oxidative stress which leads to multiple disorders and impacting human health. Biological tests for mutagen detection are crucial; therefore, we also discuss several approaches (Ames test and Mutatox test) to estimate mutagenic factors in the environment. The potential risks of environmental mutagens impacting humans require a deeper basic knowledge of human genetics as well as ongoing research on humans, animals, and their tissues and fluids.

Keywords Mutagens · Mutagenic factors · Metals · Ames test · DNA damage · Toxicity · Human health

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Introduction

Mutagens are substances that induce DNA damage and alterations in the DNA sequence. Organisms effectively restore damaged DNA, but complications occur when the damage is not repaired before the cell duplicates (Minamoto et al. 1999). When the life system undergoes mutagenesis, mutagenic substances in the environment have the potential to generate physiological, biochemical, and genetic modifications in all species. Environmental contamination is gaining noteworthy consciousness due to various anthropogenic, natural, and human sources such as volcanic eruptions, inefficient combustion of fossil fuels, oil spills, industrial emissions, process of smelting, incineration, coal scorching, and outpouring from motor vehicles; heavy metals discharged into the environment combined with other environmental stresses have adverse impacts on human and aquatic life (Lu et al. 2021; Wu et al. 2015; Mouchet et al. 2006; Iwegbue et al. 2016; Wang et al. 2004; Wang et al. 2018). Recent investigations reveals that chemical mutagens observed in the environment may cause alterations at both genomic and proteomic levels. Chemical mutagens (cigarette smoke, dietary contaminants, mycotoxin aflatoxin B1, DNA alkylating agents) and physical mutagens (X-rays, UV irradiation, asbestos, radon, infectious pathogens like bacteria and viruses, such as *Helicobacter pylori*, human papilloma virus, and human hepatitis B and C viruses), as well as lifestyle factors (sunlight exposure), are recognized as critical environmental factors that lead to the development of multiple diseases as shown in Figs. 1, 2, and 3 as reported by a group of researchers (Li et al. 2020; Foster et al. 1983; Hsu et al. 1991). Physical mutagens like ultraviolet (UV) radiation begin a chemical bonding process connecting two substances nearby bases of pyrimidine (CC, TC, CT, and TT) to create dimers of pyrimidine that cause DNA damage. In contrast, ionizing radiation primarily influences the hematopoietic characteristics observed in animals and humans (Rozgaj et al. 1999; Taqi et al. 2018). Chemical mutagens such as dimethyl sulfate (DMS), bisphenol A (BPA), polycyclic aromatic hydrocarbons (PAHs), and 5-chlorocytosine (5ClC) chemical proved hazardous to humans, and generate ROS, creating mutations, chromosomal abnormalities, carcinogenicity, genotoxicity, and distinct genetic changes that have been associated with a broad range of acute and chronic health effects in humans (Zhu et al. 2015; Grimalt et al. 2004; Pribylova et al. 2012; Nekhavhambe et al. 2014). Various heavy metals toxicants such as Cr, Pb, Hg, Cd, As, and Al induced DNA damage with the cell and responsible for generation of neurological disorders in humans. UV-related CT and CCTT conversion, GT modifications produced by dietary aflatoxin B1 exposure, GT and GC mutations linked with tobacco-derived carcinogens, and AT and TA modifications linked with vinyl chloride exposure are also instances of hallmark mutations.

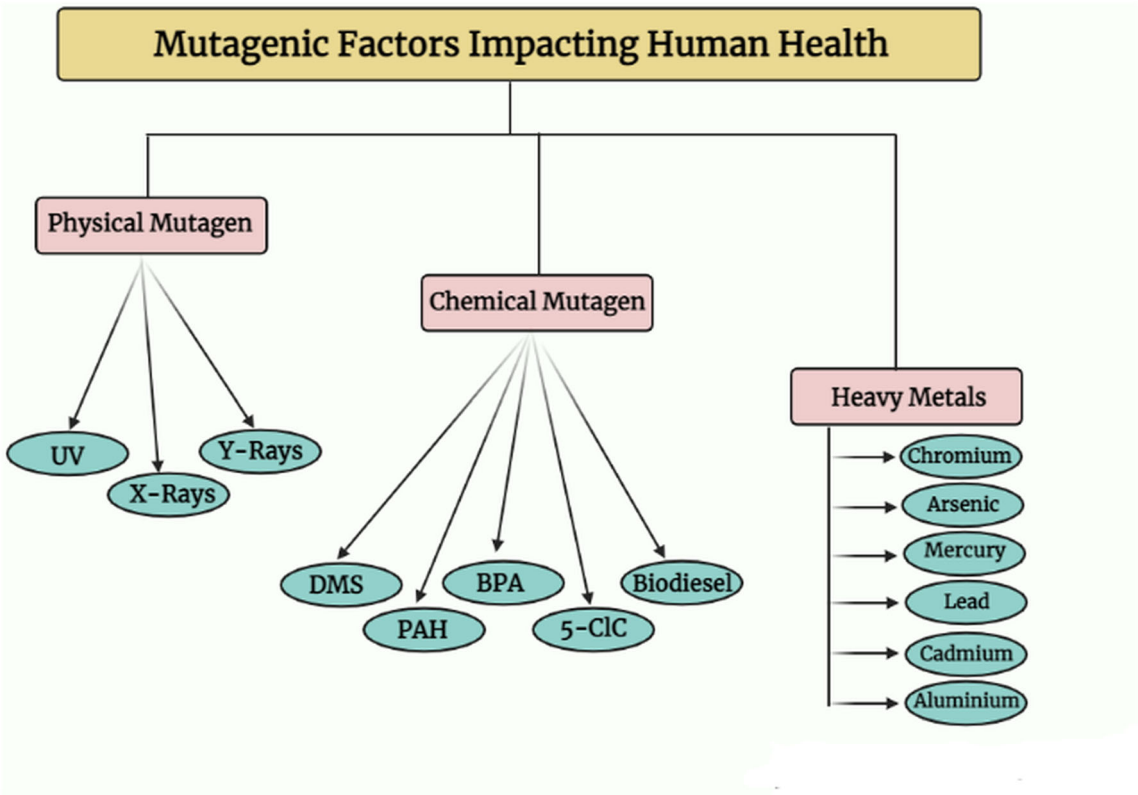

Fig. 1 Classification and mechanism of environmental mutagens impacting human health

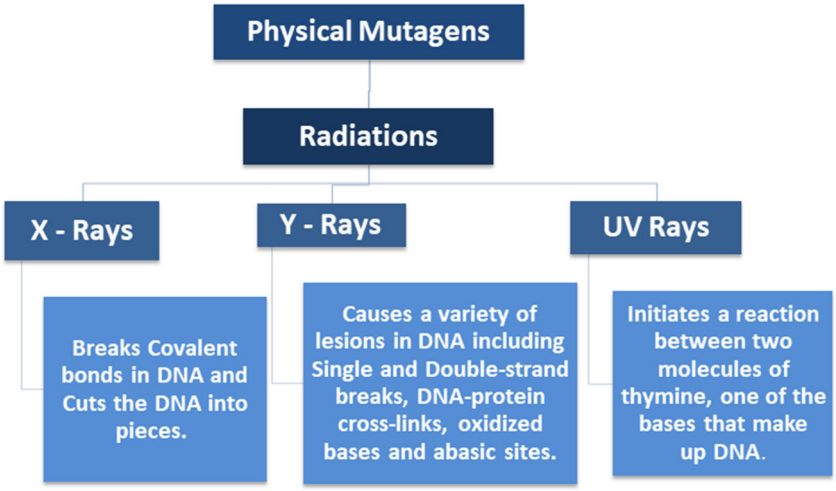

Fig. 2 Shows the molecular mechanisms of physical mutagens in environment

The discovery of so-called signature mutations has given evidence linking certain environmental variables to the mutation spectrum associated with tumorigenesis (Hsu et al. 1991; Foster et al. 1983; Denissenko et al. 1996; Spruck et al. 1993). Food also carries mutagens ranging from heterocyclic amines created by barbecuing meats to aflatoxin generated by certain fungal diseases of cereals and peanuts (Rosette and Karin 1996). Exogenous mutagens may also be observed at the workplace and home. In the year 1775, the first report of occupational cancer caused by mutagens in the workplace was observed among males who worked as chimney sweeps that release polycyclic aromatic hydrocarbons known as DNA-damaging agents. Over time, the extended exposure of hydrocarbons caused damaging of DNA and successive mutations, which triggered the emergence of cancer in the scrotum (Palmer and Paulson 1997). Human feces include a family of carcinogenic chemicals called as fecapentaenes, and the foremost type of fecapentaenes are fecapentaene-14 as well as fecapentaene-12. These fecapentaenes are lipid-dissolvable, straight-acting frameshift and base pair mutagens seem to be produced by gut bacteria. Escalated exchanges of sister chromatid, oxidative destruction, and mutagenesis of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) are also caused by fecapentaene-12. Salts of bile

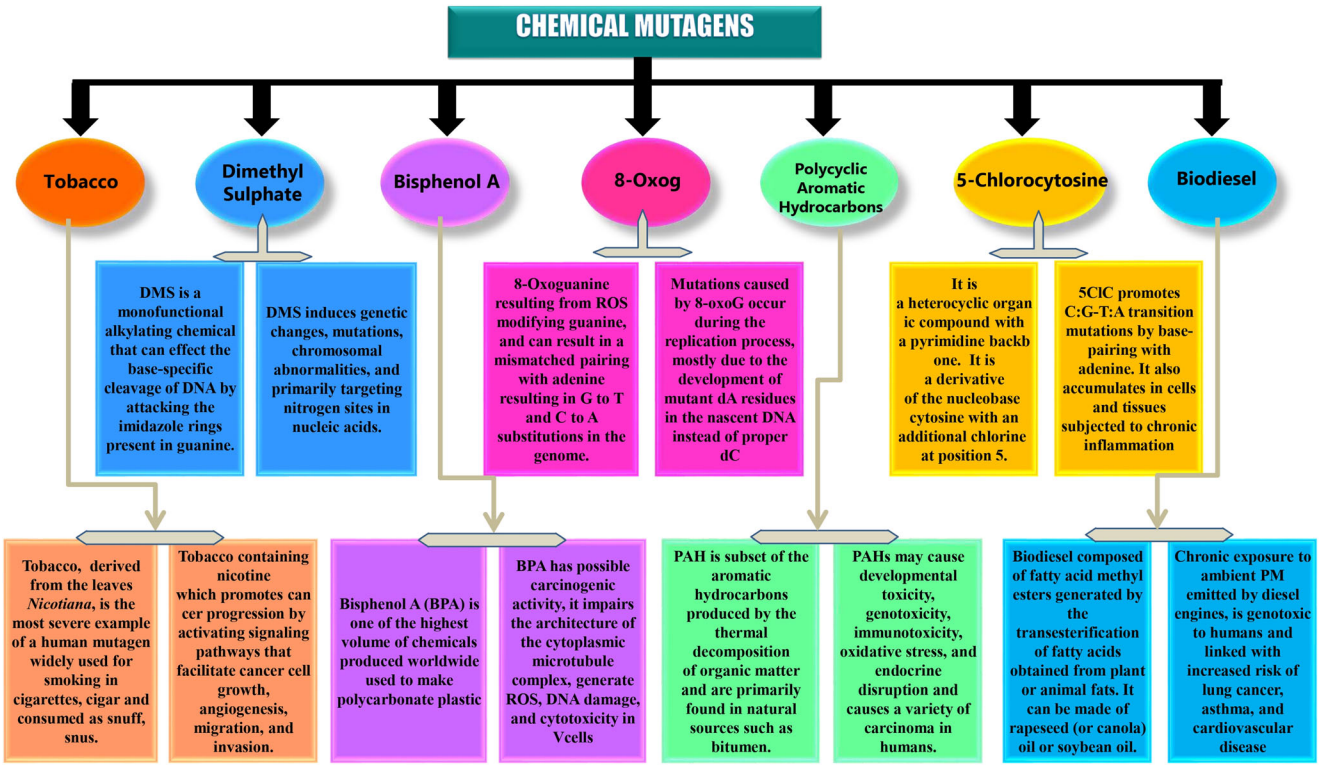

Fig. 3 Shows the molecular mechanisms of chemical mutagens in environment

were shown to increase overall capability of fecapentaenes-14 as well as -12 to activate repair of DNA in the bacteria and highlight the significance of high-fat, low-fiber diets for colon cancer development (Schrader and Cooke 2003). This review discusses the molecular mechanism of physical mutagens, chemical mutagens, and several heavy metals involved in DNA damage, carcinogenesis, chromosomal abnormalities, and oxidative stress, which lead to complicated ailments and influencing human health. Biological tests for mutagen detection are essential; hence, we also elaborated several methods (Ames test and Mutatox test) to evaluate mutagenic factors in the environment.

Molecular mechanisms of mutagens in environment impacting human health

Physical mutagens (UV rays, X-rays, gamma rays)

Sunlight and UV rays

Molecular mechanisms of physical mutagens in the environment are shown in Fig. 2, the absorption of sunlight directly causes DNA damage, and ultraviolet radiation (UVR) may be an initial genotoxic factor in the environment. Ultraviolet radiation (UVR) exhibits varied effects impacting human health, as explained in Table 1, and it can cause mutagenic DNA damage in the skin. The induction of DNA damage by UV radiation from the sun is an important event in the development of skin malignancies. UV radiation (UVR) is a key environmental stressor for the skin. UVR is made up of three wavelengths: UV-C (200–280 nm), UV-B (280–315 nm), and UV-A (315–400 nm). UV-C and short UV-B (<295 nm) are particularly damaging to cells, although the ozone layer prevents them (Gary and Rochette 2020; Courdavault et al. 2005; Chelladurai et al. 2020). As previously stated, a 10% reduction in total stratospheric ozone concentration enhances UV radiation at 305, 290, and 287 nm by 20, 250, and 500%, respectively (Misra et al. 2002). Sunlight's mutagenicity and lethality action spectra have two maxima, both in the UV section of the spectrum. The majority of the chemical effects of UVB light on DNA are explained by the conception of dimeric photoproducts involving two neighboring pyrimidine nucleotides (Ravanat et al. 2001). Pyrimidine dimers inhibit most of the DNA polymerases; despite the translesion, DNA polymerases avoid damaging of DNA through incorporation of dAMP contrary to the lesion. Incorporating dAMP opposite to the template T is proper; however, incorporating dAMP opposing to the template C is improper. Although the translesion's replication permits replication of chromosome to proceed, in pyrimidine dimers, the presence of dAMP opposing template C leads in an AT base pair swap rather than the appropriate GC base pair. Translesion duplication of a -CC- dimer of pyrimidine resulted in base pair changes from GC to AT (Brash 1997). Recent in vitro and in vivo studies revealed p53 gene alterations in UV-exposed skin cells (Nakazawa et al. 1994). Additional investigations have observed that p53 mutation spectra in squamous cell carcinomas of the skin were considered distinct from those seen in internal tumors and remained consistent with the occurrence of CT transitions or CC to TT transitions at sites of dipyrimidine photoproducts, wherein the predominance of CCTT double transitions is thus clearly a sunlight-induced phenomenon. UVC causes skin layer destruction, interfering with chloragogen and epithelial development in intestinal tissues. Furthermore, UV-C induces DNA damage, followed by overexpression of H2AX, a crucial protein implicated in causing DNA repair mechanisms, in a dose-dependent way. Multiple findings illustrate that UVC-induced DNA damage is directly proportional to H2AX expression. The genomic impacts of UV-C light exposure occur through a variety of pathways, the most prominent of which are charge transfer via

Table 1 Shows the multiple effects of ultraviolet radiation (UVR) impacting human health

The effects of UVA and UVB exposure	Biomarkers	References
Induction of transcription factors	NF-kB, Nrf-2, AP-1	Mineshiba et al. 2005; Muthusamy and Piva 2010; Schafer and Werner 2015; Raval et al. 2012
Synthesis of vitamin D	Presence of	25-hydroxyvitamin D in the serum
Holick 1999; Webb et al. 1988		
Swelling	Cytokines (IL-1, TNF-alpha, IL-12, IL-10, and IL-6) COX-2	Syed et al. 2012; Bermudez et al. 2000; Farrukh et al. 2015
Modification of microenvironment	Breakdown of collagen	Yamaba et al. 2016
Redox process	Oxidation of biomolecules	Douki et al. 2003; Cadet et al. 2015; Sage et al. 2012
Damaging of DNA	Oxidized bases, CPD, breaks in single strand, 6-4PP	Douki et al. 2003; Mouret et al. 2006; Schuch et al. 2009
Cell death	Necrosis and apoptosis	Cortat et al. 2013; Batista et al. 2009; Kaufmann and Cleaver 1981; Shindo and Hashimoto 1998
Immunosuppression	IL-10, prostaglandins	Boonstra et al. 2000; Halliday 2005; Ullrich 1994; Nishigori et al. 1996

endogenous chromophores to DNA modifying molecules or direct photon absorption by nitrogenous bases (Sanchez-Navarrete et al. 2020). Apparently, photo-excited configurations of DNA bases that play a role in the predictable outcomes of damage production were illustrated (Markovitsi 2016). The condensation state of the DNA also influences the creation of these pyrimidine dimers. Dipyrimidine photoproducts in sunlight-induced mutagenesis and carcinogenesis, such as cyclobutane pyrimidine dimers (CPD), pyrimidine (6-4), pyrimidone photoproducts (P6-4P), and Dewar photoisomers of P6-4P, are neighboring pyrimidine bases following direct absorption of UVB photons by DNA (Sage et al. 1996). CPDs may develop in both euchromatin and heterochromatin areas, but 6-4PPs can only evolve in euchromatin (Han et al. 2016). Moreover, 5-methylcytosine, loops of G-quadruplex, and telomeres are vulnerable to the generation of CPD. CPDs (cyclobutane pyrimidine dimers) are generated by two covalent connections produced by Frenkel excitons in between carbon atoms C5 and C6 of adjacent bases of nitrogen, resulting in a diastereomeric ring consisting of four components. In the double helix, the cis-syn isomer is more varied than with the trans-syn isomer, whereas the trans-syn isomer predominates in the single-stranded DNA. A charge-transfer connection seen between 5′-end C6 and the 3′-end C4 carbons of nearby pyrimidines produces 6-4PPs, while oxetane and azetidine refinements (unbalanced intermediate) occur when the 3′-end is C or T, accordingly (Markovitsi 2016; Cadet et al. 2012). CPD is a 4-carbon cyclic and rigid ring which is less distortionary than 6-4PP (Taylor et al. 1990; Rastogi et al. 2010; Lee et al. 1998). The intramolecular four electrocyclizations of the pyrimidone ring following photon absorption contribute to just the conversion of 6-4PPs into the isomers of Dewar valence (Perdiz et al. 2010; Douki 2016). A photochemical interaction with an excited state singlet is proposed as the mechanism. The formation of Dewar isomers necessitates the use of two photons: one to stimulate the formation of the 6-4PP and the other to isomerize such DNA lesion. In this case, the second photon is somewhat more expected to be in the UVA range, which is poorly absorbed by ordinary DNA bases but quickly absorbed by 6-4PPs; this is essential for isomerization into the Dewar state. The pyrimidone moiety of 6-4PPs absorbs at around 320 nm: 315 nm for TC 6-4PP and 325 nm for TT 6-4PP. Dewar valence isomers generate an intermediate distortion in structure of DNA when compared to CPDs and 6-4PPs (Lee et al. 1998). In numerous studies employing skin samples, plants, bacteria, and cultured cells, as well as mammals, the 6-4PPs' isomerization into isomers of Dewar has been developed and evaluated using mass spectrometry and immunological identification (Takeuchi et al. 1998; Pogoda De La Vega et al. 2005; Moeller et al. 2007; Moeller et al. 2010). According to a large-scale study that used microorganisms exposure to natural sunlight, 20% of the 6-4PPs were converted into isomers of Dewar (Maron and Ames 1983). Isomers of Dewar and 6-4PPs are considered to be more harmful than CPDs in terms of pyrimidine dimer mutagenicity. 6-4PPs are principally responsible for TT to TC transitions, whereas Dewar isomers transform TC to TT transitions and CPDs provide C-T transitions (Douki 2016). UVB- and UVA-induced DNA damage preferentially promote C-T transitions in both in vitro and in vivo models (Pfeifer et al. 2005; Kappes et al. 2006; Ikehata et al. 2008). Furthermore, despite the fact that at equimutagenic levels, UVB generates more CPDs than UVA, UVA-induced photoproducts of DNA are possibly more mutagenic than UVB-induced DNA photoproducts. This might be addressed by a less robust arrest of cell cycle, as well as ineffective p95 and p53 activation. As a result, an insufficient cell cycle checkpoint after UVA irradiation may result in the replication of the buildup of mutations and the damaged DNA (Runger et al. 2012). DNA single-strand breaks and double-strand breaks and cross-related DNA linkages can form directly or as a co-product of cellular metabolism after UVA exposure (Dunn et al. 2006; Elvers et al. 2011; Vallerga et al. 2015; Federico et al. 2016). These lesions are very cytotoxic and, if left untreated, may result in chromosomal abnormalities as well as tumorigenic remodeling of keratinocytes. However, UVA radiation's capacity to effectively trigger double-strand cracks has lately been disproven. This kind of lesion may be an unintended outcome of DNA destruction replication, or it could be caused by UVA-induced bunches of single-strand segments or the repair of nearby oxidized bases in the DNA (Wischermann et al. 2008; Cadet and Douki 2011; Rizzo et al. 2011; Greinert et al. 2012). Immunohistochemical staining of CPDs is now the most extensively used approach for monitoring changes in UV photoproduct levels in human skin. However, since CPDs are very slowly eliminated from the genome, this approach typically requires long periods after irradiation to observe a significant decrease in staining intensity. Furthermore, CPD dilution owing to DNA replication and cell division or death in the skin may result in artifactually lower apparent CPD levels. Finally, methods that use formaldehyde to heal skin tissue may cross-link DNAs to genomic DNA, causing excised UV photoproducts to appear as unrepaired damage (Pouget et al. 2000; Brash et al. 1991; Sawicka et al. 2020).

Ionizing radiations

Ionizing radiation comprises radiation emitted by both naturally occurring and artificial radioactive materials. Hematopoiesis is one of the most radiation-sensitive mechanisms. Ionizing radiation primarily affects the hematopoietic characteristics observed in animals and humans after whole-body irradiation and might be used as a bio-indicator to evaluate ionizing radiation damage (Shafiee et al. 2016; Taqi et al. 2018). Chronic X-ray exposure can result in a significant

increase in mean corpuscular volume (MCV), reactive lymphocytes, and a substantial reduction in mean cell hemoglobin concentration (MCHC), WBC, and platelet (PLT) parameters in both male and female (Shafiee et al. 2016; Taqi et al. 2018). Low doses of gamma and X-rays showed high sensitivity of erythrocyte lipid metabolism characteristics. Human leukocyte antigens (HLA) are genes found in major histocompatibility complexes (MHC) that help code for proteins that distinguish self from non-self (Carey et al. 2019). Loss of HLA antigen expression in human lymphoblastoid cell lines may be prompted by 300 R gamma radiation and selection with HLA antiserum. (i) HLA-B8, (ii) HLA-B8, A1, (iii) HLA-B8, A1, DRw3, or (iv) HLA-B8, A1, DRw3 expression is lost (Kavathas et al. 1980).

Chemical mutagens

Environmental pollutants may wreak havoc on genetic material, resulting in a wide range of mutations. Somatic tissue mutations induce cancer, but germinal mutations create a variety of genetic disorders. The frequency, nature (point mutation versus chromosomal change, dominant versus recessive), and strategies that guide a specific mutation in the population will define the influence of germinal mutations on wellbeing (Motulsky 1984). Mutations in somatic cell genetic material may give rise to the neoplasms which are malignant. These carcinogenic implications are mostly limited to the time period between the initial mutation and the diagnosis of clinical cancer. Several environmental toxins have previously been linked to cancer growth and development, including vinyl chloride (liver cancer), benzene (bone marrow malignancies), asbestos (lung and pleural cancer), and others (Doll and Peto 1981). Molecular mechanisms of various chemical mutagens (DMS, BPA, PAHs, 5ClC, biodiesel) are recognized as critical environmental factors that lead to the development of multiple diseases as shown in Fig. 3 (Li et al. 2020; Foster et al. 1983; Hsu et al. 1991).

Dimethyl sulfate

Dimethyl sulfate is a monofunctional alkylating chemical shown hazardous to humans, producing mutations, chromosomal abnormalities, and distinct genetic changes. There are adequate clinical or epidemiological data explicating that dimethyl sulfate is carcinogenic in experimental animals and most likely carcinogenic to humans (Group 2A). It is considered that dimethyl sulfate is a potent genotoxic compound that may directly alkylate DNA both in vitro and in vivo (World Health Organization 1985). DMS is a classic SN2 agent, primarily targeting nitrogen sites in nucleic acids (Hoffmann 1980).

BPA

Humans and animals are exposed to synthetic estrogens that negatively impact both humans and animals (Soto et al. 1997). BPA and its derivatives are xenobiotic estrogens that exist in natural surroundings. BPA is predominantly utilized as a raw chemical in polymer and plastics industries (Fukazawa et al. 2001). Some investigations looked into the genotoxicity of bisphenols at non-cytotoxic levels in the human hepatoma cell line (HepG2) (Fic et al. 2013). BPA is one of the most common endocrine disruptors, and estrogenic substance bisphenol A (BPA, 4,4isopropylidenediphenol) interacts with thyroid hormone receptors in addition to ERs. BPA is the first recognized environmental agent to attach to the TR and influence TH signaling in vitro. BPA inhibits TH-negative feedback on the -TR while leaving the -TR unopposed in reacting to increased T4 in the hippocampus and possibly elsewhere. BPA binds to both the alpha and beta nuclear estrogen receptors (ER) (Maffini et al. 2006; Zoeller et al. 2005). About 40–70% of sporadic spontaneous abortions are associated with chromosomal abnormalities of the conceptus, particularly aneuploidy. High BPA exposure may be linked to recurrent miscarriage, particularly in individuals with ANA (antinuclear antibodies) (Sugiura-Ogasawara et al. 2005). Prenatal exposure to ecologically relevant amounts of BPA caused changes in the reproductive tract and mammary gland visible years after the exposure ceased. Prenatal exposure to environmental BPA levels causes long-term alterations in mammary gland development (Munoz-de-Toro et al. 2005). The cellular transformation being triggered by numerical chromosomal changes in the closer diploid range driven by BPA treatment. Cells were exposed to BPA, which resulted in the production of DNA adducts in a dose-dependent manner. According to several investigations, in cultivated mammalian cells, BPA has cell-transforming and genotoxic consequences, as well as possible carcinogenic activity (Tsutsui et al. 1998). A recent study of BPA was examined for genotoxicity in Swiss albino mice. BPA exhibited genotoxic potential in the bone marrow cells as achromatic lesion and c-mitotic effects (Naik and Vijayalaxmi 2009). BPA has been shown in different species and cell types to alter the topology of the spindle at mitotic and meiotic stage and cytoplasmic microtubule complex, notably human MCL-5 cells and hamster V79 cells. Micronuclei were also found in blood reticulocytes of rats fed nitrite-pretreated BPA but not BPA independently (Pacchierotti et al. 2008). In some studies, the hazardous potential of BPA is due to the development of reactive quinone metabolites and oxidative stress (Fic et al. 2013). BPA may also bind to androgen receptors directly, making it potentially antiandrogenic by inhibiting natural androgen activity (Rochester 2013). The enzymatic metabolism of BPA by cytochrome P450 creates the DNA-reactive quinone form of BPA and generates ROS through enzymatic (H2O2/peroxidase and NADPH/CYP450) and non-

enzymatic (peroxynitrite/CO2 and OCl/HOCl) phenoxyl radical production, DNA damage, and cytotoxicity in bone mesenchymal stem cells (hBMSC), hepatocytes, hepatocellular carcinoma (HepG2), neuronal cells (Neuro2a), and spermatogonia (GC-1) (Gassman 2017). Hoxa10, a homeobox gene that regulates uterine organogenesis, is altered due to BPA exposure. BPA has been shown to change global gene expression and interfere with complex cell regulatory networks. BPA induces an adaptive response that modifies the microcellular environment and modifies DNA repair (Gassman et al. 2015).

PAHs

PAHs are hydrophobic environmental contaminants with two or more fused aromatic rings (Zhu et al. 2015; Iwegbue et al. 2016). Anthropogenic sources of polycyclic aromatic hydrocarbons comprise fossil fuel burning, oil spills, and industrial emanation (Iwegbue et al. 2016; Wang et al. 2004; Wang et al. 2018). Natural sources of polycyclic aromatic hydrocarbons incorporate wildfires and volcanic eruptions (Yang et al. 2014; Samburova et al. 2017). Although there are hundreds of PAHs, the United States Environmental Protection Agency (USEPA) has assigned 16 PAHs as precedence carcinogenic and mutagenic substances (Kumar et al. 2012; Liu et al. 2016). Polycyclic aromatic hydrocarbons have been linked with a wide range of acute and chronic health effects, including malformation, mutagenesis, and endocrine system abnormalities (Zhu et al. 2015; Grimalt et al. 2004; Pribylova et al. 2012; Nekhavhambe et al. 2014). Persistent organic pollutants may affect human health via skin contact, ingestion, and inhalation (Yang et al. 2014; Kumar et al. 2014). Researchers routinely use indicative ratios of Phe/Ant to evaluate PAHs' distribution and presumable sources in the environment (Magi et al. 2002). According to the Center for Children's Environmental Health studies, children who are more prone to PAH exposure during pregnancy are liable for unfavorable birth outcomes such as birth underweight, early-maturing delivery, and organ defects. Prenatal PAH exposure is associated with a lowering IQ, behavioral difficulties, and childhood asthma in young children (Rengarajan et al. 2015; Perera et al. 2014). PAHs have been found at high concentrations in the marine ecosystem, including fish and benthic invertebrates (Chizhova et al. 2013; Honda et al. 2018; Hu et al. 2009; Kannan and Perrotta 2008; Miki et al. 2014; Pereira et al. 2009; Uno et al. 2010). PAHs in the aquatic environment are classified into four types: those that originated from fuels (petrogenic), combustion process (pyrogenic), organic metabolism (biogenic), and sediment conversion process (diagenetic) (Hylland 2006). Oil spill incidents are among the most disquieting vulnerability events for PAH contamination in aquatic environments (Hayakawa 2018; Koyama et al. 2004, 2016; Ladwani et al. 2013; Tronczyński et al. 2004; Uno et al. 2017). The carcinogenicity and mutagenicity of PAHs are the most concerning perspectives of their toxicity (Collins et al. 1998; Devi et al. 2016; Kuo et al. 1998; Rengarajan et al. 2015). Because of their hydrophobicity, PAHs are transported into cells and activate gene expression of the cytochrome P450 (CYP) (Bekki et al. 2013; Ikenaka et al. 2013; Jacob 2008; Jorgensen et al. 2008). PAHs are metabolized by CYP enzymes when they are expressed. It should be noted that various intermediates in this metabolic pathway have the potential to bind with DNA and become mutagenic/carcinogenic. Additional toxicological research has intimated that PAHs may cause developmental toxicity, genotoxicity, immunotoxicity, oxidative stress, and endocrine disruption (Bekki et al. 2009; Cherr et al. 2017; Hannam et al. 2010; Lee et al. 2011; MacDonald et al. 2013). PAHs have been studied for their carcinogenicity to animals, including humans. It has been shown that mutations generated by benzo[a]pyrene are a polycyclic aromatic hydrocarbon (PAH), and were responsible for 60% of lung cancer cases (Denissenko et al. 1996). BaP exposure dramatically enhances the mRNA levels of apoptotic genes such as p53, bax, and bcl-2 and the activity of caspases 3, 8, and 9 (Zha et al. 2017). Furthermore, there is a link between BaP-induced endoplasmic reticulum dysfunction and lipid metabolism (Cai et al. 2019). Embryotoxicity in experimental animals has been documented as a result of PAH exposure. PAHs may influence critical reproductive hormones such as LH, FSH, GnRH, and aromatase enzyme (Bolden et al. 2017). Moreover, it is well recognized that BaP provokes various carcinogenic effects in multiple cancer, including cervix, breast, and prostate cancer (Rengarajan et al. 2015; Abdel-Shafy and Mansour 2016; Verma et al. 2012). Besides, animal knock-out experiments showing that PAH exposure may disrupt the AhR-regulated gene expression needed for a cardiovascular system induce structural and functional alterations in bone marrow, deregulation of genes involved in ocular development, overexpressed cytochrome P450, which has serious health repercussions (Hrudkova et al. 2004; Holme et al. 2019; Magnuson et al. 2018; Burchiel and Luster 2001; Marris et al. 2020). In experimental animals, PAH exposure profoundly impacted hypertension linked to eNOS inactivation, resulting in the abolition of NO-mediated vaso-relaxation and increased blood pressure (Chang et al. 2017; Gentner and Weber 2011). Monohydroxylated PAHs (OHPAHs) proved to be hazardous in animals and may have a severe deleterious impact on vertebrate endocrine systems (Idowu et al. 2019; Hayakawa et al. 2006). In rat bone marrow cells, BaP was demonstrated to inhibit osteogenesis (Andreou et al. 2004). PAHs are hazardous to the gonads as well as the liver. BaP exposure affects the gene expression and androgen metabolic pathways in humans (Colli-Dula et al. 2018). Furthermore, PAHs have been linked to DNA damage prevalent in atherosclerosis, human endothelium, and smooth vascular muscle

cells because of their mutagenesis properties (Zhang et al. 1998; Pulliero et al. 2015; Penn 1990). In cells, PAHs may absorb UVA light and generate reactive intermediates, damaging the cell membrane, DNA breakage, and protein degradation (Yu 2002; Yan et al. 2004). Long-term exposure to PAHs may cause tumor growth in many organs, including the lung, skin, esophagus, and breast cancer (Rajpara et al. 2017; Yu 2002).

5ClC

5ClC is the most prevalent chlorinated nucleobase. Mutagenesis of 5ClC is observed in inflammation-associated malignancies, and it crystallized human polymerase (pol) facing the lesion. 5ClC interacts with DNA methyltransferases, causes alterations in DNA methylation patterns, and blocks replication (Winterbourn and Kettle 2000; Kawai et al. 2004; Whiteman et al. 1997; Kang Jr and Sowers 2008; Mangerich et al. 2012; Knutson et al. 2013; Fedeles et al. 2015; Lao et al. 2009; Delaney and Essigmann 2006; Shrivastav et al. 2014; Li et al. 2014). According to both in vivo and in vitro data, 5ClC promotes base anti-conformation by preferring the major over minor DNA groove location. The constrained minor groove of most DNA polymerases, the anti-conformation of the 5ClC base, assumed to hold the 5Cl substituent in the DNA major groove, is a crucial constituent that develops a positive hydrogen-bonding interaction between 5ClC and the incoming dATP, which feasible forms the molecular evidence for 5ClC's mutagenic mispairing ability and this kind of interaction and the configuration of a manifest a basic site templating pocket are enough to serve the mutagenic inclusion of dATP contrary 5ClC via an "enhanced A-rule" mechanism in which a polymerase includes an A converse structure that resembles a basic site (Li et al. 2014). The structural snapshots demonstrate that 5ClC assumes a conformation in which the 5Cl substituent is positioned in the groove of DNA during the mutagenic detour of the lesion (Fedeles et al. 2015). 5ClC joins many other substituted cytosine analogs identified as mutagenic and generates CT mutations. 5ClC may contribute C: GT: A transition mutations which identified in tissues exposed to chronic inflammation, increasing the likelihood those tissues may develop cancer (Sato et al. 2006; Sheh et al. 2010; Fedeles et al. 2015; Mangerich et al. 2012; Knutson et al. 2013; Sato et al. 2006; Sheh et al. 2010; Li et al. 2014).

Biodiesel

Fatty acid trans-esterification produces fatty acid methyl esters, which are used to make biodiesel. The effects of diesel exhaust from petroleum diesel engines on human health have received substantial attention since the first comprehensive toxicological research in 1986 (McClellan 1986). Particulate matter (PM) of diesel exhaust contributes to air pollution to varying degrees, especially in urban areas. Prolonged exposure to environmental PM, generated mainly by gasoline or diesel engines, is genotoxic to people (DeMarini 2013) and is found to be associated with an enhanced risk of asthma, lung cancer, and several cardiovascular diseases (Gichner 1991; Loprieno 1975). Several studies found that extractable organic compounds from biodiesel PM are much less oncogenic in the *Salmonella* (Ames) mutagenicity assay than those found in petroleum diesel pollutants (Mutlu et al. 2015). Recent research studies on rapeseed biodiesel showed just a minute change in mutagenicity in Salmonella and lethality in human embryonic renal 293T cells between peels and extracts of petroleum diesel as well as rapeseed biodiesel (Agarwal et al. 2018). One study revealed a substantial relationship between both the mutagenicity emission rate (rev/L) and the proportion of unsaturated fats using data from biodiesels made from linseed oil, rapeseed oil, coconut oil, and palm tree oil. As a function, the higher the proportion of double bonding in fatty acids, the higher the rate of mutagenicity generation (Bunger et al. 2016). When comparing biodiesels to petroleum diesel, the mutagenicity emission factors computed for canola, soy, and WVO under combustion conditions are often lower for biodiesels (DeMarini et al. 2019). According to a recent study, WVO may have the most negligible environmental impact and the most significant economic benefit compared to pure plant-derived fuels (Liang et al. 2013; Fawaz and Salam 2018). More study may aid in providing an additional full life-cycle review of biodiesel fuels and their mutagenicity and more evidence to help policy decisions on the encouragement and use of biodiesel fuels.

Multiple approaches to estimate mutagenic factors in the environment

Biological tests for mutagen detection are crucial in assessing materials generated from natural habitats. The test must be sensitive enough to identify typically meager amounts of mutagenic compounds prevalent in varied environments (Węgrzyn and Czyz 2003). The following approaches were used to estimate mutagenic factors in the environment as shown in Fig. 4.

Ames test

The Ames test has earlier been used to evaluate the mutagenicity of thousands of compounds as shown in Fig. 5. This is an undeniable benefit since no other mutagenicity test now available can offer a comparable quantity of the sample for comparison reasons. In the research lab, the Ames test is suitable for determining the mutagenic activity of specific substances. However, there are just some challenges with using it in studies on various environmental samples. In this assay, genetically engineered *S. typhimurium* strains are employed.

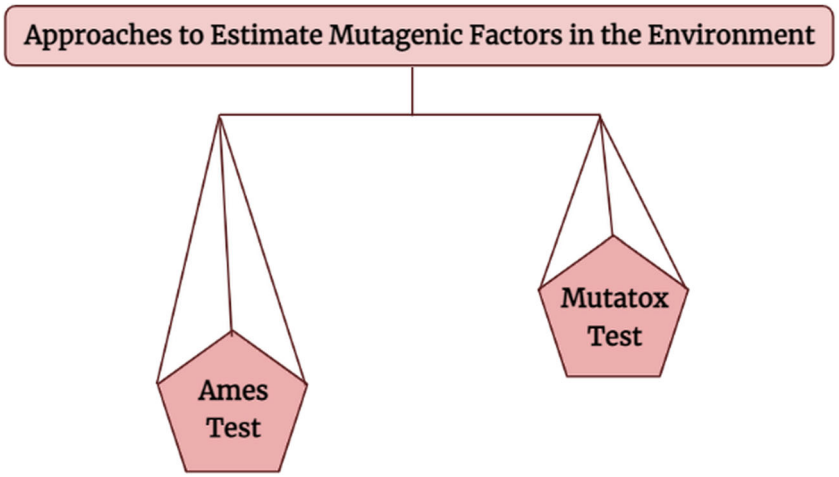

Fig. 4 Shows multiple detection test to estimate mutagenic factors in environment

The existence of mutations in *his* genes, which induce anomalies in a metabolic pathway leading to the synthesis of histidine, enables positive selection of *his*+ revertants on minimal agar plates lacking histidine. Only mutants with his function restored can form colonies on such plates. Ordinarily, the tested medication and tester bacterium are cultivated for 48 h before measuring the bacterial colonies on the petri dishes. Although the sensitivity of the Ames test is suitable for assessing the mutagenicity of known compounds in the research lab, it could be too limited for identifying low amounts of mutagens in the samples of the environment (Węgrzyn and Czyz 2003; Ames et al. 1975).

Mutatox test

The Mutatox test is a commonly available microbial mutagenicity testing that uses a unique dark strain of luminous bacterial species (designated M169). The M169 strain is a darkish mutant with a genetic defect in the regulatory framework instead of one of the lux component genes' coding sequences. In the existence of relatively low dosages of genotoxic substances in a growth media, light generation is regained in this variant. Mutatox can detect mutagens' presence, comprising DNA-damaging agents, base substitution agents, DNA synthesis blockers, and DNA intercalating agents. The Mutatox test necessitates the use of certain materials and equipment, including Microtox Model 500 Analyzer, Mutatox reagent (freeze-dried M169 cells), dry test medium with and without rat-liver microsomal enzymes (S-9 mix), and suitable co-factors. In a hydrated Mutatox medium, dilutions of the analyzed substance are applied to the tester bacterial cells. Following a 24-h incubation period, light measurements are taken using the Microtox Model 500 Analyzer. Mutatox has been demonstrated to exhibit sensitivity comparable to the Ames test for both pure compounds and ambient specimens. Mutatox benefits from being simple to execute; nevertheless, specific

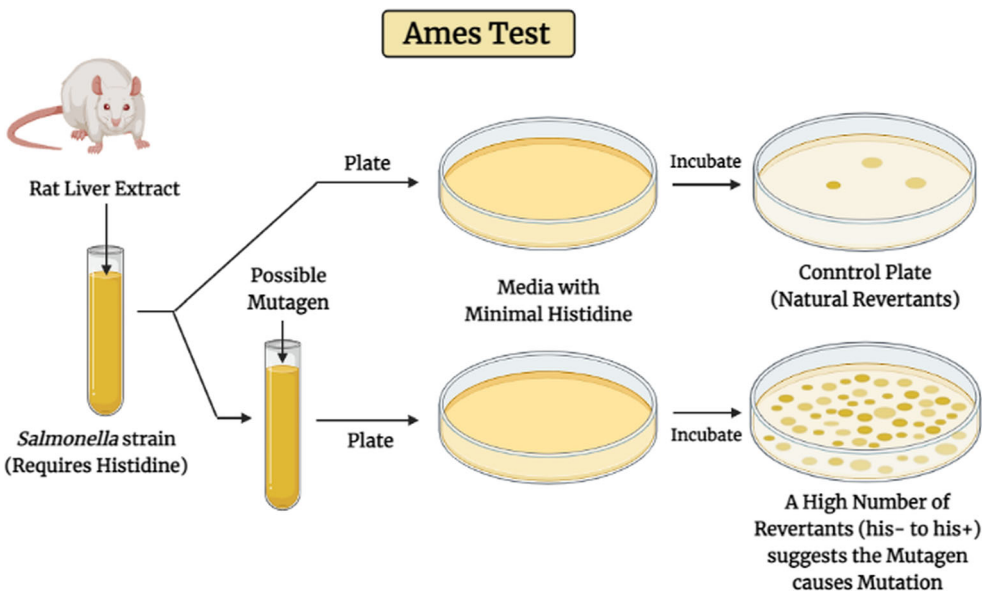

Fig. 5 Shows mechanism of Ames test to estimate mutagenic factors in environment

equipment is required (it might be a logistical problem if unusual analyses are performed than normal genotoxic research). Although the whole assay may be completed in 24 h, which is an improvement over the Ames test (which requires plates to be incubated for 48 h), this is still not the fastest method (Schrader and Cooke 2003).

Molecular mechanisms of heavy metals induced DNA damage and its role in multiple disorders

Many environmental toxicants are genotoxic that cause DNA damage within the cell. Physical mutagens, chemical mutagens, heavy metals are usually implicated in DNA damage. Molecular mechanisms of heavy metals present in the environment are implicated in DNA damage and multiple disorders as shown in Fig. 6.

Chromium

Chromium compounds are the most common inorganic environmental contaminants that interact with DNA, producing substantial DNA damage and leading to hazardous illnesses. Some of the ions are discharged into the environment by a variety of natural as well as anthropogenic sources such as rock component weathering and wet precipitation, and dry fallout from the sky is the primary source of Cr in natural and terrestrial systems (Kotas and Stasicka 2000). The organism can absorb chromium ions in three forms: via inhalation, oral administration, or percutaneous administration; however, the absorption efficacy is primarily determined by the oxidation grade of these compounds. Cr primarily occurs in two stable oxidation forms: Hexavalent (Cr (VI)) and trivalent (Cr (III)). Cr species are considered hazardous to various degrees at various phases; the reduction of Cr (VI) to Cr (III) generates free radicals inside. Trivalent Cr (Cr (III)) occurs as cationic species and is utilized as micronutrients and nutritional supplements required for insulin control and glucose metabolism. Cr (III) may induce hazardous consequences if present in high quantities owing to its capacity to coordinate diverse chemical molecules, resulting in inhibition of specific metalloenzyme systems (Shanker et al. 2005). Hexavalent (Cr (VI)), which is mostly anthropogenic in origin and exists as anionic species, is poisonous and proven as a human carcinogen (Sawicka et al. 2020; Hamilton et al. 2018). Chromium (VI) much more effectively enters the body via all three modes of exposure: inhalation, ingestion, and skin absorption compared to its trivalent state, and this might be related to its genotoxic impact. Chromium Cr (VI) may enter the cell via the sulfate-anion channel and be reductively metabolized to stable trivalent species Cr (III). Animals that are exposed to chromium (VI) in their drinkable water exhibited gastrointestinal malignancy, with linear and supralinear responses in the

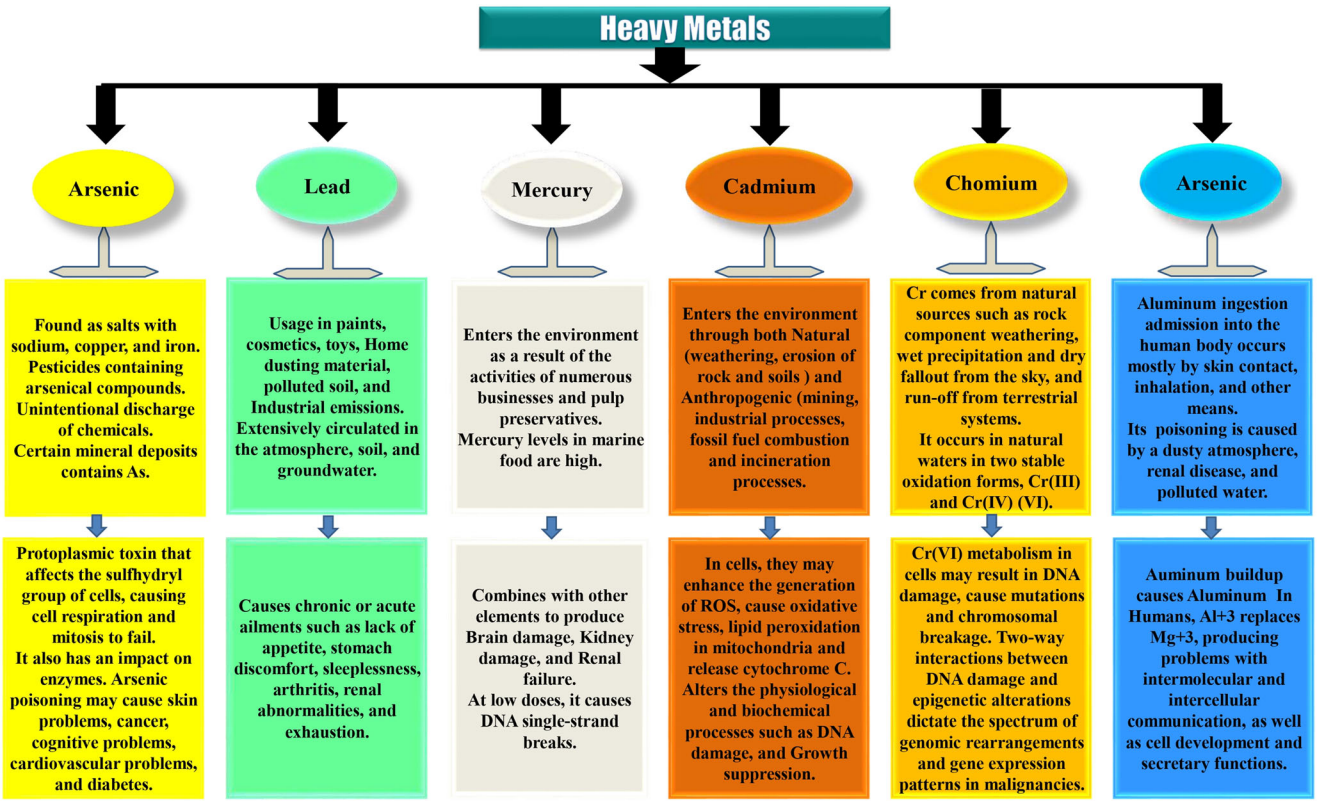

Fig. 6 Shows mechanism the molecular mechanisms of heavy metals present in environment induced DNA damage and its role in multiple disorders

small intestine of mouse. At neutral pH, chromate, the most prevalent form of chromium (VI), is carried in by certain cells via sulfate routes and triggered non-enzymatically by small thiols and ascorbate. Cr (VI) metabolism in cells may result in both oxidative and non-oxidative DNA damage. Adducts of chromium-DNA are responsible for mutations and chromosomal shattering, and are the most common DNA damage caused by Cr (VI). Emerging data suggest that the two-way connections between epigenetic alterations and damage of DNA dictate the spectrum of genomic rearrangements and gene expression patterns in malignancies (Zhitkovich 2011). Chromate has been shown to create various DNA lesions, including DNA, DNA-protein, DNA-amino acid cross-links, single strand, and double breaks, as well as alkali labile places, which might influence to its mutagenic consequences (Błasiak and Kowalik 2000). Cr (VI) may cause various localized toxicities, including carcinogenicity, under certain extremely high-exposure situations. Some of this toxicity seems to be connected to its fast decrease, connected with oxidation of tissue components and subsequent tissue damage (O' Flaherty et al. 2001). Recent research found that chromate exposure causes the production of Cr (III)–DNA adducts and Cr (III)-mediated cross-links of amino acids and glutathione with DNA. By changing the speed and fidelity of DNA replication, Cr (III) cross-links amino acids and glutathione with DNA, causing primary forms of DNA lesions that lead to mutagenesis and carcinogenesis (Khan et al. 2012). Scientists conducted a series of tests to investigate the interaction between DNA and the cancer-causing chromium Cr (VI). It has been discovered that a connection that is solely defined to the DNA nucleotide (guanine) sequence causes genetic modifications, because chromium converts the bases to 8-oxo-Guanine in order to have the oxidation of a specific site, the connection between the Cr (V) in complex form and the guanine base. The DNA damage site splits into two molecules. These two lesions were identified as guanidinohydantoin and spiroiminohydantoin after additional investigation. The DNA polymerase was paused, and adenine was added to the opposite location of the DNA to generate the 8-oxo-Guaniosine base. As a result, lesions are made up of G—>T transversions. Because of its high valent, chromium functions as a cancer-causing agent. Chromate exposure causes DNA damage, which leads to toxicity in humans. It demonstrates that Cr (V) interacts with xenobiotics that produce 8-oxo-Guaniosine (Morales et al. 2016; Sawicka et al. 2020). Hexavalent chromium (Cr (VI)) is recognized as an etiological factor for lung cancer, and Cr (VI) genotoxicity was also observed in bacterial and mammalian cell lines (Proctor et al. 2002). Numerous in vivo studies have found that Cr (III) and Cr (VI) both significantly induce genetic mutation in *S. cerevisiae* and induce damage of DNA inside both cells of Jurkat and yeast, suggesting that each may act as genotoxic substances. Additionally, Cr (III) has a greater influence than Cr (VI). According to the findings, Cr (III) simply disturbs with base-pair mounting, whereas Cr (VI) presumably intercalates further into spaces between base pairs of DNA (Fang et al. 2014). Cr (VI) may be converted to trivalent chromium, leading to ROS generation such as H_2O_2, OH•, and O_2. ROS-regulated redox-sensitive protein kinases and transcription factors, such as those implicated in the Akt, NF-B, and MAPK pathways, may influence the release of cytokines such as TNF and IL-1 in specific kinds of cells (Wang et al. 2010).

Arsenic

Arsenic seems to be the twentieth very common constituent of the mother earth's mantle. Much of this is obtained in the oxide and sulfide forms, although it is also seen as salts with sodium, copper, and iron, which is poisonous and causes multiple diseases. Arsenate and arsenate these two inorganic forms of arsenic that are hazardous to humans and the environment (Morales et al. 2016). Arsenic may enter the body via a variety of natural and industrial sources via uncommon routes. Pesticides containing arsenical compounds and unintentional discharge of such chemicals and certain mineral deposits may pollute drinking water. Arsenic is a protoplasmic toxin that affects the sulfhydryl group of cells, causing cell respiration and mitosis to fail. It also has an impact on enzymes, and poisoning of arsenic may cause skin problems, cancer, cognitive problems, cardiovascular problems, and diabetes which makes it an incurable illness (Morales et al. 2016).

Lead

Human exposure to lead compounds is owing to their usage in paints, cosmetics, toys, home dusting material, polluted soil, and industrial emissions. Drinking water may potentially be poisonous due to lead contamination and exposure of lead affecting humans' neurological systems and gastrointestinal tract. According to the Environmental Protection Agency, lead is a carcinogenic chemical. Lead poisoning is another term for lead toxicity, which may cause chronic or acute ailments such as lack of appetite, stomach discomfort, sleeplessness, arthritis, renal abnormalities, and exhaustion (Jan et al. 2015).

Mercury

Mercury is the most dangerous heavy metal present in the environment as a result of numerous activities. The level of mercury is very high, especially in marine foods, and its exposure is widely established to cause acute heavy metal toxicity. Mercury (Hg), both organic and inorganic, combined with other elements leads to brain damage, kidney damage,

and renal failure. It may also induce a disruption in calcium homeostasis, protein denaturation by interfering with its activity, and disrupts transcription and translation by causing ribosomes and endoplasmic reticulum to disintegrate. Microtubule destruction and mitochondrial damage inside cells and oxidative oxidation of fluids is caused by neurotoxin compounds such as methyl mercury (Compeau and Bartha 1985).

Cadmium

Cadmium (Cd) is a toxic heavy metal concern for many researchers, and it has been studied in a wide range of species, including algae, crustaceans (shrimps), rodents (mice), amphibians (tadpoles), and mammals (Lu et al. 2021; Verheyen and Versieren 2014; Zhang et al. 2021; Liu et al. 2014). Cadmium is released into the environment through both anthropogenic (farming, activities in urban areas, and toxic waste discharges from industry, charcoal ashes lagoons, combustion of fossil fuels, burning, and municipal hazardous effluent) and natural (erosion and weathering of soil and rock conditions, natural burning from volcanic eruptions and forest fires) processes (Mouchet et al. 2006). It may enter cells in various methods, including ion membrane transfer and passive diffusion of neutral chemical species. In cells, they may enhance the generation of reactive oxygen species (ROS) and therefore cause oxidative stress, leading to lipid peroxidation in mitochondria and, ultimately, one of the final phases of cell damage is the generation of the cytochrome C. *Xenopuslaevis* exposing to ecologically Cd produce genotoxicity through oxidative stress, DNA binding, or inhibition of DNA repair processes (Mouchet et al. 2006). Recent investigations on Cd toxicity on gut flora demonstrated that Cd stress significantly decreased the development rate of gut microbiota in vitro (Liu et al. 2014). Cd has been identified as a human carcinogen and may induce a broad range of toxicological effects on aquatic creatures, including alterations in physiological and biochemical processes, energy metabolic dysfunction, histopathological damage, DNA damage, and growth suppression. Chronic exposure to non-lethal cadmium doses (3 M and 5 M) resulted in petite mutants in addition to nuclear alterations (Zhang et al. 2021; Liu et al. 2014; Jin et al. 2003). A growing number of studies have shown early detrimental health consequences from cadmium exposure at far lower levels than previously thought. The majority of the research has focused on kidney and bone impacts, but new studies have also shown increased cancer risks with low-level environmental exposure. Cadmium has a lengthy biological half-life in the human kidneys, lasting 10–30 years. Chronic low levels of Cd can cause renal failure, unregulated blood pressure, diabetes problems, and bone structural changes, resulting in osteoporosis. Furthermore, Cd has been linked to airway inflammation, cardiovascular disease, diabetes, neurological disorders, and several malignancies (Liu et al. 2014; Messner and Bernhard 2010; Jarup and Akesson 2009; Johri et al. 2010). Chronic Cd exposure and toxicity have the most significant impact on the kidney. Cd accumulates in the kidney due to receptor-mediated endocytosis of freely filtered and metallothionein-bound Cd (Cd-MT) in the proximal renal tubule (Jarup and Akesson 2009; Johri et al. 2010). Since the 1950s, it has been known that extended exposure to high cadmium levels may cause bone disease, which has initially been recorded from the Jinzu river basin in Japan. Multiple fractures and deformation of the long bones in the skeleton define itai-itai ("ouch-ouch") illness, which causes intense discomfort in afflicted persons. The International Agency for Research on Cancer (IARC) classified cadmium as a human carcinogen (class I) in the year 1993, based on substantial evidence indicating carcinogenicity in both people and experimental animals. According to recent research, cadmium may have a role in coronary heart disease (Jarup and Akesson 2009; Everett and Frithsen 2008). Cadmium inhibits the ability of minor misalignments and base-base mismatches to be repaired post-replication mismatch repair (MMR). Cadmium hindered at least one process leading to mismatch elimination in human cell extracts. Several findings reveal that an environmental hindrance to a mutation-avoidance mechanism might result in a high amount of genomic instability (Jin et al. 2003).

Aluminum

Aluminum is the third most prevalent element in the earth's crust. Aluminum ingestion admission into the human body occurs mainly by skin contact, inhalation, and other means. Symptoms of high aluminum content in the body include vomiting, ulcers, skin rashes, and bone discomfort. These symptoms last just a short time. Aluminum poisoning is caused by a dusty atmosphere, renal disease, and polluted water. The aluminum buildup causes interactions between aluminum and the plasma membrane and apoplastic and symplastic targets. In humans, Al+3 replaces Mg+3, producing problems with intermolecular and intercellular communication, cell development, and secretary functions (Jan et al. 2015).

Environmental mutagens and their role in multiple disorders in humans

Various environmental mutagens such as radiation, chemical, and biological agents are responsible for multiple human disorders as shown in Table 2. Radiation is induced by X-rays, and UV rays prompt bone cancer, breast tumors, enlarged hearts, blocked blood vessels, and several infectious diseases (Morley 2012). 8-oxoG promotes cancer and neurodegeneration by accumulating in mitochondrial DNA of neurons,

Table 2 Shows the role of environmental mutagens in multiple disorders in humans

Mutagens	Role	Disease cause	References
X-rays	X-ray radiation is a penetrating form of high-energy electromagnetic radiation may produce mutations, alterations in the structure of single genes or chromosomes; changes in gene expression and oncogenic viruses, which, in turn, may cause neoplasia.	Bone cancer, breast tumor, blockened blood vessel and infectious diseases	Mozdarani 2012
8-oxoG	8-oxoG accumulates in neurons mitochondrial DNA, causing calpain-dependent neuronal death.	Cancer, neurodegeneration	Sheng et al. 2012
Cadmium	Cadmium activates calmodulin, which regulates smooth muscle contraction by detecting calcium levels.	Itai-Itai disease and renal tubular dysfunction	Nishijo et al. 2017
Bisphenol A	BPA is a xenoestrogen, exhibiting estrogen-mimicking, hormone-like properties. BPA markedly increased the frequency of ectopic ventricular beats.	Angina, coronary arterial disease, hypertension, atherosclerosis	Gao and Wang 2014
Mercury	Mercury disrupts normal cell physiology in a variety of organ systems, primarily through covalent binding to intracellular sulfhydryl-containing enzymes and proteins.	Pneumonitis, non-cardiogenic pulmonary edema, acute respiratory distress	Glezos et al. 2006
Lead	Lead increased oxidative stress and renin-angiotensin system stimulation and interfering with the heart's autonomic nerve regulation.	Hypertension, coronary heart disease, stroke, peripheral arterial disease	Navas-Acien et al. 2007
Arsenic	Arsenic interrupts with DNA repair pathways, leading to an increase in the incidence of chromosomal abnormalities, somatic mutation, oxidative stress, and apoptosis.	Blackfoot disease, skin and lung cancer	Tseng 2005
Aluminum	Aluminum sequesters many transport systems in order to actively cross brain boundaries. Al poisoning reproduces the neuropathological markers of Alzheimer's disease. Aluminum causes acute poisoning and can cause confusion, delirium, tremors, and hallucinations.	Acute encephalopathy, Alzheimer's disease	Tomljenovic 2011

resulting in calpain-dependent neuronal death. Delayed nuclear deposit of 8-oxoG in microglia results in PARP-dependent production of an apoptosis-inducing signal and worsening of microgliosis (Sheng et al. 2012). Cadmium accumulates mainly in the liver and kidneys, binds to metallothionein in the blood, moves to the glomerulus, and is secreted from the tubular cells of the kidneys. Cadmium accumulates in the renal cortex and inhibits metal-dependent enzymes or activates calmodulin, which regulates smooth muscle contraction by sensing calcium levels. When the kidneys are significantly injured, they begin to suffer from a musculoskeletal injury due to calcium homeostasis disruption. The bone pain and abnormalities that define Itai-Itai illness are caused by musculoskeletal injury (Nishijo et al. 2017). Contact dermatitis, bronchial asthma, allergic rhinitis, and contact allergic eczemas are caused by chromium exposure. While causing contact dermatitis, it predominantly affects keratinocytes. These cells can be directly activated by expressing the membrane antigen ICAM-I, a ligand for the leucocyte antigen LFA-I, and releasing cytokines, including a substantial release of TNF-alpha (Shrivastav et al. 2014). BPA generated multiple diseases such as angina, coronary arterial disease, hypertension, heart attack, and atherosclerosis. Many signaling pathways are activated by low-dose BPA exposure, including Protein Kinase A (PKA) and Ca2+/CaM-dependent protein kinase II (CAMKII). Acute BPA exposure increased cAMP production, PKA activation, and phosphorylation of the ryanodine receptor (RyR). BPA also stimulates phospholipase C (PLC), which leads to the formation of triphosphoinositol (IP3), IP3 receptor-mediated Ca2+ release, most likely from endoplasmic reticulum Ca2+ storage, and activates CAMKII, which phosphorylates phospholamban (PLN). Phosphorylation of RyR enhanced channel opening and SR Ca2+ leak, whereas phosphorylation of PLN resulted in PLN inhibition of Sarco/Endoplasmic Reticulum Ca2+-ATPase (SERCA) and enhanced SR Ca2+ reuptake (Gao and Wang 2014). Mercury is the cause of pneumonitis, non-cardiogenic pneumonitis, pulmonary edema, and acute respiratory distress. It disrupts normal cell physiology in various organ systems, often by covalently binding to sulfhydryl-containing enzymes and proteins within the cell. Inhaling high-temperature vapor damages lung tissue thermally, whereas oxidized mercury ions cause direct airway irritation and cellular poisoning. Mercury travels through the alveolar membrane during breathing, resulting in rapid systemic absorption and extensive dispersion throughout organs (Glezos et al. 2006). Lead is responsible for hypertension, coronary heart disease, stroke mortality, and peripheral arterial disease. The reduction in renal function caused by lead may play a substantial influence in hypertension. It also causes an increase in oxidative stress. It also increases the activity of the renin-angiotensin system. Nitric oxide and soluble guanylate cyclase are both inhibited. It influences heart rate variability by interfering with autonomic nerve control of the heart (Navas-Acien et al. 2007). Arsenic can cause blackfoot disease, skin cancer, and lung cancer. The effects of arsenic on hypercoagulability, endothelial damage, smooth muscle cell

proliferation, somatic mutation, oxidative stress, and apoptosis may be connected to arsenic atherogenicity. Its interactions with various trace elements and its links to hypertension and diabetes may explain a portion of its elevated risk of atherosclerosis. It disrupts DNA repair mechanisms, increasing chromosomal abnormalities (Tseng 2005; Pershagen 1981). Aluminum is responsible for acute encephalopathy and Alzheimer's disease. Aluminum accumulation in the brain's gray matter has been related to acute aluminum neurotoxicity. Aluminum acute poisoning can result in confusion, delirium, tremors, hallucinations, and slurred speech and trigger neurotoxicity in humans. In order to actively transverse brain borders, Al sequesters multiple transport mechanisms. Small amounts of Al absorbed progressively during a lifetime promote preferential accumulation in brain tissues (Malaki 2013; Tomljenovic 2011).

Future perspectives

Environmental mutagens comprise chemical and physical substances in the environment that can alter genetic material and cause mutations and a variety of negative consequences on human and animal health. Most mutagens are carcinogenic in humans or even have genotoxic effects on the following generation via germ cells. These mutagens have been associated with multiple neurological disorders. Various unresolved environmental challenges with mutagens exist all around the world and become study topics. To expedite environmental mutagen investigation, scientists in this field should make an effort to utilize modern tactics, prominently scientific instruments and molecular and cellular biology techniques, and must use artificial intelligence and information technology, which will open up new research areas in the field. Researchers from multiple disciplines must consider exchanging mutually beneficial ideas that are more prominent than competitiveness to research at a higher level. Furthermore, there is a need to understand the molecular basis of epigenetic regulation and how it is critical to incorporate biological control into the repertoire of environmental health research and medicine, thus, focusing on the cutting-edge study of the genetic and epigenetic consequences of environmental mutagens and carcinogens.

Conclusion

Exposure of humans and animals to environmental mutagens has indeed been documented, but more study is needed. A few of them, such as chromium, are necessary for humans, although they are also hazardous due to a variety of action mechanisms. Most mutagens are carcinogenic in humans or have genotoxic effects on the following generation through germ cells. For the detection of environmental mutagens, several different kinds of biological systems have been utilized. Each system has its own set of pros and downsides. Heavy metals may cause genetic damage by causing double-strand breaks (DSBs) and blocking key proteins from various DNA repair pathways. Arsenic is mutagenic to endogenous genes in mammalian cells, causing typically massive multilocus deletions mediated by ROS. The ionic process of oxidative stress is followed by lead metal. Human cells are harmed as a result of this process. Mercury is the most dangerous heavy metal present in the environment. Mercury compounds are very carcinogenic, and the human brain system is very susceptible to any and all mercury compounds. Mercury buildup may disrupt brain functioning, causing memory issues as well as alterations in vision or hearing. Cadmium causes apoptosis in cells. Cadmium poisoning results from DNA strand breaks. Cadmium carcinogenesis is caused by a number of mechanisms, including DNA repair inhibition. Exposure to cadmium may cause genomic mutations and hyper mutability of mismatch repair depression in yeast. Cr III interferes with the interaction of the DNA template and the polymerase, which leads to chromium-mediated carcinogenesis. Al has been shown to have pro-oxidant action, enhancing cellular oxidation by superoxide and iron. Al induces the expression of oxidative distress in plants and stimulates antioxidant defense network. Mycotoxin is a diverse group of naturally occurring fungus secondary metabolites having harmful effects on humans and animals. Aflatoxins, ochratoxin A, sterigmatocystin, and numerous other mycotoxins have been identified as carcinogenic; numerous others have been proven to be mutagenic. Electromagnetic, ionizing radiations, such as X-rays and rays released by radioisotopes, and UV light are the most often employed types of physical mutagens, as are particle radiations such as fast and thermal neutrons and beta and alpha particles. Assimilation of sunlight effectively destroys DNA, and the large proportions of these illnesses are clearly caused by wavelengths of UVB and UVA. Tobacco, DMS, BPA, 8-Oxog, PAHs, and 5-CIC are all exceedingly genotoxic. Tobacco smoke is the most potent human mutagen in the system. BPA affects cell transformation as well as other genetic consequences. Reactive oxygen species produced inside the mammalian cell may result in 8-oxoG in mRNA, causing base mispairing during gene translation. The buildup of 8-oxoG in mRNA may affect protein synthesis in mammalian cells. PAHs are widespread environmental pollutants that are being fabricated mostly as a result of deficient combustion of organic compounds as well as have poisonous, mutagenic, and/or carcinogenic effects. 5-Chlorocytosine is innately miscoding during DNA replication, and it may cause a high frequency of C-to-T mutations, a form of mutation that is common in human malignancies. Preliminary biological tests are performed to determine the presence of mutagenic chemicals. Following that, if required, a full chemical analysis may be undertaken to establish the precise kind of mutagen.

Availability of data and materials Not applicable.

Author contribution TKU, PT, NKJ, and KKK developed the concept. KG, HG, PB, AD, AP, MB, VY, AM, and RSS wrote the initial draft the manuscript; KG, HG, PB, AD, AP, MB, VY, and AM collected the data; KG, HG, PB, and MP prepared the figures. KG, HG, PB, AD, VY, AM, MB, and AP performed the literature review and improved the manuscript. FK, NKJ, KKK, PP, SM, PT, and TKU significantly reviewed and critically revised the paper; KG, HG, PB, AD, FK, NKJ, KKK, PP, AP, MB, AM, VY, RSS, SM, PT, and TKU approved the final version of the manuscript.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication All contributors agreed and given consent to publish.

Competing interests The authors declare no competing interests.

References

Abdel-Shafy HI, Mansour MS (2016) A review on polycyclic aromatic hydrocarbons: source, environmental impact, effect on human health and remediation. Egyptian Journal of Petroleum 25:107–123

Agarwal AK, Singh AP, Gupta T, Agarwal RA, Sharma N, Rajput P, Pandey SK, Ateeq B (2018) Mutagenicity and cytotoxicity of particulate matter emitted from biodiesel-fueled engines. Environmental Science & Technology 52:14496–14507

Ames BN, McCann J, Yamasaki E (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res 1:31

Andreou V, Addario DM, Zohar R, Sukhu B, Casper RF, Ellen RP, Tenenbaum HC (2004) Inhibition of osteogenesis in vitro by a cigarette smoke-associated hydrocarbon combined with Porphyromonas gingivalis lipopolysaccharide: reversal by resveratrol. Journal of Periodontology 75:939–948

Batista LF, Kaina B, Meneghini R, Menck CF (2009) How DNA lesions are turned into powerful killing structures: insights from UV-induced apoptosis. Mutation Research/Reviews in Mutation Research 681:197–208

Bekki K, Takigami H, Suzuki G, Tang N, Hayakawa K (2009) Evaluation of toxic activities of polycyclic aromatic hydrocarbon derivatives using in vitro bioassays. Journal of Health Science 55: 601–610

Bekki K, Toriba A, Tang N, Kameda T, Hayakawa K (2013) Biological effects of polycyclic aromatic hydrocarbon derivatives. J UOEH 35: 17–24

Bermudez Y, Stratton SP, Curiel-Lewandrowski C, Warneke J, Hu C, Bowden GT, Dickinson SE, Dong Z, Bode AM, Saboda K, Brooks CA (2000) Activation of the PI3K/Akt/mTOR and MAPK signaling pathways in response to acute solar-simulated light exposure of human skin. Cancer Prevention Research 8:720–728

Błasiak J, Kowalik J (2000) A comparison of the in vitro genotoxicity of tri-and hexavalent chromium. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 469:135–145

Bolden AL, Rochester JR, Schultz K, Kwiatkowski CF (2017) Polycyclic aromatic hydrocarbons and female reproductive health: a scoping review. Reproductive Toxicology 73:61–74

Boonstra A, van Oudenaren A, Barendregt B, An L, Leenen PJ, Savelkoul HF (2000) UVB irradiation modulates systemic immune responses by affecting cytokine production of antigen-presenting cells. International Immunology 12:1531–1538

Brash DE (1997) Sunlight and the onset of skin cancer. Trends in Genetics 13:410–414

Brash DE, Rudolph JA, Simon JA, Lin A, McKenna GJ, Baden HP, Halperin AJ, Ponten J (1991) A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proceedings of the National Academy of Sciences 88:10124–10128

Bunger J, Bunger JF, Krahl J, Munack A, Schroder O, Bruning T, Hallier E, Westphal GA (2016) Combusting vegetable oils in diesel engines: the impact of unsaturated fatty acids on particle emissions and mutagenic effects of the exhaust. Archives of toxicology 90: 1471–1479

Burchiel SW, Luster MI (2001) Signaling by environmental polycyclic aromatic hydrocarbons in human lymphocytes. Clinical Immunology 98:2–10

Cadet J, Douki T (2011) Oxidatively generated damage to DNA by UVA radiation in cells and human skin. Journal of Investigative Dermatology 131:1005–1007

Cadet J, Mouret S, Ravanat JL, Douki T (2012) Photoinduced damage to cellular DNA: direct and photosensitized reactions. Photochemistry and Photobiology 88:1048–1065

Cadet J, Douki T, Ravanat JL (2015) Oxidatively generated damage to cellular DNA by UVB and UVA radiation. Photochemistry and photobiology 91:140–155

Cai L, Li J, Yu L, Wei Y, Miao Z, Chen M, Huang R (2019) Characterization of transcriptional responses mediated by benzo[a]pyrene stress in a new marine fish model of goby, Mugilogobius chulae. Genes & genomics 41:113–123

Carey BS, Poulton KV, Poles A (2019) Factors affecting HLA expression: a review. International journal of immunogenetics 46:307–320

Chang CC, Hsu YH, Chou HC, Lee YC, Juan SH (2017) 3-Methylcholanthrene/aryl-hydrocarbon receptor-mediated hypertension through eNOS inactivation. Journal of Cellular Physiology 232: 1020–1029

Chelladurai KS, Christyraj JD, Azhagesan A, Paulraj VD, Jothimani M, Yesudhason BV, Vasantha NC, Ganesan M, Rajagopalan K, Venkatachalam S, Benedict J (2020) Exploring the effect of UV-C radiation on earthworm and understanding its genomic integrity in the context of H2AX expression. Scientific Reports 10:1–4

Cherr GN, Fairbairn E, Whitehead A (2017) Impacts of petroleum-derived pollutants on fish development. Annual Review of Animal Biosciences 8:185–203

Chizhova T, Hayakawa K, Tishchenko P, Nakase H, Koudryashova Y (2013) Distribution of PAHs in the northwestern part of the Japan Sea. Deep Sea Research Part II: Topical Studies in Oceanography 86:19–24

Colli-Dula RC, Fang X, Moraga-Amador D, Albornoz-Abud N, Zamora-Bustillos R, Conesa A, Zapata-Perez O, Moreno D, Hernandez-Nunez E (2018) Transcriptome analysis reveals novel insights into the response of low-dose benzo(a)pyrene exposure in male tilapia. Aquatic Toxicology 201:162–173

Collins JF, Brown JP, Alexeeff GV, Salmon AG (1998) Potency equivalency factors for some polycyclic aromatic hydrocarbons and polycyclic aromatic hydrocarbon derivatives. Regulatory toxicology and pharmacology 28:45–54

Compeau GC, Bartha R (1985) Sulfate-reducing bacteria: principal methylators of mercury in anoxic estuarine sediment. Applied and environmental microbiology 50:498–502

Cortat B, Garcia CC, Quinet A, Schuch AP, de Lima-Bessa KM, Menck CF (2013) The relative roles of DNA damage induced by UVA irradiation in human cells. Photochemical & Photobiological Sciences 12:1483–1495

Courdavault S, Baudouin C, Charveron M, Canguilhem B, Favier A, Cadet J, Douki T (2005) Repair of the three main types of

bipyrimidine DNA photoproducts in human keratinocytes exposed to UVB and UVA radiations. DNA repair 4:836–844

Delaney JC, Essigmann JM (2006) Assays for determining lesion bypass efficiency and mutagenicity of site-specific DNA lesions in vivo. Methods in Enzymology 408:1–5

DeMarini DM (2013) Genotoxicity biomarkers associated with exposure to traffic and near-road atmospheres: a review. Mutagenesis 28:485–505

DeMarini DM, Mutlu E, Warren SH, King C, Gilmour MI, Linak WP (2019) Mutagenicity emission factors of canola oil and waste vegetable oil biodiesel: comparison to soy biodiesel. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 846:403057

Denissenko MF, Pao A, Tang MS, Pfeifer GP (1996) Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Science 274:430–432

Devi NL, Yadav IC, Shihua Q, Dan Y, Zhang G, Raha P (2016) Environmental carcinogenic polycyclic aromatic hydrocarbons in soil from Himalayas, India: Implications for spatial distribution, sources apportionment and risk assessment. Chemosphere 144: 493–502

Doll R, Peto R (1981) The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. JNCI: Journal of the National Cancer Institute 66:1192–1308

Douki T (2016) Relative contributions of UVB and UVA to the photoconversion of (6-4) photoproducts into their Dewar valence isomers. Photochemistry and photobiology 92:587–594

Douki T, Reynaud-Angelin A, Cadet J, Sage E (2003) Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation. Biochemistry 42:9221–9226

Dunn J, Potter M, Rees A, Runger TM (2006) Activation of the Fanconi anemia/BRCA pathway and recombination repair in the cellular response to solar ultraviolet light. Cancer research 66:11140–11147

Elvers I, Johansson F, Groth P, Erixon K, Helleday T (2011) UV stalled replication forks restart by re-priming in human fibroblasts. Nucleic acids research 39:7049–7057

Everett CJ, Frithsen IL (2008) Association of urinary cadmium and myocardial infarction. Environmental research 106:284–286

Fang Z, Zhao M, Zhen H, Chen L, Shi P, Huang Z (2014) Genotoxicity of tri-and hexavalent chromium compounds in vivo and their modes of action on DNA damage in vitro. Plos one 9:e103194

Farrukh MR, Nissar UA, Kaiser PJ, Afnan Q, Sharma PR, Bhushan S, Tasduq SA (2015) Glycyrrhizic acid (GA) inhibits reactive oxygen Species mediated photodamage by blocking ER stress and MAPK pathway in UV-B irradiated human skin fibroblasts. Journal of Photochemistry and Photobiology B: Biology 148:351–317

Fawaz EG, Salam DA (2018) Preliminary economic assessment of the use of waste frying oils for biodiesel production in Beirut, Lebanon. Science of The Total Environment 637:1230–1240

Fedeles BI, Freudenthal BD, Yau E, Singh V, Chang SC, Li D, Delaney JC, Wilson SH, Essigmann JM (2015) Intrinsic mutagenic properties of 5-chlorocytosine: a mechanistic connection between chronic inflammation and cancer. Proceedings of the National Academy of Sciences 112:E4571–E4580

Federico MB, Vallerga MB, Radl A, Paviolo NS, Bocco JL, Di Giorgio M, Soria G, Gottifredi V (2016) Chromosomal integrity after UV irradiation requires FANCD2-mediated repair of double strand breaks. PLoS genetics 12:e1005792

Fic A, Sollner DM, Filipič M, Peterlin ML (2013) Mutagenicity and DNA damage of bisphenol A and its structural analogues in HepG2 cells. *Arhiv za higijenu rada i toksikologiju 64*(2):189–199

Flaherty OEJ, Kerger BD, Hays SM, Paustenbach DJ (2001) A physiologically based model for the ingestion of chromium (III) and chromium (VI) by humans. Toxicological Sciences 60:196–213

Foster PL, Eisenstadt E, Miller JH (1983) Base substitution mutations induced by metabolically activated aflatoxin B1. Proceedings of the National Academy of Sciences 80:2695–2698

Fukazawa H, Hoshino K, Shiozawa T, Matsushita H, Terao Y (2001) Identification and quantification of chlorinated bisphenol A in wastewater from wastepaper recycling plants. Chemosphere 44: 973–979

Gao X, Wang HS (2014) Impact of bisphenol A on the cardiovascular system-epidemiological and experimental evidence and molecular mechanisms. International journal of environmental research and public health 11:8399–8413

Gary AS, Rochette PJ (2020) Apoptosis, the only cell death pathway that can be measured in human diploid dermal fibroblasts following lethal UVB irradiation. Scientific reports 10:1–1

Gassman NR (2017) Induction of oxidative stress by bisphenol A and its pleiotropic effects. Environmental and molecular mutagenesis 58: 60–71

Gassman NR, Coskun E, Stefanick DF, Horton JK, Jaruga P, Dizdaroglu M, Wilson SH (2015) Bisphenol a promotes cell survival following oxidative DNA damage in mouse fibroblasts. PloS one 10: e0118819

Gentner NJ, Weber LP (2011) Intranasal benzo[a]pyrene alters circadian blood pressure patterns and causes lung inflammation in rats. Archives of toxicology 85:337–346

Gichner T (1991) IARC monographs on the evaluation of carcinogenic risks to humans: diesel and gasoline engine exhausts and some nitroarenes. Volume 46. Biologia Plantarum 33:174

Glezos JD, Albrecht JE, Gair RD (2006) Pneumonitis after inhalation of mercury vapours. Canadian respiratory journal 13:150–152

Greinert R, Volkmer B, Henning S, Breitbart EW, Greulich KO, Cardoso MC, Rapp A (2012) UVA-induced DNA double-strand breaks result from the repair of clustered oxidative DNA damages. Nucleic acids research 40:10263–10273

Grimalt JO, Van Drooge BL, Ribes A, Fernandez P, Appleby P (2004) Polycyclic aromatic hydrocarbon composition in soils and sediments of high altitude lakes. Environmental Pollution 131:13–24

Halliday GM (2005) Inflammation, gene mutation and photoimmunosuppression in response to UVR-induced oxidative damage contributes to photocarcinogenesis. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 571: 107–120

Hamilton EM, Young SD, Bailey EH, Watts MJ (2018) Chromium speciation in foodstuffs: a review. Food chemistry 250:105–112

Han C, Srivastava AK, Cui T, Wang QE, Wani AA (2016) Differential DNA lesion formation and repair in heterochromatin and euchromatin. Carcinogenesis 37:129–138

Hannam ML, Bamber SD, Moody AJ, Galloway TS, Jones MB (2010) Immunotoxicity and oxidative stress in the Arctic scallop Chlamysislandica: effects of acute oil exposure. Ecotoxicology and environmental safety 73:1440–1448

Hayakawa K (2018) Oil spills and polycyclic aromatic hydrocarbons. In: Hayakama K (ed) Polycyclic aromatic hydrocarbons. Springer, Singapore, pp 213–223

Hayakawa K, Nomura M, Nakagawa T, Oguri S, Kawanishi T, Toriba A, Kizu R, Sakaguchi T, Tamiya E (2006) Damage to and recovery of coastlines polluted with C-heavy oil spilled from the Nakhodka. Water Research 40:981–989

Hoffmann GR (1980) Genetic effects of dimethyl sulfate, diethyl sulfate, and related compounds. Mutation Research/Reviews in Genetic Toxicology 75:63–129

Holick MF (1999) Evolution, biologic functions, and recommended dietary allowances for vitamin D. InVitamin D. In: Holick MF (ed) Vitamin D. Nutrition and Health. Humana Press, Totowa, pp 1–16

Holme JA, Brinchmann BC, Refsnes M, Lag M, Ovrevik J (2019) Potential role of polycyclic aromatic hydrocarbons as mediators of

cardiovascular effects from combustion particles. Environmental Health 18:1–8

Honda M, Qiu X, Koyama J, Uno S, Undap SL, Shimasaki Y, Oshima Y (2018) The wharf roach, Ligia sp., a novel indicator of polycyclic aromatic hydrocarbon contamination in coastal areas. International Journal of Environmental Research 12:1–11

Hrudkova M, Fiala Z, Borska L, Novosad J, Smolej L (2004) The effect of polycyclic aromatic hydrocarbons to bone marrow. Actamedica 47:75–81

Hsu IC, Metcalf RA, Sun T, Welsh JA, Wang NJ, Harris CC (1991) Mutational hot spot in the p53 gene in human hepatocellular carcinomas. Nature 350:427–438

Hu G, Sun C, Li J, Zhao Y, Wang H, Li Y (2009) POPs accumulated in fish and benthos bodies taken from Yangtze River in Jiangsu area. Ecotoxicology 18:647–651

Hylland K (2006) Polycyclic aromatic hydrocarbon (PAH) ecotoxicology in marine ecosystems. Journal of Toxicology and Environmental Health 69:109–123

Idowu O, Semple KT, Ramadass K, O Connor W, Hansbro P, Thavamani P (2019) Beyond the obvious: environmental health implications of polar polycyclic aromatic hydrocarbons. Environ Int 123:543–557

Ikehata H, Kawai K, Komura JI, Sakatsume K, Wang L, Imai M, Higashi S, Nikaido O, Yamamoto K, Hieda K, Watanabe M (2008) UVA1 genotoxicity is mediated not by oxidative damage but by cyclobutane pyrimidine dimers in normal mouse skin. Journal of Investigative Dermatology 128:2289–2296

Ikenaka Y, Oguri M, Saengtienchai A, Nakayama SM, Ijiri S, Ishizuka M (2013) Characterization of phase-II conjugation reaction of polycyclic aromatic hydrocarbons in fish species: unique pyrene metabolism and species specificity observed in fish species. Environmental toxicology and pharmacology 36:567–578

Iwegbue CM, Obi G, Aganbi E, Ogala JE, Omo-Irabor OO, Martincigh BS (2016) Concentrations and health risk assessment of polycyclic aromatic hydrocarbons in soils of an urban environment in the Niger Delta, Nigeria. Toxicology and Environmental Health Sciences 8:221–233

Jacob J (2008) The significance of polycyclic aromatic hydrocarbons as environmental carcinogens. 35 years research on PAH—a retrospective. Polycyclic Aromatic Compounds 28:242–272

Jan AT, Azam M, Siddiqui K, Ali A, Choi I, Haq QM (2015) Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants. International journal of molecular sciences 16:29592–29630

Jarup L, Akesson A (2009) Current status of cadmium as an environmental health problem. Toxicology and applied pharmacology 238:201–208

Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, Resnick MA, Gordenin DA (2003) Cadmium is a mutagen that acts by inhibiting mismatch repair. Nature genetics 34:326–329

Johri N, Jacquillet G, Unwin R (2010) Biometals: an international journal on the role of metal ions in biology, biochemistry, and medicine. Biometals 23:783–792

Jorgensen A, Giessing AM, Rasmussen LJ, Andersen O (2008) Biotransformation of polycyclic aromatic hydrocarbons in marine polychaetes. Marine Environmental Research 65:171–186

Kang JI Jr, Sowers LC (2008) Examination of hypochlorous acid-induced damage to cytosine residues in a CpG dinucleotide in DNA. Chemical research in toxicology 21:1211–1218

Kannan K, Perrotta E (2008) Polycyclic aromatic hydrocarbons (PAHs) in livers of California sea otters. Chemosphere 71:649–655

Kappes UP, Luo D, Potter M, Schulmeister K, Runger TM (2006) Short- and long-wave UV light (UVB and UVA) induce similar mutations in human skin cells. Journal of Investigative Dermatology 126:667–675

Kaufmann WK, Cleaver JE (1981) Mechanisms of inhibition of DNA replication by ultraviolet light in normal human and xerodermapigmentosum fibroblasts. Journal of molecular biology 149:171–187

Kavathas P, Bach FH, DeMars R (1980) Gamma ray-induced loss of expression of HLA and glyoxalase I alleles in lymphoblastoid cells. Proceedings of the National Academy of Sciences 77:4251–4255

Kawai Y, Morinaga H, Kondo H, Miyoshi N, Nakamura Y, Uchida K, Osawa T (2004) Endogenous formation of novel halogenated 2′-deoxycytidine: hypohalous acid-mediated DNA modification at the site of inflammation. Journal of Biological Chemistry 279:51241–51249

Khan FH, Ambreen K, Fatima G, Kumar S (2012) Assessment of health risks with reference to oxidative stress and DNA damage in chromium exposed population. Science of the total environment 430:68–74

Knutson CG, Mangerich A, Zeng Y, Raczynski AR, Liberman RG, Kang P, Ye W, Prestwich EG, Lu K, Wishnok JS, Korzenik JR (2013) Chemical and cytokine features of innate immunity characterize serum and tissue profiles in inflammatory bowel disease. Proceedings of the National Academy of Sciences 110:E2332–E2341

Kotas J, Stasicka ZJ (2000) Chromium occurrence in the environment and methods of its speciation. Environmental pollution 107:263–283

Koyama J, Uno S, Kohno K (2004) Polycyclic aromatic hydrocarbon contamination and recovery characteristics in some organisms after the Nakhodka oil spill. Marine pollution bulletin 49:1054–1061

Koyama J, Uno S, Nagai Y, Anukorn B (2016) Early monitoring of spilled oil contamination in Rayong, Thailand. Journal of the Society of Environmental Toxicity 19:25–33

Kumar R, Routh J, Ramanathan AL, Klump JV (2012) Organic Geochemistry Polycyclic aromatic hydrocarbon fingerprints in the Pichavaram mangrove—Estuarine sediments, southeastern India. Org Geochem 53:88–94

Kumar AV, Kothiyal NC, Kumari S, Mehra R, Parkash A, Sinha RR, Tayagi SK, Gaba R (2014) Determination of some carcinogenic PAHs with toxic equivalency factor along roadside soil within a fast developing northern city of India. Journal of Earth System Science 123:479–489

Kuo CY, Cheng YW, Chen CY, Lee H (1998) Correlation between the amounts of polycyclic aromatic hydrocarbons and mutagenicity of airborne particulate samples from Taichung City, Taiwan. Environmental research 78:43–49

Ladwani KD, Ladwani KD, Ramteke DS (2013) Assessment of poly aromatic hydrocarbon (PAH) dispersion in the near shore environment of Mumbai, India after a large scale oil spill. Bulletin of environmental contamination and toxicology 90:515–520

Lao VV, Herring JL, Kim CH, Darwanto A, Soto U, Sowers LC (2009) Incorporation of 5-chlorocytosine into mammalian DNA results in heritable gene silencing and altered cytosine methylation patterns. Carcinogenesis 30:886–893

Lee JH, Hwang GS, Kim JK, Choi BS (1998) The solution structure of DNA decamer duplex containing the Dewar product of thymidylyl (3′→ 5′) thymidine by NMR and full relaxation matrix refinement. FEBS letters 428:269–274

Lee HJ, Shim WJ, Lee J, Kim GB (2011) Temporal and geographical trends in the genotoxic effects of marine sediments after accidental oil spill on the blood cells of striped beakperch (Oplegnathusfasciatus). Marine pollution bulletin 62:2264–2268

Li D, Fedeles BI, Singh V, Peng CS, Silvestre KJ, Simi AK, Simpson JH, Tokmakoff A, Essigmann JM (2014) Tautomerism provides a molecular explanation for the mutagenic properties of the anti-HIV nucleoside 5-aza-5, 6-dihydro-2′-deoxycytidine. Proceedings of the National Academy of Sciences 111:E3252–E3259

Li X, Sun S, Yao J, Sun Z (2020) Using relaxation time to characterize biological effects of different mutagens. Scientific Reports 10:1–10

Liang S, Xu M, Zhang T (2013) Life cycle assessment of biodiesel production in China. Bioresource technology 129:72–77

Liu Y, Li Y, Liu K, Shen J (2014) Exposing to cadmium stress cause profound toxic effect on microbiota of the mice intestinal tract. PloS one 9:e85323

Liu MX, Yang YY, Yun XY, Zhang MM, Wang J (2016) Occurrence, sources, and cancer risk of polycyclic aromatic hydrocarbons and polychlorinated biphenyls in agricultural soils from the Three Gorges Dam region, China. Journal of Soil and Water Conservation 71:327–334

Loprieno N (1975) International Agency for Research on Cancer (IARC) Monographs on the evaluation of carcinogenic risk of chemicals to man: relevance of data on mutagenicity. Mutation research 31:210

Lu H, Hu Y, Kang C, Meng Q, Lin Z (2021) Cadmium-induced toxicity to amphibian tadpoles might be exacerbated by alkaline not acidic pH level. Ecotoxicology and Environmental Safety 218:112288

MacDonald GZ, Hogan NS, Kollner B, Thorpe KL, Phalen LJ, Wagner BD, Van Den Heuvel MR (2013) Immunotoxic effects of oil sands-derived naphthenic acids to rainbow trout. Aquatic Toxicology 126: 95–103

Maffini MV, Rubin BS, Sonnenschein C, Soto AM (2006) Endocrine disruptors and reproductive health: the case of bisphenol-A. Molecular and Cellular Endocrinology 254:179–186

Magi E, Bianco R, Ianni C, Di Carro M (2002) Distribution of polycyclic aromatic hydrocarbons in the sediments of the Adriatic Sea. Environmental pollution 119:91–98

Magnuson JT, Khursigara AJ, Allmon EB, Esbaugh AJ, Roberts AP (2018) Effects of Deepwater Horizon crude oil on ocular development in two estuarine fish species, red drum (Sciaenopsocellatus) and sheepshead minnow (Cyprinodonvariegatus). Ecotoxicology and Environmental Safety 166:186–191

Malaki M (2013) Acute encephalopathy following the use of aluminum hydroxide in a boy affected with chronic kidney disease. Journal of pediatric neurosciences 8:81–82

Mangerich A, Knutson CG, Parry NM, Muthupalani S, Ye W, Prestwich E, Cui L, McFaline JL, Mobley M, Ge Z, Taghizadeh K (2012) Infection-induced colitis in mice causes dynamic and tissue-specific changes in stress response and DNA damage leading to colon cancer. Proceedings of the National Academy of Sciences 109:E1820–E1819

Markovitsi D (2016) UV-induced DNA damage: the role of electronic excited states. Photochemistry and photobiology 92:45–51

Maron DM, Ames BN (1983) Revised methods for the Salmonella mutagenicity test. Mutat Res-Environ Mutagen Relat Subj 113:173–215

Marris CR, Kompella SN, Miller MR, Incardona JP, Brette F, Hancox JC, Sorhus E, Shiels HA (2020) Polyaromatic hydrocarbons in pollution: a heart-breaking matter. The Journal of physiology 598:227–247

McClellan RO (1986) Toxicological effects of emissions from diesel engines. Dev Toxicol Environ Sci 13:3–8

Messner B, Bernhard D (2010) Cadmium and cardiovascular diseases: cell biology, pathophysiology, and epidemiological relevance. Biometals 23:811–822

Miki S, Uno S, Ito K, Koyama J, Tanaka H (2014) Distributions of polycyclic aromatic hydrocarbons and alkylated polycyclic aromatic hydrocarbons in Osaka Bay, Japan. Marine pollution bulletin 85: 558–565

Minamoto T, Mai M, Ronai ZE (1999) Environmental factors as regulators and effectors of multistep carcinogenesis. Carcinogenesis 20: 519–527

Mineshiba J, Myokai F, Mineshiba F, Matsuura K, Nishimura F, Takashiba S (2005) Transcriptional regulation of β-defensin-2 by lipopolysaccharide in cultured human cervical carcinoma (HeLa) cells. FEMS Immunology & Medical Microbiology 45:37–44

Misra RB, Babu GS, Ray RS, Hans RK (2002) Tubifex: a sensitive model for UV-B-induced phototoxicity. Ecotoxicology and environmental safety 52:288–295

Moeller R, Stackebrandt E, Douki T, Cadet J, Rettberg P, Mollenkopf HJ, Reitz G, Horneck G (2007) DNA bipyrimidine photoproduct repair and transcriptional response of UV-C irradiated Bacillus subtilis. Archives of microbiology 188:421–431

Moeller R, Douki T, Rettberg P, Reitz G, Cadet J, Nicholson WL, Horneck G (2010) Genomic bipyrimidine nucleotide frequency and microbial reactions to germicidal UV radiation. Archives of microbiology 192:521–529

Morales ME, Derbes RS, Ade CM, Ortego JC, Stark J, Deininger PL, Roy-Engel AM (2016) Heavy metal exposure influences double strand break DNA repair outcomes. PloS one 11:e0151367

Morley NJ (2012) The effects of radioactive pollution on the dynamics of infectious diseases in wildlife. Journal of environmental radioactivity 106:81–97

Motulsky AG (1984) Environmental mutagenesis and disease in human populations. In: Chu EHY, Generoso WM (eds) Mutation, cancer, and malformation. Environmental Science Research. Springer, Boston, pp 1–11

Mouchet F, Baudrimont M, Gonzalez P, Cuenot Y, Bourdineaud JP, Boudou A, Gauthier L (2006) Genotoxic and stress inductive potential of cadmium in Xenopuslaevis larvae. Aquatic Toxicology 78: 157–166

Mouret S, Baudouin C, Charveron M, Favier A, Cadet J, Douki T (2006) Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. Proceedings of the National Academy of Sciences 103:13765–13670

Mozdarani H (2012) Biological complexities in radiation carcinogenesis and cancer radiotherapy: impact of new biological paradigms. Genes (Basel) 3:90–114

Munoz-de-Toro M, Markey CM, Wadia PR, Luque EH, Rubin BS, Sonnenschein C, Soto AM (2005) Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. Endocrinology 146:4138–4147

Muthusamy V, Piva TJ (2010) The UV response of the skin: a review of the MAPK, NFκB and TNFα signal transduction pathways. Archives of dermatological research 302:5–17

Mutlu E, Warren SH, Matthews PP, King C, Walsh L, Kligerman AD, Schmid JE, Janek D, Kooter IM, Linak WP, Gilmour MI (2015) Health effects of soy-biodiesel emissions: mutagenicity-emission factors. Inhalation Toxicology 27:585–596

Naik P, Vijayalaxmi KK (2009) Cytogenetic evaluation for genotoxicity of bisphenol-A in bone marrow cells of Swiss albino mice. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 676: 106–112

Nakazawa H, English D, Randell PL, Nakazawa K, Martel N, Armstrong BK, Yamasaki H (1994) UV and skin cancer: specific p53 gene mutation in normal skin as a biologically relevant exposure measurement. Proceedings of the National Academy of Sciences 91: 360–364

Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ (2007) Lead exposure and cardiovascular disease—a systematic review. Environmental Health Perspectives 115:472–482

Nekhavhambe TJ, Van Ree T, Fatoki OS (2014) Determination and distribution of polycyclic aromatic hydrocarbons in rivers, surface runoff, and sediments in and around Thohoyandou, Limpopo Province, South Africa. Water SA 40:415–424

Nishigori C, Yarosh DB, Ullrich SE, Vink AA, Bucana CD, Roza L, Kripke ML (1996) Evidence that DNA damage triggers interleukin 10 cytokine production in UV-irradiated murine keratinocytes. Proceedings of the National Academy of Sciences 93:10354–10359

Nishijo M, Nakagawa H, Suwazono Y, Nogawa K, Kido T (2017) Causes of death in patients with Itai-itai disease suffering from

severe chronic cadmium poisoning: a nested case–control analysis of a follow-up study in Japan. BMJ open 7:e015694

Pacchierotti F, Ranaldi R, Eichenlaub-Ritter U, Attia S, Adler ID (2008) Evaluation of aneugenic effects of bisphenol A in somatic and germ cells of the mouse. Mutat Res Genet Toxicol Environ Mutagen 651: 64–70

Palmer HJ, Paulson KE (1997) Reactive oxygen species and antioxidants in signal transduction and gene expression. Nutrition reviews 55: 353–361

Penn A (1990) International commission for protection against environmental mutagens and carcinogens. ICPEMC Working Paper 7/1/1. Mutational events in the etiology of arteriosclerotic plaques. Mutat Res 239:149–162

Pereira MG, Walker LA, Wright J, Best J, Shore RF (2009) Concentrations of polycyclic aromatic hydrocarbons (PAHs) in the eggs of predatory birds in Britain. Environmental science & technology 43:9010–9015

Perera FP, Chang HW, Tang D, Roen EL, Herbstman J, Margolis A, Huang TJ, Miller RL, Wang S, Rauh V (2014) Early-life exposure to polycyclic aromatic hydrocarbons and ADHD behavior problems. PloS one 9:e111670

Pershagen G (1981) The carcinogenicity of arsenic. Environmental Health Perspectives 40:93–100

Pfeifer GP, You YH, Besaratinia A (2005) Mutations induced by ultraviolet light. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 571:19–31

Pogoda De La Vega U, Rettberg P, Douki T, Cadet J, Horneck G (2005) Sensitivity to polychromatic UV-radiation of strains of Deinococcusradiodurans differing in their DNA repair capacity. International journal of radiation biology 81:601–611

Pouget JP, Douki T, Richard MJ, Cadet J (2000) DNA damage induced in cells by γ and UVA radiation as measured by HPLC/GC− MS and HPLC− EC and comet assay. Chemical research in toxicology 13: 541–549

Pribylova P, Kares R, Boruvkova J, Cupr P, Prokes R, KohoutekJ HI, Klanova J (2012) Levels of persistent organic pollutants and polycyclic aromatic hydrocarbons in ambient air of Central and Eastern Europe. Atmospheric Pollution Research 3:494–505

Proctor DM, Otani JM, Finley BL, Paustenbach DJ, Bland JA, Speizer N, Sargent EV (2002) Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. Journal of Toxicology and Environmental Health Part A 65:701–746

Pulliero A, Godschalk R, Andreassi MG, Curfs D, Van Schooten FJ, Izzotti A (2015) Environmental carcinogens and mutational pathways in atherosclerosis. Int J Hyg Environ Health 218:293–312

Rajpara RK, Dudhagara DR, Bhatt JK, Gosai HB, Dave BP (2017) Polycyclic aromatic hydrocarbons (PAHs) at the Gulf of Kutch, Gujarat, India: occurrence, source apportionment, and toxicity of PAHs as an emerging issue. Marine pollution bulletin 119:231–238

Rastogi RP, Kumar A, Tyagi MB, Sinha RP (2010) Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair. Journal of nucleic acids 2010:592980

Raval CM, Zhong JL, Mitchell SA (2012) Tyrrell RM (2012) The role of Bach1 in ultraviolet A-mediated human heme oxygenase 1 regulation in human skin fibroblasts. Free Radical Biology and Medicine. 52:227–236

Ravanat JL, Douki T, Cadet J (2001) Direct and indirect effects of UV radiation on DNA and its components. Journal of Photochemistry and Photobiology B: Biology 63:88–102

Rengarajan T, Rajendran P, Nandakumar N, Lokeshkumar B, Rajendran P, Nishigaki I (2015) Exposure to polycyclic aromatic hydrocarbons with special focus on cancer. Asian Pacific Journal of Tropical Biomedicine 5:182–189

Rizzo JL, Dunn J, Rees A, Runger TM (2011) No formation of DNA double-strand breaks and no activation of recombination repair with UVA. Journal of Investigative Dermatology 131:1139–1148

Rochester JR (2013) Bisphenol A and human health: a review of the literature. Reproductive toxicology 42:132–155

Rosette C, Karin M (1996) Ultraviolet light and osmotic stress: activation of the JNK cascade through multiple growth factor and cytokine receptors. Science 274:1194–1197

Rozgaj R, Kasuba V, Sentija K, Prlic I (1999) Radiation-induced chromosomal aberrations and haematological alterations in hospital workers. Occupational medicine 49:353–360

Runger TM, Farahvash B, Hatvani Z, Rees A (2012) Comparison of DNA damage responses following equimutagenic doses of UVA and UVB: a less effective cell cycle arrest with UVA may render UVA-induced pyrimidine dimers more mutagenic than UVB-induced ones. Photochemical &Photobiological Sciences 11:207–215

Sage E, Lamolet B, Brulay E, Moustacchi E, Chteauneuf A, Drobetsky EA (1996) Mutagenic specificity of solar UV light in nucleotide excision repair-deficient rodent cells. Proceedings of the National Academy of Sciences 93:176–180

Sage E, Girard PM, Francesconi S (2012) Unravelling UVA-induced mutagenesis. Photochemical &Photobiological Sciences 11:74–80

Samburova V, Zielinska B, Khlystov A (2017) Do 16 polycyclic aromatic hydrocarbons represent PAH air toxicity? Toxics 5:17

Sanchez-Navarrete J, Ruiz-Pérez NJ, Guerra-Trejo A, Toscano-Garibay JD (2020) Simplified modeling of E. coli mortality after genome damage induced by UV-C light exposure. Scientific Reports 10:1–5

Sato Y, Takahashi S, Kinouchi Y, Shiraki M, Endo K, Matsumura Y, Kakuta Y, Tosa M, Motida A, Abe H, Imai G (2006) IL-10 deficiency leads to somatic mutations in a model of IBD. Carcinogenesis 27:1068–1073

Sawicka E, Jurkowska K, Piwowar A (2020) Chromium (III) and chromium (VI) as important players in the induction of genotoxicity-current view. Annals of Agricultural and Environmental Medicine: AAEM 28:1–10

Schafer M, Werner S (2015) Nrf2—a regulator of keratinocyte redox signaling. Free Radical Biology and Medicine 88:243–252

Schrader TJ, Cooke GM (2003) Effects of Aroclors and individual PCB congeners on activation of the human androgen receptor in vitro. Reproductive Toxicology 17:15–23

Schuch AP, da Silva GR, de Lima-Bessa KM, Schuch NJ, Menck CF (2009) Development of a DNA-dosimeter system for monitoring the effects of solar-ultraviolet radiation. Photochemical &Photobiological Sciences 8:111–120

Shafiee M, Hoseinnezhad E, Vafapour H, Borzoueisileh S, Ghorbani M, Rashidfar R (2016) Hematological findings in medical professionals involved at intraoperative fluoroscopy. Global Journal of Health Science 8:232–238

Shanker AK, Cervantes C, Loza-Tavera H, Avudainayagam S (2005) Chromium toxicity in plants. Environment international 31:739–753

Sheh A, Lee CW, Masumura K, Rickman BH, Nohmi T, Wogan GN, Fox JG, Schauer DB (2010) Mutagenic potency of Helicobacter pylori in the gastric mucosa of mice is determined by sex and duration of infection. Proceedings of the National Academy of Sciences 107:15217–115222

Sheng Z, Oka S, Tsuchimoto D, Abolhassani N, Nomaru H, Sakumi K, Yamada H, Nakabeppu Y (2012) 8-Oxoguanine causes neurodegeneration during MUTYH-mediated DNA base excision repair. The Journal of clinical investigation 122:4344–4361

Shindo Y, Hashimoto T (1998) Ultraviolet B-induced cell death in four cutaneous cell lines exhibiting different enzymatic antioxidant defences: involvement of apoptosis. Journal of dermatological science 17:140–150

Shrivastav N, Fedeles BI, Li D, Delaney JC, Frick LE, Foti JJ, Walker GC, Essigmann JM (2014) A chemical genetics analysis of the roles of bypass polymerase DinB and DNA repair protein AlkB in processing N 2-alkylguanine lesions in vivo 9:e94716

Soto AM, Fernandez MF, Luizzi MF, OlesKarasko AS, Sonnenschein C (1997) Developing a marker of exposure to xenoestrogen mixtures in human serum. Environmental Health Perspectives 105:647–654

Spruck CH, Rideout WM, Olumi AF, Ohneseit PF, Yang AS, Tsai YC, Nichols PW, Horn T, Hermann GG, Steven K, Ross RK (1993) Distinct pattern of p53 mutations in bladder cancer: relationship to tobacco usage. Cancer research 53:1162–1166

Sugiura-Ogasawara M, Ozaki Y, Sonta SI, Makino T, Suzumori K (2005) Exposure to bisphenol A is associated with recurrent miscarriage. Human Reproduction 20:2325–2329

Syed DN, Afaq F, Mukhtar H (2012) Differential activation of signaling pathways by UVA and UVB radiation in normal human epidermal keratinocytes. Photochemistry and Photobiology 88:1184–1190

Takeuchi Y, Murakami M, Nakajima N, Kondo N, Nikaido O (1998) The photorepair and photoisomerization of DNA lesions in etiolated cucumber cotyledons after irradiation by UV-B depends on wavelength. Plant and cell physiology 39:745–750

Taqi AH, Faraj KA, Zaynal SA, Hameed AM, Mahmood AA (2018) Effects of occupational exposure of x-ray on hematological parameters of diagnostic technicians. Radiation Physics and Chemistry 147:45–52

Taylor JS, Lu HF, Kotyk JJ (1990) Quantitative conversion of the (6–4) photoproduct of TpdC to its Dewar valence isomer upon exposure to simulated sunlight. Photochemistry and photobiology 51:161–167

Tomljenovic L (2011) Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? Journal of Alzheimer's Disease 23:567–598

Tronczyński J, Munschy C, Heas-Moisan K, Guiot N, Truquet I, Olivier N, Men S, Furaut A (2004) Contamination of the Bay of Biscay by polycyclic aromatic hydrocarbons (PAHs) following the T/V "Erika" oil spill. Aquatic Living Resources 17:243–259

Tseng CH (2005) Blackfoot disease and arsenic: a never-ending story. Journal of Environmental Science and Health 23:55–74

Tsutsui T, Tamura Y, Yagi E, Hasegawa K, Takahashi M, Maizumi N, Yamaguchi F, Barrett JC (1998) Bisphenol-A induces cellular transformation, aneuploidy and DNA adduct formation in cultured Syrian hamster embryo cells. International journal of cancer 75: 290–294

Ullrich SE (1994) Mechanism involved in the systemic suppression of antigen-presenting cell function by UV irradiation. Keratinocyte-derived IL-10 modulates antigen-presenting cell function of splenic adherent cells. The Journal of Immunology 152:3410–3416

Uno S, Koyama J, Kokushi E, Monteclaro H, Santander S, Cheikyula JO, Miki S, Añasco N, Pahila IG, Taberna HS, Matsuoka T (2010) Monitoring of PAHs and alkylated PAHs in aquatic organisms after 1 month from the Solar I oil spill off the coast of Guimaras Island, Philippines. Environmental Monitoring and Assessment 165:501–515

Uno S, Kokushi E, Anasco NC, Iwai T, Ito K, Koyama J (2017) Oil spill off the coast of Guimaras Island, Philippines: distributions and changes of polycyclic aromatic hydrocarbons in shellfish. Marine pollution bulletin 124:962–973

Vallerga MB, Mansilla SF, Federico MB, Bertolin AP, Gottifredi V (2015) Rad51 recombinase prevents Mre11 nuclease-dependent degradation and excessive PrimPol-mediated elongation of nascent DNA after UV irradiation. Proceedings of the National Academy of Sciences 112:E6624–E6633

Verheyen L, Versieren L (2014) Smolders E (2014) Natural dissolved organic matter mobilizes Cd but does not affect the Cd uptake by the green algae Pseudokirchneriella subcapitata (Korschikov) in resin buffered solutions. Aquatic Toxicology. 154:80–86

Verma N, Pink M, Rettenmeier AW, Schmitz-Spanke S (2012) Review on proteomic analyses of benzo[a]pyrene toxicity. Proteomics 12: 1731–1755

Wang G, Mielke HW, Quach VA, Gonzales C, Zhang Q (2004) Determination of polycyclic aromatic hydrocarbons and trace metals in New Orleans soils and sediments. Soil & Sediment Contamination 13:313–327

Wang BJ, Sheu HM, Guo YL, Lee YH, Lai CS, Pan MH, Wang YJ (2010) Hexavalent chromium induced ROS formation, Akt, NF-κB, and MAPK activation, and TNF-α and IL-1α production in keratinocytes. Toxicology letters 198:216–224

Wang L, Zhang S, Wang L, Zhang W, Shi X, Lu X, Li X, Li X (2018) Concentration and risk evaluation of polycyclic aromatic hydrocarbons in urban soil in the typical semi-arid city of Xi'an in Northwest China. International journal of environmental research and public health 15:607

Webb AR, Kline L, Holick MF (1988) Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. The Journal of Clinical Endocrinology & Metabolism 67:373–378

Węgrzyn G, Czyz A (2003) Detection of mutagenic pollution of natural environment using microbiological assays. Journal of applied microbiology 95:1175–1181

Whiteman M, Jenner A, Halliwell B (1997) Hypochlorous acid-induced base modifications in isolated calf thymus DNA. Chemical research in toxicology 10:1240–1246

Winterbourn CC, Kettle AJ (2000) Biomarkers of myeloperoxidase-derived hypochlorous acid. Free Radical Biology and Medicine 29:403–409

Wischermann K, Popp S, Moshir S, Scharfetter-Kochanek K, Wlaschek M, De Gruijl F, Hartschuh W, Greinert R, Volkmer B, Faust A, Rapp A (2008) UVA radiation causes DNA strand breaks, chromosomal aberrations and tumorigenic transformation in HaCaT skin keratinocytes. Oncogene 27:4269–4280

World Health Organization (1985) Dimethyl sulfate World Health Organization. World Health Organization. https://apps.who.int/iris/handle/10665/39595. Accessed 10 May 2021

Wu Q, Leung JY, Geng X, Chen S, Huang X, Li H, Huang Z, Zhu L, Chen J, Lu Y (2015) Heavy metal contamination of soil and water in the vicinity of an abandoned e-waste recycling site: implications for dissemination of heavy metals. Science of the Total Environment 506:217–225

Yamaba H, Haba M, Kunita M, Sakaida T, Tanaka H, Yashiro Y, Nakata S (2016) Morphological change of skin fibroblasts induced by UV irradiation is involved in photoaging. Experimental dermatology 25: 45–51

Yan J, Wang L, Fu PP, Yu H (2004) Photomutagenicity of 16 polycyclic aromatic hydrocarbons from the US EPA priority pollutant list. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 557:99–108

Yang Y, Woodward LA, Li QX, Wang J (2014) Concentrations, source and risk assessment of polycyclic aromatic hydrocarbons in soils from Midway Atoll, North Pacific Ocean. PLoS One 9:e86441

Yu H (2002) Environmental carcinogenic polycyclic aromatic hydrocarbons: photochemistry and phototoxicity. Journal of Environmental Science and Health 20:149–183

Zha J, Hong X, Rao H, Yuan L, Wang Z, Kumaran SS (2017) Benzo(a)pyrene-induced a mitochondria-independent apoptosis of liver in juvenile Chinese rare minnows (Gobiocypris rarus). Environmental Pollution 231:191–199

Zhang YJ, Weksler BB, Wang L, Schwartz J, Santella RM (1998) Immunohistochemical detection of polycyclic aromatic hydrocarbon-DNA damage in human blood vessels of smokers and non-smokers. Atherosclerosis 140:325–331

Zhang C, Jin Y, Yu Y, Xiang J, Li F (2021) Cadmium-induced oxidative stress, metabolic dysfunction and metal bioaccumulation in adult palaemonid shrimp Palaemon macrodactylus (Rathbun, 1902). Ecotoxicology and Environmental Safety 208:111591

Zhitkovich A (2011) Chromium in drinking water: sources, metabolism, and cancer risks. Chemical research in toxicology 24:1617–1629

Zhu Y, Yang Y, Liu M, Zhang M, Wang J (2015) Concentration, distribution, source, and risk assessment of PAHs and heavy metals in surface water from the Three Gorges Reservoir, China. Human and Ecological Risk Assessment: An International Journal 21:1593–1607

Zoeller RT, Bansal R, Parris C (2005) Bisphenol-A, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters RC3/neurogranin expression in the developing rat brain. Endocrinology 146:607–612