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Mini-Review

Environmental and health hazards of hazardous air pollutants with relevance to their persistence, endocrine-disrupting property and carcinogenicity

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ABSTRACT

About 190 toxic substances have been designated as hazardous air pollutants (HAPs) by USA under the Clean Air Act Amendment of 1990. Some HAPs possess specific chemical & physical properties, and are grouped into persistent organic pollutants (POPs) and endocrine-disrupting chemicals (EDCs). More seriously, a few of HAPs are known carcinogens to humans. The objective of this paper was to review the hazards of HAPs in line with the international concern about their environmental and carcinogenic risks in recent years. To protect human health and the environment from POPs, the Stockholm Convention on POPs and the national programs on EDCs were established. Furthermore, several international organizations or programs have developed a classification system to evaluate the carcinogenicity of an agent to humans. They include the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services, the U.S. Environmental Protection Agency (USEPA), and the American Conference of Governmental Industrial Hygienists (ACGIH). It was found that some organochlorine pesticides (i.e., chlordane, heptachlor, hexachlorobenzene, pentachlorophenol and toxaphene) and unintentional byproducts (i.e., dioxins) are blanketed into HAPs, POPs and EDCs. These semivolatile organic compounds can be released into the atmospheric environment by anthropogenic sources as a result of their volatilization and deposition, thus posing a potential health risk when exposed to inhaled air and food chain.

KEYWORDS: hazardous air pollutant, persistent organic pollutant, endocrine-disrupting chemicals, human carcinogen, health risk

INTRODUCTION

Since the 1960s, many studies have been focused on the health effects of non-criteria air pollutants in the atmospheric environment because they could pose health risks of a more serious nature than criteria air pollutants such as carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3) [1]. For example, very high incidences of leukemia have occurred in the outdoor environment [2], giving evidence of the presence of a large number of carcinogenic air pollutants in the ambient air. In this regard, benzene may be the most notable environmental carcinogen because it has been listed as the Class 1 carcinogen (confirmed as a human carcinogen) by the International Agency for Research on Cancer (IARC). Under the Section 112 of the 1970 Clean Air Act Amendments, the U.S. Congress authorized the Environmental Protection Agency (EPA) to promulgate the

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national emission standards for harmful substances designated as hazardous air pollutants (HAPs). A group of carcinogenic chemicals were initially designated as HAPs in the National Emission Standards for Hazardous Air Pollutants (NESHAP) under the Clean Air Act Amendments of 1970 and 1977, including asbestos, beryllium (Be) and mercury (Hg) in 1973, vinyl chloride in 1975, benzene in 1977, radionuclides in 1979, inorganic arsenic (As) in 1980, and coke oven emissions in 1984 [3]. Subsequently, the Title III of Clean Air Act Amendments was passed in 1990, and the U.S. Congress listed another 189 substances and groups of substances as HAPs by using technology-based rather than health-based standards. Major hazard concerns not only include acute toxicity (e.g., irritation, neurotoxicity and asthma) and chronic toxicity (e.g., carcinogenicity, mutagenicity, teratogenicity and reproductive toxicity), but also involve adverse impacts on wildlife, aquatic life and other natural resources.

In the past two decades, the occurrence of some specific chemicals has become more and more concerning. These anthropogenic pollutants are persistent organic pollutants (POPs) [4], and endocrine-disrupting chemicals or compounds (EDCs) [5]. The former are synthetic organic substances and/or unintentionally produced substances, which possess a high chemical stability and lipophilicity. As a result of release into the environment, POPs remain intact for a long period and are liable to bioaccumulate in the fatty tissues of living organisms, thus causing potential effects on humans and wildlife due to their worldwide distributions in ambient air [6] and in groundwater [7]. Among POPs, organochlorine pesticides (OCPs) have shown a variety of adverse effects on the biodiversity *via* atmospheric pathways [8], suggesting that OCPs can be designated as HAPs. EDCs, however, are exogenous substances or agents that can interfere with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the living organisms [9]. More notably, some EDCs (e.g., bisphenol-A) are produced in large quantities to be incorporated into daily commodities and chemical products, including plastics, food packaging materials and pesticides [10]. Due to the increasing growth in the intentional and unintentional production of EDCs, the prevalence of neurodevelopmental disorders in relation to autism (ASD) and attention deficit hyperactivity (ADHD) has been observed in recent years [11]. A potential association between autism and ambient concentrations of EDCs (i.e. heavy metals and solvents) has also been found [12].

The term HAPs or air toxics generally refers to those that when present in the atmosphere could be associated with adverse human health effects [13]. In this regard, HAPs include a diverse set of non-criteria pollutants that are reflected in the various health effects when exposed to them, causing acute illness such as nausea, narcosis, and other respiratory injuries, and chronic diseases such as cancer, infertility and developmental disorders. Although the management of HAPs has been reviewed [14-16], there is no literature addressing HAPs with relevance to the public concern about the human health and environmental risks, including environmental persistence, endocrine-disrupting property and carcinogenicity in humans.

HAPs with relevance to POPs

In the past decades, people were very concerned about the environment persistence of a diverse number of xenobiotic chemicals in the environment for a long time, thus becoming widely distributed around the world, bioaccumulating in the fatty tissue and blood of humans and wildlife, and causing harmful impacts on human health or on the ecosystem [17-19]. These chemical substances may be grouped into persistent organic pollutants (POPs), which are very stable compounds that resist photolytic, biological and chemical degradation at normal conditions. Since 1970s, the risks posed by POPs, especially by organochlorine insecticides, have aroused increasing concern among international organizations and scientific communities. Several regional and global treaties and/or initiatives have been negotiated for identifying POPs and for developing risk management countermeasures to reduce the exposure of humans to these xenobiotics [20, 21]. Among them, the most important treaty is the Stockholm Convention on

POPs, which was signed in 2001 and came into force in 2004, requiring its parties to take measures to eliminate or reduce the release of POPs into the environment. In the first stage, twelve POPs, consisting primarily of insecticides and/or unintentional byproducts (i.e., polychlorinated aromatic compounds), were initially listed in the Stockholm Convention. The industrial chemicals identified in the Convention include aldrin, chlordane, DDT, dieldrin, endrin, Heptachlor, hexachlorobenzene (HCB), Mirex, polychlorinated biphenyls (PCBs), and toxaphene. By contrast, the unintentional byproducts are polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDDs/ PCDFs, or dioxins), PCBs and HCB. As reviewed by Breivik *et al*. [22], the main sources of historic dioxin emissions were largely associated with the production of chlorinated organics (including pesticides) and chlorine (chlor-alkali plants with graphite electrodes). It means that pesticides may contain dioxins and can be relevant dioxin sources for a country [23]. As a consequence, several organic compounds are continuously blanketed under the Convention on the Conference of the Parties (COP), and these are listed in table 1. The Convention requires each party to eliminate, restrict and reduce the production and/or use of POPs listed in Annex. A, Annex. B and Annex. C, respectively.

Due to their long persistence in the environment, POPs could bioaccumulate in organisms through the respiratory route and food chain, posing potential significant impacts on human health, including certain cancers, birth defects, dysfunctional immune and reproductive systems, greater susceptibility to disease and damages to the central and peripheral nervous systems. On the other hand, some POPs occur at ppb concentrations in ambient air, especially in the urban environment and industrial park zones. As shown in table 1, some POPs, which are unintentionally produced by the combustion and other high-temperature processes, have been listed as HAPs. These compounds include polychlorinated naphthalenes (PCNs), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzo-*p*-furans (PCDFs), polychlorinated biphenyls (PCBs) and chlorobenzenes (i.e., pentachlorobenzene and hexachlorobenzene). Table 1 also shows other POPs, including chlordane, heptachlor, hexachlorobutadiene, pentachlorophenol and toxaphene, which are listed as HAPs. These are known to be extensively used as pesticides or industrial chemicals, but can be reasonably expected to cause a health hazard based on toxicity, ambient concentration and exposure risk.

HAPs with relevance to EDCs

Endocrine-disruptors or EDCs are a great diversity of xenobiotic chemicals that cause harmful effects on the endocrine (hormone) system in which the body's development, growth, reproduction, metabolism, immunity and behavior are regulated through a complex network of glands, hormones and receptors [24]. The endocrine and reproductive effects of these compounds (e.g., pesticides, or phenols) are believed to have similar effects as the endogenous estrogens [25]. More seriously, exposure to EDCs in the environment can have life-long effects and can even have adverse consequences linked to sexual differentiation for the next generation [26]. Therefore, there has been considerable concern regarding the potential adverse effects of environmental and human exposure to a class of synthetic EDCs on human health since the 1990s. At present, these chemicals are collectively termed as endocrine-disrupting chemicals (EDCs). However, the list of EDCs varies among scientific organizations and official agencies in different countries. In order to regulate these xenobiotics, environmental pollutants suspected to pose endocrine threat are generally classified based on the following criteria [27]: health risk; possible high concentration in given portion of the environment; risk perception of the consumers; annual production volume; environmental, occupational, and exposure data; speciation form (e.g., tissue analysis); fate and transport models; and persistence.

The developed countries like USA, EU and Japan have been very proactive in the past two decades in their investigation on endocrine-disruptors. In 1998, the Ministry of Environment under the Japanese Government started Strategic Programs on Environmental Endocrine-Disruptors (SPEED) with a focus on screening of EDCs.

Table 1. List of persistent organic compounds (POPs) designated as HAPs by USA.

POPs[a]	Category of use			HAPs	Annex.[b]
	Pesticide	Industrial chemical	(Unintentional production)		
Aldrin	V				A
Chlordane	V			V	A
Chlordecone	V				A
DDT	V				B
Dieldrin	V				A
Endosulfan and its related isomers	V				A
Endrin	V				A
Heptachlor	V			V	A
Hexabromobiphenyl		V			A
Hexabromocyclododecane		V			A
Hexabromobiphenyl ether		V			A
Heptabromobiphenyl ether		V			A
Hexachlorobenzene	V	V	V	V	A, C
Hexachlorobutadiene		V		V	A
α-Hexachlorocyclohexane	V				A
β-Hexachlorocyclohexane	V				A
Lindane	V				A
Mirex	V				A
Pentabromodiphenyl ether		V			A
Pentachlorobenzene	V	V	V		A, C
Pentachlorophenol and its salts and esters	V			V	A
Perfluorooctane sulfonic acid and its salts		V			B
Perfluorooctane sulfonyl fluoride		V			B
Polychlorinated biphenyls		V	V	V	A, C
Polychlorinated dibenzo-*p*-dioxins			V	V[c]	C
Polychlorinated dibenzo-*p*-furans			V		C
Polychlorinated naphthalenes		V	V		A, C
Tetrabromodiphenyl ether		V			A
Toxaphene	V			V	A

[a]: List of POPs in the Stockholm Convention.
[b]: Annex. A (Elimination), Annex. B (Restriction) and Annex. C (Unintentional production).
[c]: 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Under the Program, the officials prioritized 67 suspected EDCs for further investigation. In Nov. 2000, the officials revised the list down to 65 chemicals, which will be regulated under Japan's Chemical Substance Control Law (CSCL) and be subjected to restrictions or even ban. Basically, these EDCs have been commercially and industrially used in a wide range of products and/or commodities. As shown in table 2, some EDCs have been also listed as HAPs. These compounds include heavy metals (i.e., cadmium, lead and mercury), pesticides (i.e., carbaryl, chlordane, DDE, 1,2-dibromo-3-chloropropane, heptachlor, hexachlorobenzene, hexachlorocyclohexanes, methoxychlor, pentachlorophenol, toxaphene, and trifluralin), polychlorinated/polyaromatic hydrocarbons (i.e., BaP, PCDDs, and PCBs), phthalates (i.e., di-n-butyl phthalate), and industrial chemicals (i.e., styrenes). Table 2 also reports some EDCs to be also listed as POPs under the Stockholm Convention, including chlordane, heptachlor, hexachlorobenzene, hexachlorocyclohexanes, pentachlorophenol, PCBs, PCDDs (2,3,7,8-tetrachlorodibenzo-p-dioxin) and toxaphene.

Table 2. List of endocrine-disrupting chemicals (EDCs) designated as HAPs by USA.

EDCs[a] (CAS Registry No.)	Major uses	POPs[b]
Benzo(a)pyrene[b] (50-32-8)	(Unintended product)	
Cadmium (7440-43-9)	Battery, pigments, coating & plating	
Carbaryl (63-25-2)	Insecticide	
Chlordane (57-74-9)	Insecticide	V
DDE (72-55-9)	Insecticide	
1,2-Dibromo-3-chloropropane (96-12-8)	Insecticide	
Di-n-butyl phthalate (84-74-2)	Plasticizer for plastics	
Heptachlor (76-44-8)	Insecticide	V
Hexachlorobenzene (118-74-1)	Bactericide, organic synthetic raw material	V
α-Hexachlorocyclohexane (319-84-6)	Insecticide	V
β-Hexachlorocyclohexane (319-85-7)		
γ-Hexachlorocyclohexane (Lindane) (58-89-9)		
Lead (7439-92-1)	Battery, rolled extrusions, ammunition, pigments	
Mercury (7439-97-6)	Battery, fluorescent light, medical instrument, dental fillings	
Methoxychlor (72-43-5)	Insecticide	
Pentachlorophenol (87-86-5)	Antiseptic, herbicide, bactericide	V
Polychlorinated biphenyls (1336-16-3)	Heat medium, non-carbon paper, electric product (Unintended product)	V
Styrene[c] (100-42-5)	Non-reacting substances of styrene-rubber plastic	
2,3,7,8-tetrachlorodibenzo-p-dioxin[d] (1746-01-6)	(Unintended product)	V
Toxaphene (8001-35-2)	Insecticide	V
Trifluralin (1582-09-8)	Antifouling paints on ships, antiseptic for fishnets	

[a]: List of EDCs under Japan's Chemical Substance Control Law (CSCL).
[b]: The most toxic chemical contained in polycyclic organic matter (POM) designated as HAPs by USA.
[c]: Styrenes (dimers and trimers) are listed as EDCs under Japan's Chemical Substance Control Law (CSCL), but styrene has been designated as HAPs by USA.
[d]: It has been designated as HAPs by USA. Also, it is one of the polychlorinated dibenzo-*p*-dioxins (PCDDs or dioxins) regulated under Japan's Chemical Substance Control Law (CSCL).

HAPs with relevance to human carcinogens

As described above, these designated HAPs include heavy metals & inorganics, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons and dioxins, and have been associated with adverse health effects [28]. More noticeably, these inorganics and VOCs could be carcinogenic to humans. With regard to the assessment and designation of a chemical substance or a mixture of chemicals or exposure environment as carcinogenic to humans, the most important classification system was devised by the IARC. The IARC approach categorizes the chemical agent or mixture into five groups based on the strength of evidence being carcinogenic to humans [29]: Group 1 - Carcinogenic to humans; Group 2A - Probably carcinogenic to humans; Group 2B - Possibly carcinogenic to humans; Group 3 - Not classifiable to be carcinogenic to humans; Group 4 - Probably not carcinogenic to humans.

Currently, 120 chemical agents or mixtures or exposure circumstances have been classified by IARC as Group 1.

Other official classifications exist for the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services, and the U.S Environmental Protection Agency (EPA). The former is mandated to produce a biennial *Report on Carcinogens*. Their 14th report was the latest edition, showing that 248 agents, substances, mixtures and exposure circumstances have been classified into two groups of carcinogenicity for human beings [30]: “Known to be a human carcinogen”, and “Reasonably anticipated to be a human carcinogen”. The latter is an electronic database, which is available through the Integrated Risk Information System (IRIS). Prior to 2005, the USEPA had derived inhalation cancer potency factors and also classified some toxic air pollutants into five categories based on the weight-of-evidence (WOE) being carcinogenic to human [31]: Group A - Human carcinogen; Group B - Probably human carcinogen; Group C - Possibly human carcinogen; Group D - Not classified; Group E - No evidence of carcinogenicity to humans. However, new USEPA Guidelines for Cancer Risk Assessment was finalized in 2005, in which human and animal data on carcinogenicity, and supporting evidence are combined to characterize the WOE regarding the agent's potential as a human carcinogen. These USEPA cancer descriptors recognized by 2005 are given below [31]: “Carcinogenic to humans”, “Likely to be carcinogenic to humans”; “Suggestive evidence of carcinogenic potential”; “Inadequate information to assess carcinogenic potential”; and “Not likely to be carcinogenic to humans”. On the other hand, the American Conference of Governmental Industrial Hygienists (ACGIH), a non-profit professional association of industrial hygienists known for its establishment of threshold limit values (TLVs) for occupational exposure, assesses and classifies carcinogenicity as part of a wider assessment of the occupational hazards of chemicals [32]: Group A1 - Confirmed human carcinogen; Group A2 - Suspected human carcinogen; Group A3 - Confirmed animal carcinogen with unknown relevance to humans; Group A4 - Not classifiable as a human carcinogen; Group A5 - Not suspected as a human carcinogen.

Table 3, mainly compiled from the database of international agencies such as the IARC, USEPA and ACGIH, summarizes the carcinogenicity classifications of HAPs designated by USEPA. Furthermore, most of these designated HAPs belong to VOCs, which are also precursors for triggering the formation of ozone in the atmospheric photochemical smog. On the other hand, it is well known that cancer can start almost anywhere in the human body. There are more than 100 types of cancers, which are generally named for the organs or tissues where the cancers form or the cancer cells begin to develop. For example, leukemia originates in tissues that form blood cells. Also, lymphoma originates in lymphatic tissue. In addition, cancer is a complex disease, which is driven by the combination of genetic, environmental, and lifestyle factors. In order to connect human cancer to the environmental exposure to HAPs, table 4 lists the classifications of carcinogenic agents by cancer sites with sufficient or limited evidence in humans [29]. It shows that some human tissues, including lung, lymph, nasal cavity, paranasal sinus, liver, and bile duct, could be more involved in the development of human cancer when people get exposed to chemical agents through the inhalation route.

Table 3. Carcinogenicity group of hazardous air pollutants (HAPs) listed in USA.

HAPs	Carcinogenicity			
	IARC	USNTP	USEPA	ACGIH
Acetaldehyde	2B	Reasonably anticipated	B2	A2
Acrylonitrile	2B	Reasonably anticipated	B1	A3
Aniline	3	--[d]	B2	A3
Arsenic and its compounds	1	Known	A	A1
Asbestos	1	Known	A	A1
Benzene	1	Known	A	A1
Benzidine	1	Known	A	A1
Beryllium and its compounds	1	Known	B1	A1
1,3-Butadiene	1	Known	A	A2
Cadmium and its compounds	1	Known	B1	A2
Carbon tetrachloride	2B	Reasonably anticipated	(B1/B2)[e]	A2
Chloroform	2B	Reasonably anticipated	B2	A3
Chloromethyl methyl ether	1	Known	A	A2
Chrome (Cr VI) and its compounds	1	Known	A	A1
1,2-Dichloroethane	2B	Reasonably anticipated	B2	A4
Dichloromethane	2A	Reasonably anticipated	(B1/B2)	A3
Dioxins[a]	1	Known	--	--
Ethylbenzene	2B	--	D	A3
Ethylene oxide	1	Known	--	A2
Formaldehyde	1	Known	B1	A2
Hydrazine	2B	Reasonably anticipated	B2	A3
Lead and its compounds	2A/2B	Reasonably anticipated	B2	A3
Nickel and its compounds	1	Known	A	A1
Polychlorinated biphenyls	1	Reasonably anticipated	B2	--
Polychlorophenols[b]	2B	Reasonably anticipated		A3
Polyaromatic hydrocarbons[c]	1	Reasonably anticipated	B2	A2
Propylene oxide	2B	Reasonably anticipated	B2	A3
Styrene	2B	Reasonably anticipated	--	A4
Tetrachloroethylene	2A	Reasonably anticipated	(B1/B2)	A3
Trichloroethylene	1	Reasonably anticipated	A	A2
Vinyl chloride	1	Known	A	A1

[a]: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.
[b]: Pentachlorophenol.
[c]: Benzo(a)pyrene.
[d]: Not classified.
[e]: This category under the 2005 guidelines means “likely to be carcinogenic to human”.

Table 4. Cancer sites of hazardous air pollutants (HAPs) with sufficient or limited evidence in humans.[a]

HAPs	Cancer sites
Acetaldehyde	Digestive tract, Esophagus
Arsenic and its compounds	Lung, Skin (other malignant neoplasms), Urinary bladder, Kidney, Prostate, Liver and bile duct
Asbestos	Larynx, Lung, Mesothelium (pleura/peritoneum), Ovary, Colon and rectum, Stomach, Pharynx
Benzene	Leukemia and/or lymphoma
Benzidine	Urinary bladder
Beryllium and its compounds	Lung
1,3-Butadiene	Leukemia and/or lymphoma
Cadmium and its compounds	Lung, Kidney, Prostate
Chloromethyl methyl ether	Lung
Chrome and its compounds	Lung, Nasal cavity and paranasal sinus
Dichloromethane	Leukemia and/or lymphoma, Liver and bile duct
Dioxins [b]	All cancer sites (combined), Soft tissue, Lung, Leukemia and/or lymphoma
Ethylene oxide	Leukemia and/or lymphoma, Breast
Formaldehyde	Nasopharynx, Leukemia and/or lymphoma, Nasal cavity and paranasal sinus
Hydrazine	Lung
Lead and its compounds	Stomach
Nickel and its compounds	Nasal cavity and paranasal sinus, Lung
Pentachlorophenol	Leukemia and/or lymphoma, Soft tissue
Polychlorinated biphenyls	Skin (melanoma), Leukemia and/or lymphoma, Breast
Polyaromatic hydrocarbons [c]	(Lung)
Styrene	Leukemia and/or lymphoma
Tetrachloroethylene	Urinary bladder
Trichloroethylene	Kidney, Leukemia and/or lymphoma, Liver and bile duct
Vinyl chloride	Liver and bile duct

[a]: Evaluated by IARC.
[b]: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.
[c]: Benzo(a)pyrene, the most toxic chemical contained in polycyclic organic matter (POM) designated as HAPs by USA.

CONCLUSION

Hazardous air pollutants (HAPs), also called air toxics, represent a designated classification for harmful substances from a variety of anthropogenic emission sources that exist at measurable quantity in the atmospheric air. According to the definition of HAPs under the US Clean Air Act Amendments, they can cause serious adverse environmental and health effects. Although about 70% of HAPs belong to the category of VOCs, others may be persistent organic pollutants (POPs) and endocrine-disrupting chemicals (EDCs). Due to their specific physicochemical properties (i.e., high stability and lipophilicity) and widespread applications, several HAPs have been found not only in the environment, but also in humans and animals. In this review paper, HAPs were linked closely with the environmental and health risks, including persistence, endocrine-disrupting property and carcinogenicity. However, it would be helpful to review the human-intake data on exposure level, time duration and exposure rate.

The following conclusions can be drawn:

- Some organochlorine pesticides, including chlordane, heptachlor, hexachlorobenzene, pentachlorophenol and toxaphene, are listed as HAPs, POPs and EDCs. These semivolatile organic compounds can transport through the atmosphere by environmental fate processes of volatilization and deposition on particles and other surfaces.
- The unintentional byproducts, including polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated biphenyls (PCBs), are also listed as HAPs, POPs and EDCs. These semivolatile organic compounds are mainly formed by the high-temperature processes, thus posing a high exposure risk as a result of their release into the atmosphere as particles.
- 2,3,7,8-tetracodibenzo-p-dioxin (TCDD), the most toxic compound of the PCDD group, has been shown to cause endocrine-disruption and adverse reproduction changes, weaken immune system, and induce carcinogenic effects. Therefore, TCDD has been confirmed as a human carcinogen by the IARC. In addition, PCBs also possess similar toxicity risks, meaning that they are listed as one of human carcinogens by the IARC.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

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