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Chapter

A Role for Heavy Metal Toxicity and Air Pollution in Respiratory Tract Cancers

Chanda Siddoo-Atwal

Abstract

Cigarette smoke and air pollution have been associated with lung cancer and naso pharyngeal and laryngeal cancer, respectively. Significant concentrations of select heavy metals including lead and cadmium have been isolated in popular cigarette brands, and these heavy metals can be inhaled via smoking. Lead is able to mimic the activity of calcium in the human body, thereby leading to toxic effects in a variety of target organs. Lead perturbs and alters the release of intracellular calcium stores from organelles like the endoplasmic reticulum (ER) and mitochondria. A rise in mitochondrial calcium stimulates the generation of reactive oxygen species (ROS) and free fatty acids which can further promote calcium release and, ultimately, result in cell death. In the case of cadmium, the renal proximal tubule of the kidney accumulates freely filtered and metallothionein-bound metal, which is degraded in endosomes and lysosomes. This results in the release of free cadmium into the cytosol where it can generate reactive oxygen species and activate cell death pathways. In developing countries, indoor air pollution due to the domestic use of unprocessed biomass fuels such as wood, dung, and coal is another cause of respiratory tract cancers in humans. In some developed countries such as Australia and Canada, the alarming increase in forest fire frequency due to climate change and the associated smoke released into the environment is also likely to pose a future human health risk. Polycyclic organic particles in biomass and forest fire smoke can include carcinogens such as benzo[a]pyrene, which is also found in cigarette smoke. Benzo[a]pyrene can induce apoptosis in mammalian cells by initiating mitochondrial dysfunction, activating the intrinsic caspase pathway (caspase-3 and caspase-9), and via p53 activation. The constitutive activation of apoptotic pathways has been linked to carcinogenesis in a number of cancer models.

Keywords: cigarette smoke, indoor and outdoor air pollution, lead, cadmium, benzo[a]pyrene, respiratory tract cancers

1. Introduction

"Smoking is hazardous to the health" is a phrase that is commonly used and understood in many parts of the world. In actuality, "smoke" is the hazard. The inhalation of smoke from cigarettes, indoor air pollution, and forest fires currently constitutes a serious public health issue of increasing importance as environmental conditions rapidly change on the planet.

The presence of heavy metals and other toxic and trace elements in tobacco smoke is a major concern. Notably, lead (Pb), arsenic (As), chromium (Cr), nickel (Ni), and cadmium (Cd) are usually associated with its adverse health effects. Heavy metals can pass from tobacco to the smoke and smoke condensate [1]. Although cigarette filters remove a portion of these elements, environmental smoke pollution occurs via the smoke exhaled by the smoker and the sidestream smoke emitted by the burning cigarette. The sidestream smoke inhaled by non-smokers can contain a relatively high concentration of heavy metals. This process of passive smoking can result in the deposition of heavy metals deep in the lung tissue [2].

Lead and cadmium, particularly, both of which have long half-lives (10–12 years), accumulate in tissues and fluids following smoke exposure. Biomonitoring studies reveal that smokers have substantially higher lead and cadmium levels than nonsmokers. Bioaccumulation of metals has also been demonstrated in nonsmokers, who are chronically exposed to secondhand smoke [3]. Smoking-related diseases can be attributed to the inhalation of many different toxins including heavy metals. Heavy metals like lead have been shown to affect various biochemical processes in the human body including calcium metabolism and the activation of cell death pathways which are involved in carcinogenesis [4].

A significant percentage of people in developing countries utilize coal and biomass fuels like wood and dung for domestic energy. These materials are often burnt in simple stoves resulting in incomplete combustion. Consequently, women and young children are exposed to high levels of indoor air pollution daily. Many substances in biomass smoke are hazardous to the health including carbon monoxide, nitrous oxides, sulfur oxides (principally from coal), formaldehyde, and polycyclic organic matter (notably carcinogens such as benzo[a]pyrene [BaP]). Particles, particularly with diameters below 10 microns (PM10), especially those less than 2.5 microns in diameter (PM2.5), can penetrate deeply into the lungs to cause damage to these delicate organs. Epidemiological evidence suggests that indoor air pollution increases the risk of chronic obstructive pulmonary disease and of acute respiratory infections in childhood, which are the most important cause of death among preschool children in developing nations. Biomass smoke is also associated with low birth weight, increased infant and perinatal mortality, pulmonary tuberculosis, nasopharyngeal and laryngeal cancer, cataracts, and lung cancer (specifically, in the case of coal) [5].

The incidence of forest fires is strongly linked to climatic conditions. In fact, climate change is predicted to affect forests in the following ways: increased growth rates, tree-line movements, changes to forest species assemblages, increased fire incidence, more severe droughts in some areas, increased storm damage, and increased insect and pathogen damage [6]. Specifically, predicted impacts of climate change in Australia include increased fuel loadings, drier fuels, and increased dangerous fire weather [7, 8]. Model predictions for Canada have found expectations of decreased fire frequency in parts of the eastern boreal forest, while dramatic increases are expected elsewhere in the country [9]. In fact, over recent decades, the area burned by wildland fires in Canada has steadily increased and is predicted to double by the end of the century accompanied by an increase in length of the fire season [10]. At the same time, it is important to note that several climatic and non-climatic factors besides increased temperatures determine forest fire frequency including ignition sources, fuel loads, vegetation characteristics, rainfall, humidity, wind, topography, landscape fragmentation, and management policies [11]. Currently, research on the health effects of forest and wild fire smoke

Figure 1.
The same view of the Olympic Mountains in Washington State, USA, before (left) and during (right) forest fire season (2018) in British Columbia, Canada.

is limited [12]. However, smoke from these conflagrations contains the same kind of particles as indoor combustion from wood smoke. Similar to the situation of indoor air pollution from biomass smoke, forest fires generate polycyclic aromatic hydrocarbons (PAHs), which can include carcinogens such as benzo(a)pyrene [BaP] [13]. Polycyclic aromatic hydrocarbons (PAH) like BaP can stimulate various biochemical processes in the body including the continuous activation of apoptotic (cell death) pathways that have been linked to the initiation of carcinogenesis [14]. It is of interest that this chemical compound (BaP) is also found in cigarette smoke (**Figure 1**).

2. Lead [Pb]

Generally, elemental lead use and exposure have decreased significantly since the 1970s due to the innovation of unleaded gasoline and lead-free plumbing and paints. However, lead poisoning is still a serious problem. Lead is very toxic and specifically targets the kidneys, liver, central nervous system, hematopoietic system, and endocrine and reproductive systems. It can be absorbed by women during pregnancy and transferred to the developing fetus. Prenatal lead exposure has been linked to reduced birth weight, preterm delivery, and neurodevelopmental abnormalities in offspring. Exposure occurs mostly as a result of deteriorating house paints, contact at the workplace, hobbies, leaching from lead-containing vessels into food and water, cigarette smoke, and the use of lead in certain traditional medicines and cosmetics. Routes of exposure mainly include inhalation of lead-containing dust particles and ingestion of lead-contaminated food and water [15]. Lead has been classed as a probable carcinogen by the Environmental Protection Agency (EPA) and other regulatory agencies [16, 17].

Lead is able to mimic the activity of calcium in the human body, thereby leading to toxic effects in a variety of target organs [15]. These biochemical effects include the calcium-dependent inhibition of release of several neurotransmitters [18] and augmentation of calcium-dependent events involving protein kinase C and calmodulin [19, 20]. Lead can also be incorporated into the human skeleton instead of calcium.

Moreover, lead perturbs and alters the release of intracellular calcium stores from organelles like the endoplasmic reticulum (ER) and mitochondria [19, 21]. Mitochondria can accumulate large amounts of calcium, for example, in the presence of inorganic phosphate. The rise in calcium results in an upregulation of energy metabolism and an increase in mitochondrial membrane potential. Then, the release of this accumulated calcium through a special channel, permeability transition pore (PTP), can cause mitochondrial depolarization. According to the

model of glutamate toxicity, mitochondrial calcium accumulation and resultant membrane depolarization are clearly linked to the initiation of a cell death pathway in mitochondria [22, 23].

A rise in mitochondrial calcium also stimulates the generation of reactive oxygen species (ROS) and free fatty acids which can further promote opening of the PTP, resulting in calcium release and, ultimately, in cell death [23]. Many genes and proteins that respond to conditions of oxidative stress stimulated by ROS release within the cell subsequently trigger apoptosis. Because mitochondria are important regulators of cellular redox status, the induction of oxidative stress exhibits its effects upon these organelles by triggering the intrinsic apoptotic pathway via cytochrome c release and caspase cascade activation [24, 25].

In this regard, it has been reported in various experiments that lead poisoning results in cellular damage mediated by the formation of reactive oxygen species (ROS) [26]. An elevation in the relative activities of certain antioxidant enzymes such as glutathione peroxidase has also been reported in the erythrocytes of lead-exposed workers [27].

In one large epidemiological study in Eastern Europe spanning several years, an elevated risk of renal cell carcinoma was observed in the category of highest cumulative occupational lead exposure [28]. Lead has been found to induce renal tumors in rats and mice [29, 30]. Lead causes DNA strand breakage and 8-hydroxy-deoxyguanosine adduct formation in calf thymus DNA [31]. It induces sister chromatid exchanges in Chinese hamster ovary cells [32]. Lead-induced cytotoxicity and apoptosis have been demonstrated in human cancer cells via various cellular and molecular processes including oxidative stress induction and caspase-3 activation [15]. Finally, mitochondrial alterations appear to play a central role in lead-induced rod photoreceptor cell apoptosis [33].

Taken together, the above data point to the activation of apoptotic pathways as a possible mechanism of lead carcinogenesis. It clearly has the potential to initiate cancer as described in a new approach to cancer risk assessment based on an apoptotic model of tumor formation. In this two-stage model of tumor formation, Step I exposure to a carcinogen (Pb in this case), possibly facilitated by a genetic predisposition, results in an epigenetic or genetic event causing continuous apoptotic activation of cells in the target tissue. In Step II, when the carcinogen may or may not be present, resistance to apoptosis and continuous cell proliferation result due to another genetic or epigenetic event [4, 14].

3. Cadmium [Cd]

Cadmium is a heavy metal that is widely distributed in the earth's crust, while the highest level of cadmium compounds is found in sedimentary rocks and marine phosphates. Human exposure to this element can occur through employment in primary metal industries, eating contaminated food, smoking cigarettes (a major contributor), and working in cadmium-contaminated places. Other sources of cadmium include emissions from mining, smelting, manufacturing batteries, pigments, stabilizers, and alloys. The main routes of cadmium exposure are via inhalation or cigarette smoke and ingestion of food. It is a severe pulmonary and gastrointestinal irritant, which can prove fatal when inhaled or ingested in extreme cases [15].

Cadmium levels in the body can be measured in the blood or urine. Typically, blood and urine cadmium levels are higher in cigarette smokers, intermediate in former smokers, and lower in nonsmokers. The circulatory system is an important distribution route of cadmium toxicity, and blood vessels are considered to be the

primary target. Chronic cadmium inhalation exposure is associated with changes in pulmonary function and chest radiographs consistent with emphysema. Chronic low-level cadmium exposure can also cause decreases in olfactory function and bone mineral density and osteoporosis.

Cadmium compounds have been classified as human carcinogens by certain regulatory agencies including the International Agency for Research on Cancer and the US National Toxicology Program based on repeated findings of a correlation between occupational cadmium exposure and lung cancer in humans. In addition, there is strong experimental evidence that the pulmonary system is the main target site for carcinogenesis in rodents [17]. Such rodent studies reveal that chronic cadmium inhalation results in pulmonary adenocarcinomas. Oral cadmium exposure in rats is also associated with tumors of the prostate, testes, and hematopoietic system [34–36].

Cadmium is a weak mutagen and the mechanisms of its toxicity are poorly understood. It has been reported to affect signal transduction pathways, induce inositol phosphate formation, increase cytosolic free calcium levels in a variety of cell types, and block calcium channels. At lower micromolar concentrations, cadmium can induce the expression of antioxidant enzymes such as glutathione transferases and metallothioneins suggesting that it causes cellular damage via the generation of ROS, which can initiate DNA damage and activate apoptotic pathways.

Specifically, receptor-mediated endocytosis of freely filtered and metallothionein-bound cadmium causes it to accumulate in the renal proximal tubule of the kidney. Following internalization and degradation of metallothionein-cadmium complexes in endosomes and lysosomes in this kidney model, free cadmium is released into the cytosol, where it can generate ROS and activate cell death pathways [37] implicated in cancer.

4. Polycyclic aromatic hydrocarbons [PAHs] and benzo(a)pyrene [BaP]

Polycyclic aromatic hydrocarbons and their derivatives are a major class of organic compounds that are produced as a result of incomplete combustion of fossil fuels and other organic matter. Consequently, they are prevalent in the human environment and include a number of potent carcinogens. Some of the major sources of these emissions are wood and coal burning, automobiles and other fossil-fuel propelled modes of transportation, heat and power plants, and refuse burning. PAHs are not only present in the air, but are found in many common foods and drinking water and form a significant component of tobacco smoke [38].

Levels of PAHs are routinely measured in the atmosphere for air quality assessment, in sediments and mollusks for environmental monitoring, in biological tissues for monitoring of health effects, and in foodstuffs for safety reasons. Gas chromatography is often chosen for analyzing (separating, identifying, and quantifying) PAHs due to the high degree of selectivity and resolution this method provides [39].

PAH-DNA adducts have been compared in the peripheral leukocytes of non-small cell lung cancer patients and in controls. Adduct formation has been found to be significantly higher in lung cancer cases than in controls. Further, in the cancer patients, adducts were more strongly correlated with lung tumor tissue than with non-tumor lung tissue consistent with a genetic susceptibility to lung cancer as a result of adduct-induced DNA damage [40]. More specifically, BPDE-DNA adducts have been observed in the white blood cells of occupationally exposed workers and cigarette smokers. BaP is metabolically activated to its carcinogenic form benzo(*a*) pyrene diol epoxide (BPDE), and this is an important step in BaP carcinogenicity

in experimental animal studies [41]. Moreover, using a specially developed assay on peripheral blood lymphocytes, it has been determined that there is a significant association between the level of in vitro BPDE-induced DNA adducts and risk for lung cancer in humans [42]. In another molecular epidemiologic hospital-based study, DNA repair capacity was measured in cultured lymphocytes from lung cancer patients and controls. It cleverly utilized the host-cell reactivation assay with a reporter gene damaged by the known activated tobacco carcinogen, benzo[*a*] pyrene diol epoxide. It was observed that reduced DNA repair capacity was associated with increased risk of lung cancer in a dose-dependent fashion [43]. In addition, the frequency of BPDE-induced chromosomal aberrations is significantly higher in lymphocyte cultures from lung cancer patients than in controls. These chromosomal aberrations tend to be predominantly single chromatid breaks with few exchanges or isochromatid breaks [44].

There is overwhelming evidence in the scientific literature for BaP-induced lung and respiratory tract carcinogenesis in experimental animals. Highly sensitive immunoassays using antiserum specific for benzo(a)pyrene have revealed a dose-related increase in levels of BaP-DNA adducts in the lung tissue of mice and rabbits following intraperitoneal injection with this chemical carcinogen [45]. In the past, respiratory tract tumors have been induced in Syrian golden hamsters following intratracheal injections of benzo(a)pyrene and benzo(a)pyrene-ferric oxide [46, 47]. In fact, BaP-induced lung cancer in mice is so reproducible that it has become a popular model for studying the potential role of natural products in ameliorating the effects of BaP [48]. It is known that lung carcinogenesis can be induced in Swiss albino mice following biweekly treatment with BaP (50 mg/kg b. wt.) over a period of 16 weeks [49]. Supplementation with hesperidin, a naturally occurring flavonoid in citrus fruits, has been reported to have a chemopreventive activity during BaP-induced lung cancer in Swiss albino mice. It appears to attenuate the accompanying loss in tissue antioxidant function and to have an antiproliferative effect as revealed by histopathological analysis involving proliferating cell nuclear antigen (PCNA) immunostaining [50]. In another interesting chemopreventive study, BaP-induced neoplasia of mouse forestomach was inhibited by a principal component of Japanese soy sauce, 4-hydroxy-2(or 5)-ethyl-5(or 2)-methyl-3(2H)-furanone, suggesting that this *Saccharomyces cerevisiae* metabolite is a potent anticarcinogen [51].

In mouse hepatoma cells, treatment with micromolar concentrations of BaP results in caspase-3 activation, followed by apoptosis. However, caspase-3 activity is blocked and BaP-induced apoptosis attenuated by pretreatment of the cells with a specific inhibitor of caspase-3-like proteases, acetyl-Asp-Glu-Val-Asp-aldehyde [52]. It has also been demonstrated that BaP treatment of mouse hepatoma cells causes apoptosis via the catalytic activation of caspase-9, mitochondrial dysfunction including a loss in membrane potential and cytosolic release of cytochrome c, and phosphorylation of p53 (Ser15) [53]. In BaP-treated human Hep3B (p53-null) cells, necrosis is induced at 12 hours and apoptosis at 24 h, respectively, due to a dramatic increase in oxidative stress [54].

Although many epidemiological studies have been carried out on smokers with lung cancer, there is also evidence to suggest that people living in urban areas have an increased risk of lung cancer due to higher levels of air pollution in these areas. A number of studies have indicated a correlation between lung cancer risk and exposure to urban air pollutants, particularly inhalable and fine particulate matter [55]. In animal experiments, lung toxicity, inflammatory effects, genotoxicity, and rodent carcinogenicity have been demonstrated for diesel exhaust and urban air particulates. In vitro, both can cause oxidative DNA damage, mainly single-strand breaks and 8-oxo-dG (8-oxo-7,8-dihydro-2′-deoxyguanosine). In vivo, even at low-dose levels, diesel exhaust particles can induce oxidative DNA damage in

rodent lung tissue [55]. BaP is currently used as the main indicator of PAH levels in air pollution. However, recently, there has been some concern that there may be PAHs with a higher potency of carcinogenicity like dibenz[*a*, *h*]anthracene (DBA) and dibenzo[*a*, *l*]pyrene in air/PAH mixtures that pose even a greater health risk to humans [56].

5. Antioxidants and detoxification

Inside the cell, the harmful effects of free radicals are balanced by the antioxidant action of antioxidant enzymes and nonenzymatic antioxidants that help in the process of detoxification.

Metallothioneins (MTs) are small, cysteine-rich proteins that bind heavy metals and participate in an array of protective stress responses. MTs are found in bacteria, plants, invertebrates, and vertebrates. There are four main mammalian MT isoforms (MT-1 to MT-4) with distinct roles in different tissues. Aerobic organisms are susceptible to damage by reactive oxygen species (ROS) and reactive nitrogen species (RNS). MT protects cells from exposure to various free radical species like the hydroxyl, peroxyl, alkoxyl, and superoxide anion radical and the nitric oxide and nitric dioxide radicals, which react readily with sulfhydryl groups. MT is also important for the regulation of zinc levels and the distribution of this metal in the extracellular space. Since zinc cannot pass easily through membranes, zinc-transporting proteins, Zrt-Irt-like protein or zinc iron permease (ZIPs) and zinc transporters (ZnTs), help to facilitate this process. The presence of Zinc(II) within the cell causes an increase in the major zinc-binding protein metallothionein, and it binds to MTs forming a thermodynamically stable complex. MT can be activated by various stimuli including heavy metal ions, cytokines, growth factors, and oxidative stress within the cell. Cells that display high MT production are resistant to heavy metal toxicity by cadmium, whereas cell lines that cannot synthesize MTs are sensitive to the toxic effects of cadmium [57].

Cytosolic glutathione S-transferases (GSTs) are a supergene family of dimeric enzymes that detoxify a number of carcinogens including polycyclic aromatic hydrocarbons which are some of the principal substrates. The enzyme, GSTM1-1, appears to be particularly effective in dealing with certain PAH derivatives, and at least one large epidemiological study has found a highly significant correlation between the absence of GSTM1–1 activity and adenocarcinoma of the lung in smokers [58]. GSTs require the presence of glutathione in order to fulfill their function of conjugating glutathione (GSH) to cytotoxic and genotoxic lipophilic compounds for their removal from the cell. Interestingly, the presence of intracellular zinc appears to boost glutathione levels in certain cell types [59], and, thus, zinc supplementation may be a useful measure for the prevention of lung cancer from tobacco smoke and environmental factors such as heavy metals by boosting both MT and GST activities [60]. Glutathione supplementation may also be helpful.

Vitamin C (ascorbic acid) and vitamin E (DL-α-tocopherol) treatment together has been reported to result in a significant reduction in smoking-related BaP-DNA adducts in women and suggests that antioxidant supplementation may help to mitigate some of the carcinogenic effects of BaP exposure. It is particularly effective in females with the GSTM1 null genotype, whereas males do not seem to benefit from the same treatment [61].

Black tea polyphenols (theaflavins and epigallocatechin gallate) have been observed to suppress cell proliferation and induce apoptosis during BaP-induced lung carcinogenesis in mice. The occurrence of carcinoma in situ was effectively reduced as a result of this treatment [62] (**Figure 2**).

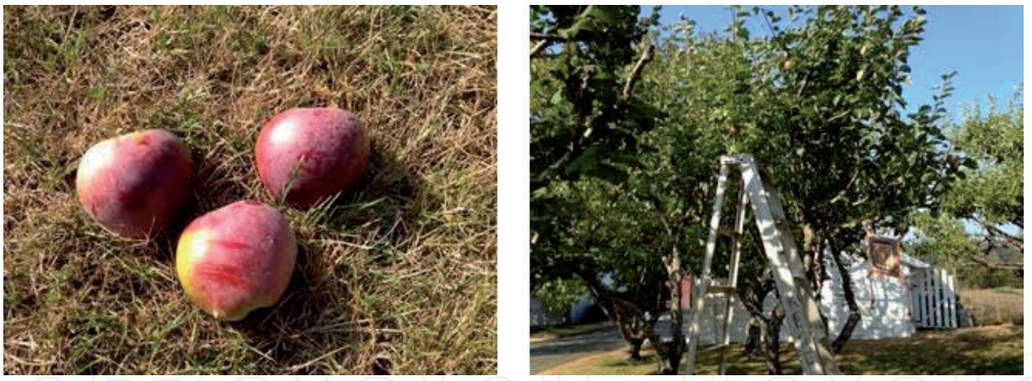

Figure 2.
A crop of BC apples covered with a layer of fine particulate matter from forest fire smoke.

6. Conclusions

Lead and cadmium are two of the heavy metals that are expelled in cigarette smoke. In epidemiological studies, lead and cadmium have been correlated with human cancers including renal and lung, respectively. In animal studies, lead has been found to induce renal tumors in rats and mice, while cadmium inhalation is associated with pulmonary adenocarcinomas in rodents. In addition, oral cadmium in the diet of rats results in tumors of the prostate, testes, and hematopoietic system. Apoptosis or oxidative stress, which can signal cell death, has been observed and reported in cell cultures in response to both metals. As such, these two heavy metals have the potential to cause cancer independently.

The polycyclic aromatic hydrocarbon, benzo(a)pyrene, which is a prominent component of indoor/outdoor air pollution and cigarette smoke, is a well-established carcinogen. BaP-DNA adducts have been observed in lung cancer patients and in experimental animals following BaP exposure. BPDE-DNA adducts have been reported in the white blood cells of occupationally exposed workers and cigarette smokers. There is a strong positive correlation between this type of BaP/BaP metabolite DNA adduct formation and risk for lung cancer in humans. An elevated frequency of BPDE-induced chromosomal aberrations has also been observed in lymphocyte cultures from lung cancer patients. Moreover, animal studies have revealed a highly reproducible association between BaP exposure and respiratory tract tumors in Syrian golden hamsters and lung cancer in mice. BaP treatment of mouse hepatoma cells can cause apoptosis via caspase-3 and caspase-9 activation, mitochondrial dysfunction including a loss in membrane potential and cytosolic release of cytochrome c, and phosphorylation of p53 (Ser15). In a BaP-treated human hepatocellular carcinoma cell line, necrosis is induced at 12 hours and apoptosis at 24 hours, respectively, due to a dramatic increase in oxidative stress. Thus, these results are consistent with a mechanism of carcinogenesis based on an apoptotic model.

Zinc supplementation may be useful for heavy metal detoxification in mammals. Certain antioxidants including vitamin C, vitamin E, black tea polyphenols (theaflavins and epigallocatechin gallate), and flavonoids have been reported to help in mitigating some of the toxic effects of polycyclic aromatic hydrocarbons. Thus, antioxidant supplementation may prove to be an effective measure in reducing the risk of respiratory tract cancers in smokers and from air pollution in developing nations where there is still a significant use of biomass fuels.

In recent years, great progress has been made in banning cigarette smoking from public places around the world due to the proven hazards of secondhand

smoke. Some developing nations have also instituted economic and educational programs to discourage the general use of biomass fuels and seasonal burning of paddy fields. Certain countries have legislated stricter laws to deal with irresponsible cigarette smokers, who often start large blazes by discarding their cigarettes and matches outdoors, and, professional arsonists. In places like British Columbia, where there are so many forests and the incidence of forest fires is increasing due to climate change, one extreme solution may be to close public parks during the peak fire season.

Nevertheless, despite these local actions, nothing short of an international effort is required to tackle climate change effectively on a global scale. If countries are to truly cooperate in combatting the rapidly changing conditions on the planet, general goodwill among nations and the cessation of all hostilities embodied in a World Peace Treaty (WPT) seem to be necessary. A ban on the use of nuclear weapons and nuclear testing should also be included in such an agreement since there is already evidence to suggest that atmospheric nuclear explosions have contributed to climate change in addition to greenhouse gases. Economic benefits are likely to be a positive outcome of "green" eco-friendly policies in the long run as awareness about their importance is raised among the general public.

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