Genes and Environment

RESEARCH Open Access

Mapping the influence of hydrocarbons mixture on molecular mechanisms, involved in breast and lung neoplasms: in silico toxicogenomic data-mining

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Abstract

Background Exposure to chemical mixtures inherent in air pollution, has been shown to be associated with the risk of breast and lung cancers. However, studies on the molecular mechanisms of exposure to a mixture of these pollutants, such as hydrocarbons, in the development of breast and lung cancers are scarce. We utilized in silico toxicogenomic analysis to elucidate the molecular pathways linked to both cancers that are influenced by exposure to a mixture of selected hydrocarbons. The Comparative Toxicogenomics Database and Cytoscape software were used for data mining and visualization.

Results Twenty-five hydrocarbons, common in air pollution with carcinogenicity classification of 1 A/B or 2 (known/presumed or suspected human carcinogen), were divided into three groups: alkanes and alkenes, halogenated hydrocarbons, and polyaromatic hydrocarbons. The in silico data-mining revealed 87 and 44 genes commonly interacted with most of the investigated hydrocarbons are linked to breast and lung cancer, respectively. The dominant interactions among the common genes are co-expression, physical interaction, genetic interaction, co-localization, and interaction in shared protein domains. Among these genes, only 16 are common in the development of both cancers. Benzo(a)pyrene and tetrachlorodibenzodioxin interacted with all 16 genes. The molecular pathways potentially affected by the investigated hydrocarbons include aryl hydrocarbon receptor, chemical carcinogenesis, ferroptosis, fluid shear stress and atherosclerosis, interleukin 17 signaling pathway, lipid and atherosclerosis, NRF2 pathway, and oxidative stress response.

Conclusions Within the inherent limitations of in silico toxicogenomics tools, we elucidated the molecular pathways associated with breast and lung cancer development potentially affected by hydrocarbons mixture. Our findings indicate adaptive responses to oxidative stress and inflammatory damages are instrumental in the development of both cancers. Additionally, ferroptosis—a non-apoptotic programmed cell death driven by lipid peroxidation and iron

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homeostasis—was identified as a new player in these responses. Finally, AHR potential involvement in modulating *IL-8*, a critical gene that mediates breast cancer invasion and metastasis to the lungs, was also highlighted. A deeper understanding of the interplay between genes associated with these pathways, and other survival signaling pathways identified in this study, will provide invaluable knowledge in assessing the risk of inhalation exposure to hydrocarbons mixture. The findings offer insights into future in vivo and in vitro laboratory investigations that focus on inhalation exposure to the hydrocarbons mixture.

Keywords Breast cancer, Lung cancer, Hydrocarbons, Toxicogenomics Analysis, Chemical mixtures, Molecular pathways

Introduction

Air pollution, a pervasive mixture of chemicals and particulate matter (PM), is one of the greatest environmental risks to health. In 2019, the World Health Organization (WHO) estimated 11% of outdoor air pollution-related premature deaths were due to cancer within the respiratory tract [1].

Polycyclic aromatic hydrocarbons (PAHs) are among the chemicals found in the complex mixture of chemicals and PM in air pollution [2, 3]. Common sources of PAHs include household combustion devices, motor vehicles, industrial activities, and forest fires [2]. Exposure to airborne PAHs in both occupational and non-occupational settings were associated with the risk of developing breast and lung cancers [2–8]. Notably, a French prospective cohort study, of a large sample size with long-term exposure data of benzo(a)pyrene (BaP), showed significant association between airborne BaP exposure and overall breast cancer risk. The association was greater among women in menopausal transition and tobacco smokers [3]. Inevitably, the International Agency for Research on Cancer (IARC) classified BaP as a Group 1 carcinogen in humans, based on sufficient experimental evidence of carcinogenicity in animals and corroborated by consistent mechanistic evidence [9].

The IARC has also declared tobacco smoking to have sufficient and limited evidence in humans to cause lung and breast cancer, respectively [10]. Arguably, tobacco smoking is a good example of adverse health effects of exposure to chemicals mixture. This is because tobacco smoke contains more than 5,000 different chemicals, including PAHs, tobacco specific nitrosamines, aromatic amines, aldehydes, phenols, nitro compounds, volatile hydrocarbons, and other organic and inorganic chemicals [11]. Tobacco smokers who work at industrial facilities are at high risk of exposure to hydrocarbons mixture and the risks of breast and lung cancers have been shown to be greater among workers who smoke tobacco [3, 12]. Studies on the mechanism by which exposure to a mixture of hydrocarbons contributes to the development of breast and lung cancers are scarce and, indeed, a complex field to venture into. However, advances in toxicogenomics provide comprehensive databases on chemicals, genes, proteins, and diseases that one can utilize to gain insights into molecular pathways that chemical mixtures potentially influence in the development of a specific disease.

This article elucidates interactions of genes influenced by a mixture of carcinogenic hydrocarbons with those related to the development of breast and lung cancer. Importantly, the article demonstrates the capability of in silico data-mining for gauging probable molecular mechanisms of mixture-induced toxic effects. This may then assist in strategizing experimental studies to better understand the impact of airborne hydrocarbons in the development of breast and lung cancers. The findings of such studies would then contribute to the risk assessment of chemical mixtures to safeguard the health of people.

Methods

Selection of hazardous air pollutants

In 2019, Ismail et al. [13] undertook to prioritize the hazard classification of 188 chemicals in the Office of Environment Health Hazard Assessment (OEHHA) list of chemicals emitted from California refineries [14]. The prioritization was in accordance with the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS). The classifications considered were carcinogenicity (C), mutagenicity (M) and reproductive toxicity (R) from databases of nine countries. Out of the 188 chemicals, 67 were identified as carcinogens 1 A (known human carcinogen), 1B (presumed human carcinogen) or 2 (suspected human carcinogen) [13].

We confirmed the classification of these chemicals by referencing databases of six countries—Australia, European Union (EU), Japan, South Korea, Malaysia, and New Zealand—to reflect the latest classification. The reference databases (Table 1) were chosen as they were accessible in English on the open World Wide Web domain.

From the revised list, chemicals with the most stringent carcinogenicity classification (1/1A/1B) (Suppl Table 1) were then screened for hydrocarbons, as they are common air pollutants and contained in tobacco smoke. These hydrocarbons were further analyzed for gene interactions in the development of breast and lung cancers. The molecular pathways potentially influenced by

Table 1 Source of the UN GHS classification database

Governmental Agency	Status of chemical list	Source
Japan	Advisory	https://www.nite.go.jp/en/chem/chrip/chrip_search/srhInput
Malaysia	Regulatory	(https://dosh.gov.my)
Australia	Advisory	http://hcis.safeworkaustralia.gov.au
New Zealand	Regulatory	https://www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/
European Chemicals Agency	Regulatory	https://echa.europa.eu/
South Korea Ministry of Environment	Regulatory	http://ncis.nier.go.kr/en/main.do

these genes were elucidated to gain insights on potential molecular pathways affected by hydrocarbons mixture.

Comparative Toxicogenomic database (CTD) analysis

The hydrocarbons were grouped into alkanes/alkenes, halogenated hydrocarbons, and PAHs. The linkages between these groups of hydrocarbons and cancers of the breast and lung, were explored by analyzing the chemical-gene/protein interactions obtained from the Comparative Toxicogenomic Database (CTD; https://ctdbase.org/). The analysis was based on data downloaded in July 2023. The CTD is a public domain database that allows the integration of data to provide a better understanding of the interactions between environmental chemicals, genes, and diseases [15]. Chemicals, chemical-phenotypes, gene ontology and chemicals-disease associations are the examples of information provided by the CTD. The search for genes associated with breast and or lung cancers was based on the CAS number of each individual carcinogenic hydrocarbon and inference network. The data-mining process flow is depicted in Fig. 1. The respective inference score and the reference links are in Supplementary Table 2.

Identifying common genes for hydrocarbons mixture and breast and lung cancer development

The lists of genes extracted from the CTD were uploaded to an Excel spreadsheet. Further analysis was done with Cytoscape version 2.5.10—a free software package—to visualize, model and analyze molecular and genetic interaction networks [16].

Gene-gene interaction network construction

The complex gene-gene interactions network of the common genes between the hydrocarbons and the selected cancers was constructed with GeneMANIA, a free in silico tool (http://www.genemania.org) that provides a flexible interface to query genomic, proteomic, and gene function data [17, 18]. The tools' dataset are from various publicly available databases, such as Gene Expression Omnibus (GEO) for co-expression data [19]; BioGRID for physical and genetic interaction data [20]; I2D for predicted protein interaction data [21]; and Pathway Commons for pathway and molecular interaction data [22–25]. The database has almost 2300 networks from eight different organisms that collectively contain nearly 600 million interactions covering almost 164,000 genes [18]. GeneMANIA generates networks from the data either directly or using an in-house analysis pipeline to convert profiles to functional association networks [26]. Co-expression networks were filtered (by default) to remove weak correlations [18]. In this study, *Homo sapiens* was selected as a target organism in GeneMANIA analysis.

Molecular pathways enrichment analysis

Pathway analysis was performed by Cytoscape ClueGO together with CluePedia plug-in version 2.5.10. The common genes found between hydrocarbons that are associated with the selected cancer development were inserted into the Load Marker List section. The Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, and WikiPathways [27–29] databases were selected in the

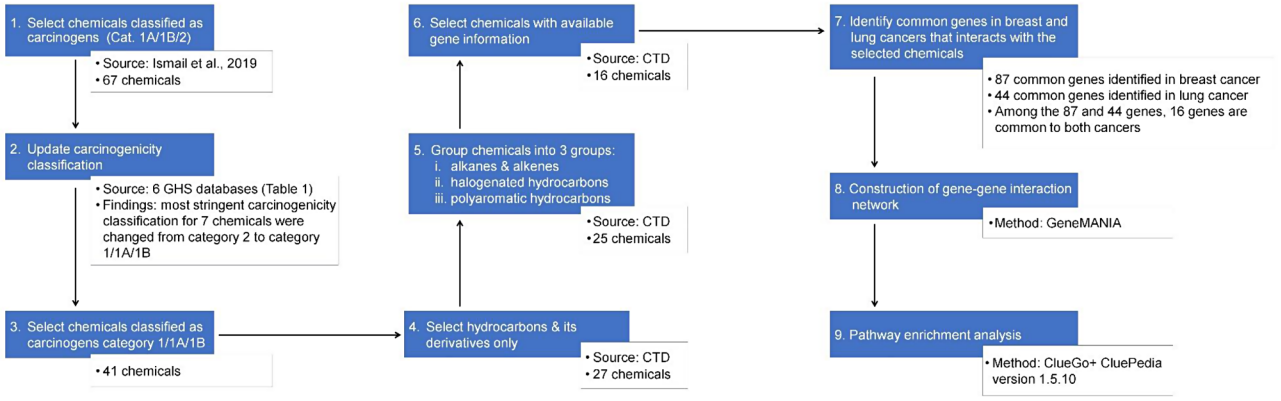

Fig. 1 Process flow for *in-silico* data-mining

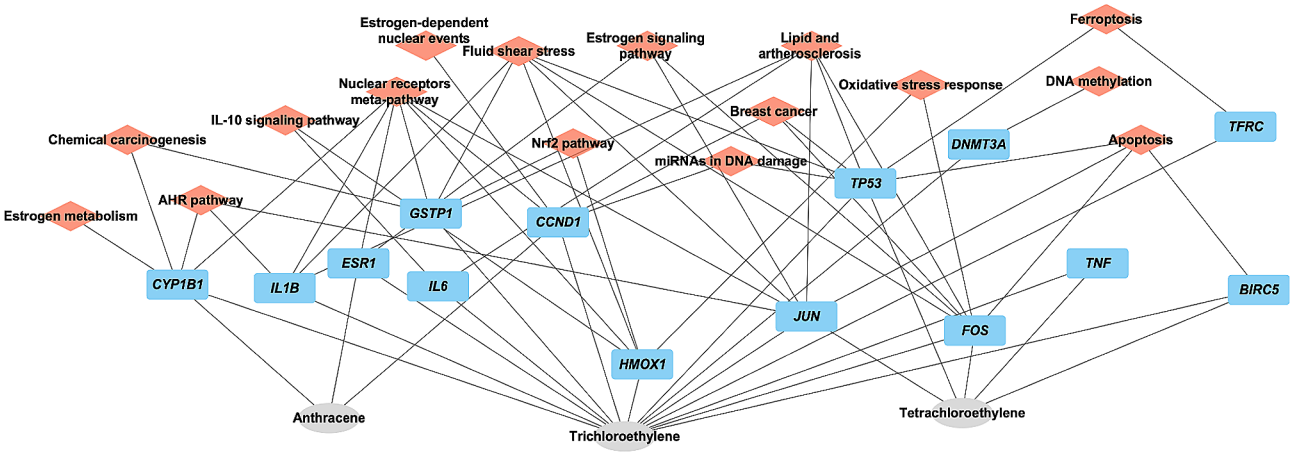

Fig. 2 Gene and molecular pathway interactions of hydrocarbons associated with breast cancer

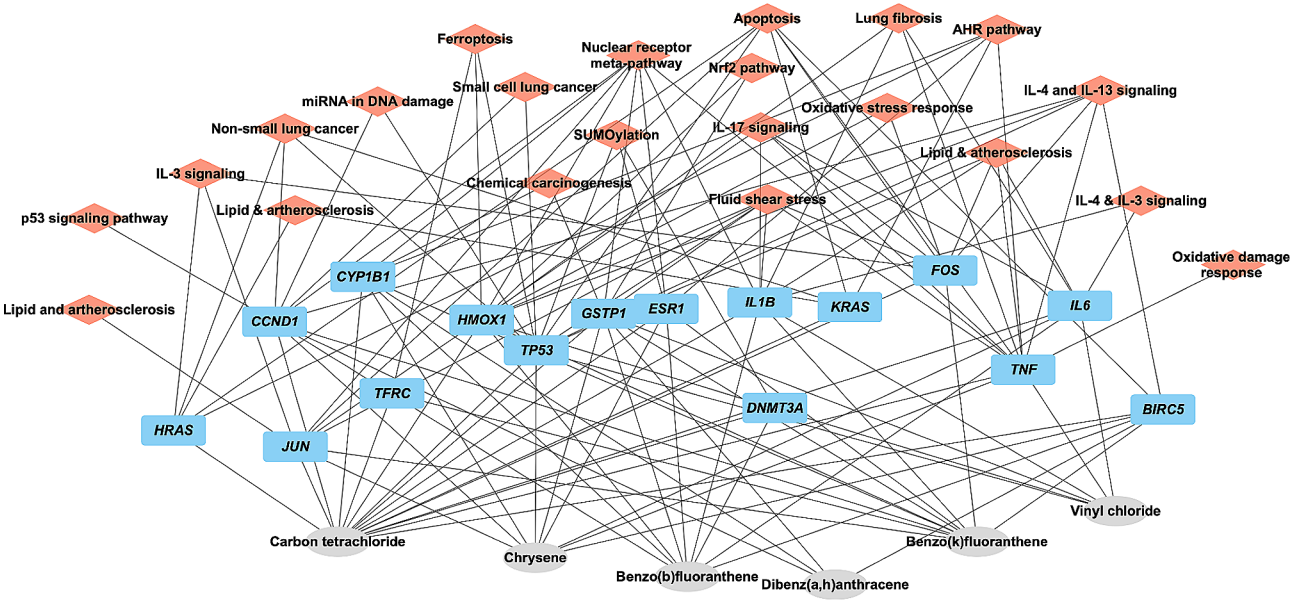

Fig. 3 Gene and molecular pathway interactions of hydrocarbons associated with lung cancer

ClueGO settings to extract the list of pathways. Enrichment right-sided hypergeometric test was used for the enrichment with a Bonferroni step-down correction and a κ score of 0.3 to link the terms [30]. ClueGO plug-in integrates GO terms and KEGG/BioCarta pathways. The plug-in was used to visualize molecular pathways and gene ontology that are linked to the examined common genes connected to the selected cancers. The organism analyzed was set to *Homo sapiens*. The output results (gene-pathway interactions) are shown in Supplementary Figs. 1 & 2 that were used to construct Figs. 2 and 3.

Results

Classification revision

Among the 67 chemicals screened, the classifications of seven chemicals were revised to a more stringent category: from category 2 (suspected human carcinogen) to category 1/1A/1B (known human carcinogen/presumed human carcinogen). This revision was based on Japan's most stringent classification. The seven chemicals are 1,1,2,2-tetrachloroethane (CAS No. 79-34-5), analine (CAS No. 62-53-3), anthracene (CAS No. 120-12-7), biphenyl (CAS No. 92-52-4), dichloromethane (CAS No. 75-09-2), methyl isobutyl ketone (CAS No. 108-10-1), and styrene (CAS No. 100-42-5) (Suppl Table 1). With the revision, 41 of the 67 chemicals are category 1/1A/1B carcinogens, of which 27 are hydrocarbons (Suppl Table 1). Among the 27 hydrocarbons, 25 were identified as alkanes, alkenes, halogenated hydrocarbons, and PAHs.

Comparative Toxicogenomic database analysis

Among the 25 hydrocarbons, nine were excluded from further toxicogenomics analysis for absence of curated data in the CTD. The nine chemicals are isobutane (CAS No. 75-28-5), n-butane (CAS No. 106-97-8), 1,1,2,2-tetrachloroethane (CAS No. 79-34-5), 1,2-dichloroethane (CAS No. 107-06-2), vinyl bromide (CAS No. 593-60-2), polychlorinated biphenyl (CAS No. 1336-36-3), benz(a) anthracene (CAS No. 56-55-3), biphenyl (CAS No. 92-52-4), and benzo(e)pyrene (CAS No. 192-97-2) (Suppl Table 2).

In the alkanes/alkenes group, only two of the four chemicals contained gene interactions data. Isoprene (2-methyl-1,3-butadiene (CAS No. 78-79-5)) affects 12 and 8 genes associated with breast and lung cancer, respectively, whilst 1,3-butadiene (CAS No. 106-99-0) affects 63 genes linked to breast cancer development and 48 genes linked to lung cancer (Suppl Table 2).

In the halogenated group, six of the twelve chemicals affect genes linked to breast or lung cancer genes. Tetrachlorodibenzodioxin (TCDD) (CAS No. 1746-01-6) interacts with the greatest number of genes related to breast cancer development (489 genes), followed by trichloroethylene (CAS No. 79-01-6; 230 genes), tetrachloroethylene (CAS No. 127-18-4; 40 genes), and dichloromethane (CAS No. 75-09-2; 35 genes). Both 1,2 dichloropropane (CAS No. 78-87-5) and 1,2-dibromoethane (CAS No. 106-93-4) affect only five genes (Suppl Table 2). Regarding genes linked to lung cancer development, TCDD, carbon tetrachloride (CAS No. 56-23-5), dichloromethane, and vinyl chloride (CAS No. 75-01-4) affect 250, 184, 25, and 16 genes, respectively, whilst 1,2-dichloropropane and 1,2-dibromoethane affect less than ten genes (Suppl Table 2).

Among the nine chemicals in the PAHs group, BaP (CAS No. 50-32-8) affects the greatest number of genes related to breast cancer development (492 genes), followed by anthracene (CAS No. 120-12-7; 12 genes) (Suppl Table 2). In regard to interactions with lung cancer-associated genes, BaP affects the greatest number of genes (259 genes), followed by benzo(b)fluoranthene (CAS No. 205-99-2; 52 genes), chrysene (CAS No. 218-01-9; 35 genes), dibenz(a, h)anthracene (CAS No. 53-70-3; 34 genes), and benzo(k)fluoranthene (CAS No. 207-08-9; 33 genes) (Suppl Table 2).

Genes interacted with hydrocarbons mixture that are connected to breast and lung cancers

The data-mining revealed 87 and 44 genes linked to breast and lung cancer, respectively, interacted with most of the investigated hydrocarbons (Suppl Table 3).

The mutual molecular pathways in the development of breast and lung cancer that are linked to these genes are aryl hydrocarbon receptor (AHR) pathway, apoptosis, chemical carcinogenesis, ferroptosis, fluid shear stress and atherosclerosis, lipid and atherosclerosis, miRNA in DNA damage response, Nrf2 pathway, nuclear receptors meta-pathway, and oxidative stress response (Suppl Figs. 1 & 2; Suppl Tables 4 & 5).

Molecular pathways involved in breast cancer but not in lung cancer development are androgen receptor signaling, DNA methylation, estrogen metabolism and signaling, and interleukin-10 (IL-10) anti-inflammatory signaling (Suppl Fig. 1 & Suppl Table 4).

Interleukin-3, 4, 13 and 17 (IL-3, IL-4, IL-13, IL-17) signaling pathways, p53 signaling, oxidative damage response, and SUMOylation are involved in the development of lung cancer (Suppl Fig. 2 & Suppl Table 5) but not breast cancer.

Gene-gene interaction network affected by the common genes

GeneMANIA Cytoscape predictive plug-in provides information on interaction types between the common genes. The interaction types include: (a) Co-expression—two gene products are linked if their expression levels are similar across conditions in a gene expression study; (b) Genetic interaction—two genes are functionally associated if one gene is affected by alterations that occur to the second gene; (c) Physical Interaction—two genes product are linked if they interact at protein level; (d) Co-localization—genes expressed in the same tissue or proteins found in the same location; (e) Interaction in shared protein domains; and (f) Interaction predicted by the server [18].

Complex networks encompassing the whole set of interactions between the common genes linked to breast and lung cancers are presented in Supplementary Fig. 3. Co-expression (47.33% of interactions) and physical interaction (40.18%) are the dominant interactions among the common genes in breast cancer development, followed by genetic interaction (2.90%), co-localization (2.74%), and interaction in shared protein domains (0.54%) (Table 2). In the case of lung cancer development,

Table 2 Type of gene interactions among the common genes linked to breast and lung cancer

Cancer	Gene Interaction Type					
	Co-expression	Genetic Interaction	Physical Interaction	Co-localization	Shared Protein Domain	Predicted
Breast	47.33%	2.90%	40.18%	2.74%	0.54%	4.59%
Lung	46.88%	3.04%	24.17%	7.43%	7.61%	10.48%

co-expression is the dominant interaction between the common genes (46.88%), followed by physical interaction (24.17%), shared protein domain (7.61%), co-localization (7.43%), and genetic interaction (3.04%) (Table 2).

In gaining insights on the potential biological pathways that would be affected by exposure to a mixture of hydrocarbons, we focused on 16 genes common in the development of both cancers (Suppl Table 3). Among these genes, 12 are protein-coding genes and 4 are proto-oncogenes.

The protein encoded by the 12 genes are baculoviral inhibitor of apoptosis (IAP) repeat-containing 5 (BIRC5), cyclin D1 (CCNDI), cytochrome P450 1B1 (CYP1B1), DNA methyltransferase 3 alpha (DNMT3A), estrogen receptor 1 (ESR1), glutathione S-transferase pi 1 (GSTP1), heme oxygenase 1 (HMOX1), interleukin 1 β (IL1B), interleukin 6 (IL6), transferrin receptor (TFRC), tumor necrosis factor (TNF), and tumor protein p53 (TP53). The 4 proto-oncogenes are c-Fos (FOS), Jun (JUN), HRas (HRAS) and Kras (KRAS) (Suppl Table 3).

Among the investigated hydrocarbons, 3 are associated with breast cancer development only: the halogenated hydrocarbon, trichloroethylene (TCE) and tetrachloroethylene, and anthracene, a polyaromatic hydrocarbon (Table 3). The chemical-gene interactions involved changes in mRNA and protein expression. All 3 chemicals do not interact with the *HRAS* and *KRAS* genes (Table 3).

TCE interacted with the other 14 genes: it increased the expression of mRNA and/or protein of BIRC5 [31, 32], CCND1 [33], CYP1B1 [34], ESR1 [35], FOS [35], GSTP1 [35], HMOX1 [31, 35, 36], IL1B [37], IL6 [35], JUN [31, 35, 37], TNF [38], and TP53 [39]. It also decreased mRNA expression of CCND1 [40], CYP1B1 [36], DNMT3A [31, 41], IL6 [42], JUN [43], TFRC [35], TNF [44], TP53 [34], and decreased HMOX1, IL6 and TNF protein expression [38, 45] (Table 3). The potential biological pathways affected by TCE are AHR pathway, apoptosis, chemical carcinogenesis, DNA methylation, estrogen metabolism and signaling, ferroptosis, fluid shear stress & atherosclerosis, IL-10 anti-inflammatory signaling, lipid and atherosclerosis, miRNA in DNA damage, Nrf2 pathway, and oxidative stress response (Fig. 2).

Tetrachloroethylene interacted with only 5 genes (*BIRC5, FOS, JUN*, TNF, and TP53). It increased the expression of BIRC5 and TP53 mRNAs and TNF protein, as well as decreased the expression of FOS and JUN proteins (Table 3). The potential biological pathways affected by tetrachloroethylene are AHR pathway, apoptosis, estrogen signaling, ferroptosis, fluid shear stress & atherosclerosis, lipid and atherosclerosis, miRNA in DNA damage, nuclear receptors meta-pathway, and oxidative stress response (Fig. 2). Tetrachloroethylene ability to increase the expression of *BIRC5* mRNA (Table 3) suggests deregulation of apoptosis as a potential mechanism affected by tetrachloroethylene in the development of breast cancer. This is because BIRC5—a member of the inhibitor of apoptosis (IAP) family—inhibits caspase activation, which leads to deregulation of apoptosis and increase cellular proliferation [46].

Anthracene interacted with only 3 genes (*CCND1, CYP1B1*, and *ESR1*). It increased the expression of

Table 3 Chemical-gene interaction associated with breast neoplasms

Substance	Trichloroethylene (CRN 79-01-6)			Tetrachloroethylene (CRN 127-18-4)			Anthracene (CRN 120-12-7)		
Interaction	mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein	
		Expr	Activity		Expr	Activity		Expr	Activity
BIRC5	↑	↑		↑					
CCND1	↑↓	↑						↑	
CYP1B1	↑↓						↑		
DNMT3A	↓								
ESR1	↑							↑	
FOS	↑				↓				
GSTP1	↑								
HMOX1	↑	↓							
HRAS									
IL1B	↑	↑							
IL6	↑↓	↑↓							
JUN	↑↓	↑			↓				
KRAS									
TFRC	↓								
TNF	↑↓	↑↓			↑				
TP53	↓	↑		↑					

Expr: Expression; ↑ - increase; ↓ - decrease; ↑↓ - can both increase and decrease. The references link can be found in Supplementary Table 2

CYP1B1 mRNA, as well as CCND1 and ESR1 protein (Table 3). The potential biological pathways affected by anthracene are AHR pathway, chemical carcinogenesis, estrogen metabolism and signaling, estrogen-dependent nuclear events, miRNA in DNA damage, and nuclear receptors meta-pathway (Fig. 2).

In the case of lung cancer, the interactions of carbon tetrachloride, vinyl chloride,dibenz(a, h)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, and chrysene with the 16 genes, involved up- and down-regulation at mRNA and protein levels, gene polymorphism, and gene mutagenesis (Table 4).

Carbon tetrachloride affected the up- and or down-regulation of all 16 genes at mRNA and or protein levels (Table 4). It increased the activity of DNMT3A, FOS, HMOX1, IL1B, IL6, JUN, and TNF. This implicates potential involvement of biological pathways associated with AHR pathway, apoptosis, chemical carcinogenesis, ferroptosis, fluid shear stress & atherosclerosis, oxidative stress response, and SUMOylation (Fig. 3).

Vinyl chloride interacted with only 6 genes. In addition to down regulating HMOX1, IL1B, IL6, and TP53 at mRNA level, as well as decreasing HMOX1 protein expression, it increased mutagenesis of both *KRAS* [47–50] and *TP53* [47–49] genes (Table 4). When *KRAS* gene is mutated, it becomes an oncogene that can transform normal cells into cancer cells [51], whilst TP53 mutations resulted in uncontrolled cell growth leading to cancer development [52]. Thus, the potential mechanism by which vinyl chloride contributes to the development of lung cancer is associated with disruption of normal cellular processes and promotion of tumorigenesis. In the case of TNF, vinyl chloride increased the mRNA and protein activity (Table 4), indicating potential impact in tumor microenvironment.

Among the 4 PAHs associated with lung cancer, benzo(b)fluoranthene and benzo(k)fluoranthene interacted with 11 of the 16 genes, whilst chrysene and dibenz(a, h)anthracene interacted with 5 and 4 genes, respectively (Table 4). The upregulation of DNMT3A mRNA was increased by benzo(b)fluoranthene but not by the other 3 PAHs (Table 4). Similarly, the regulations of KRAS mRNA and protein were unaffected by all 4 PAHs, except for benzo(b)fluoranthene increased the mutagenesis of *KRAS* gene [53, 54]. It also increased TP53 protein expression and affected its activity [55] (Table 4). This suggests that benzo(b)fluoranthene and vinyl chloride affected similar biological pathways in the development of lung cancer. A comprehensive overview of the interaction between the 16 genes and PAHs that are linked to lung cancer is shown in Fig. 3.

In the development of both cancers, TCDD and BaP interacted with all 16 genes by affecting the respective mRNA and protein expression and or protein activity (Table 5). BaP can also affect the methylation of *BIRC5* 3'UTR, *GSTP1* promoter, *HRAS* and *IL1B* 5'UTR, and phosphorylation of TP53 protein [56–58]. The alkenes, isoprene and 1,3-butadiene increased the mutagenesis of both *HRAS* and *KRAS* genes [59], whilst BaP increased the mutagenesis of *KRAS* gene [53, 54, 60, 61] (Table 5). Isoprene also increased the expression of CCND1 protein (Table 5). This indicates similar mechanism of actions by which isoprene, 1,3-butadiene and BaP contribute to the development of both breast and lung cancers.

Discussion

In utilizing the in silico toxicogenomic data-mining approach—to explore molecular mechanisms by which exposure to hydrocarbons mixture affects cancer development—we identified 16 genes common in the development of breast and lung cancers that interact with most of the investigated hydrocarbons. Proteins encoded by these genes: *BIRC5*, *CCND1*, *TNF*, and the proto-oncogenes *FOS*, *JUN*, *HRAS*, and *KRAS*, have all been implicated in cell cycle regulation directly or indirectly. The other 9 genes, *CY1B1*, *DNMT3A, ESR1, GSTP1, HMOX1*, *IL1B, IL6, TFRC, and TP53* encode proteins involved in xenobiotic metabolism, gene regulation, oxidative damage response, inflammatory response, iron homeostasis, regulation of cell signaling pathways, and DNA damage response.

It is noted that these common genes may interact with carcinogens other than the investigated hydrocarbons. For example, acetaldehyde (CAS No. 75-07-0), asbestos (CAS No. 1332-21-4), bis(2-ethyl hexyl) phthalate (CAS No. 117-81-7), cadmium (CAS No. 7440-43-9), and chromium (CAS No. 18540-29-9) interacted with most of the 16 common genes, except *BIRC5, DNMT3A, HRAS* and *KRAS* (Suppl Table 6). The latter 4 genes interacted with carbon tetrachloride, 1,3-butadiene, TCDD, and BaP in the development of both breast and lung cancers.

The chemical-gene interactions profile suggests complex crosstalk involving DNA damage, transcriptional and post-transcriptional regulations, as well as translational and post-translational regulations, that affect various biological pathways common to cancer development. These biological pathways include gene mutation, cell cycle progression, oxidative stress and damage responses, inflammatory responses, and DNA damage responses.

In our mapping of biological pathways for breast cancer, DNMT3A, an enzyme responsible for de novo DNA methylation, is shown to be involved in miRNA expression (Suppl Fig. 1). The crosstalk between DNA methylation and miRNA expression can drive the pathogenesis of a disease. For instance, miRNAs can influence DNA methylation patterns by targeting transcripts of proteins responsible for DNA methylation, such as DNMT3A. Conversely, the methylation of miRNA promoter regions

Table 4 Chemical-gene interaction associated with lung neoplasms

Substance	Carbon tetrachloride (CRN 56-23-5)			Vinyl chloride (CRN 75-01-4)			Dibenz(a, h)anthracene (CRN 53-70-3)			Benzo(b)fluoranthene (CRN 205-99-2)			Benzo(k)fluoranthene (CRN 207-08-9)			Chrysene (CRN 218-01-9)		
Interaction	mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein	
		Expr	Activity		Expr	Activity		Expr	Activity		Expr	Activity		Expr	Activity		Expr	Activity
BIRC5	↑	↑					↑			↑	↑		↑			↑		
CCND1	↑↓	↑					↑			↑			↑			↑		
CYP1B1	↑						↑	↑		↑			↑			↑	↑	
DNMT3A			↑							↑								
ESR1	↑↓										↑	↑		↓		↑		
FOS	↑↓	↑	↑										↑			↑		
GSTP1[*]	↑	↑	↓				↓			↑			↑			↑		
HMOX1	↑↓	↑↓	↑	↓	↓					↑			↑↓					
HRAS	↑																	
IL1B	↑	↑	↑	↓						↑			↑					
IL6	↑	↑	↑	↓						↑		↑				↑		
JUN	↑	↑	↑										↑			↑		
KRAS[**]	↑↓																	
TFRC		↓											↑					
TNF	↑	↑	↑	↑		↑										↑		
TP53[***]	↑↓			↓	↑						↑	↑↓			↑↓			

Expr: Expression; ↑ - increase; ↓ - decrease; ↑↓ - can both increase and decrease; [*]GSTP1 polymorphism ↑ susceptibility to vinyl chloride (117); [**]Vinyl chloride (44–47) and benzo(b)fluoranthene (50–51) ↑ mutagenesis of *KRAS* gene; [***]Vinyl chloride ↑ mutagenesis *TP53* gene (45–46). TP53 protein increased susceptibility to dibenz(a, h)anthracene (62). The references link can be found in Supplementary Table 2

Table 5 Chemical-gene interaction associated with breast and lung neoplasms[t]

Substance	2-Methyl-1,3-butadiene (CAS No. 78-79-5)			1,3-Butadiene (CAS No. 106-99-0)			Dichloromethane (CAS No. 75-09-2)			Tetrachlorodibenzodioxin (CAS No. 1746-01-6)			Benzo(a)pyrene (CAS No. 50-32-8)		
Interaction	mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein		mRNA Expr	Protein	
		Expr	Activity		Expr	Activity		Expr	Activity		Expr	Activity		Expr	Activity
BIRC5[*]				↑						↑↓	↑		↑↓	↓	
CCND1		↑								↑↓	↑↓		↑↓	↑↓	
CYP1B1							↓			↑	↑	↑	↑↓	↑	↑
DNMT3A				↓						↑↓		↑	↑↓	↑	
ESR1							↓			↑↓	↑↓	↑↓	↑↓	↓	↑
FOS				↓			↓			↑↓	↑↓	↑	↑↓	↑	
GSTP1[**]				↑						↑↓		↑	↑↓	↑	↑
HMOX1				↑			↑			↑↓	↑↓		↑	↑↓	
HRAS[***]										↑↓	↑		↑↓	↑	
IL1B[****]				↓						↑	↑		↑	↑	↑
IL6								↑		↑↓	↑↓	↑	↑	↑	↑
JUN							↑			↑↓	↑↓	↑	↑↓	↑	↑
KRAS[#]										↑↓	↑		↑		
TFRC				↑						↑↓	↑		↑↓		
TNF								↑		↑	↑↓	↑	↑	↑	↑
TP53[###]										↑↓	↓	↓	↑↓	↑↓	↑

Expr: Expression; ↑ - increase; ↓ - decrease; ↑↓ - can both increase and decrease; [t]1,2-Dichloropropane (CAS No. 78-87-5) interacted with only one common gene, *TNF*. It ↑ the expression of TNF mRNA; [*]BaP ↑ methylation of BIRC5 3′UTR (53); [**]BaP ↓ methylation of *GSTP1* promoter (53); [***]2-Methyl-1,3-butadiene (isoprene) and 1,3-butadiene ↑ mutagenesis of *HRAS* gene (1). BaP ↓ methylation of HRAS 5′UTR (53); [****]BaP ↓ methylation of IL1B 5′UTR (53). [#]Isoprene, 1,3-butadiene and BaP ↑ mutagenesis of *KRAS* gene (50–51,57–59); [##]BaP ↓ methylation of MIR222 gene promoter (53); [###]BaP ↑ phosphorylation of TP53 protein (54–56). The references link can be found in Supplementary Table 2.

can inhibit their transcription, affecting their ability to regulate gene expression. Such crosstalk has been shown to drive the hormone-dependent phenotype of breast cancer [62].

In the case of lung cancer, the function of DNMT3A may be modified by SUMOylation a process of attaching and detaching small proteins called Small Ubiquitin-like Modifier (SUMO) to and from target proteins. This may lead to changes in the methylation of genes involved in cell growth and division, potentially contributing to uncontrolled cell proliferation. SUMOylation of other target proteins has been shown to enhance lung cancer metastasis [63].

The nature of chemical interaction in a mixture of hydrocarbons, such as additive, synergistic, potentiation, and antagonism cannot be discerned from this study due to inherent limitations of the study approach. However, the differences in chemical-gene interactions observed among the hydrocarbons provide insights into potential impact of exposure to hydrocarbons mixture.

For example, TCE—a halogenated hydrocarbon associated with increased risk of breast cancer in male and female workers [64, 65]—may potentiate the risk of lung cancer from exposure to dibenz(a, h)anthracene and the risk of both breast and lung cancer from exposure to BaP. The potential mechanism for such potentiation is increased DNA damage through DNA adduct formation and increased cellular proliferation through deregulation of apoptosis. TCE upregulates TP53 protein expression [39], as well as BIRC5 mRNA and protein expression [31, 32]. Elevated cellular TP53 protein has been shown to increase bioactivation of PAHs, such as dibenz(a, h) anthracene and BaP, by the enzyme cytochrome P450 1A1 (CYP1A1), which resulted in the elevation of DNA adduct levels [66]. BIRC5, on the other hand, inhibits caspase activation, which leads to deregulation of apoptosis and increase cellular proliferation [39].

In the case of vinyl chloride co-exposed with dibenz(a, h)anthracene and BaP, the DNA adduct formation via p53-dependent CYP1A1 bioactivation of the two PAHs, may be reduced as vinyl chloride is known to increase mutagenesis of the *TP53* gene [48, 49].

Chemical carcinogenesis

Chemical carcinogenesis that pivots on the AHR pathway appears to be the bridge linking the development and progression of breast and lung cancers. AHR plays a "double-edged sword" that promotes or suppresses tumorigenesis, depending on cell and tissue context and mode of AHR activation. In breast cancer, AHR shapes the tumor microenvironment and modifies immune tolerance [67], whilst in lung cancer, AHR is involved in the regulation of cell proliferation, angiogenesis, inflammation, and apoptosis [68].

AHR is a multi-functional transcription factor activated by a variety of ligands, such as BaP, benz(a)anthracene, TCDD, and metabolites of tryptophan, heme and arachidonic acid, indigoids, and equilenin (reviewed in [69]). These ligands can be agonist, antagonist or selective AHR modulators [70]. Upon ligand binding, the cytosolic AHR-ligand complex is translocated into the nucleus where it heterodimerizes with the aryl hydrocarbon nuclear transporter (ARNT) before binding to the xenobiotic/dioxin response elements (XREs/DREs) in the promoter of target genes and triggers their expression [71]. These genes are involved in many physiological functions, such as xenobiotic metabolism [71], immune response [72], cell cycle and proliferation [73, 74], lipid metabolism [75, 76], tumor promotion [77, 78], and negative regulation of AHR pathway [76]. Perturbations of these physiological functions have been shown to be associated with cancer development and progression, which suggests a complex role of AHR in chemical carcinogenesis.

In xenobiotic metabolism, AHR activates transcriptional up-regulation of the cytochrome P450 1A1 (*CYP1A1)* and *CYP1B1* genes. Most of the investigated hydrocarbons are linked to these two genes. Some are substrates for both enzymes. For example, the first step of BaP hydroxylation to BaP-7,8-epoxide, and the final epoxidation step to form BaP-7,8-dihydrodiol-9,10-epoxide (BPDE) are catalyzed by CYP1A1 and CYP1B1 enzymes in the lung and breast tissues [79–81], BPDE is a highly genotoxic metabolite that binds to deoxyguanosine at position N-2 to form DNA adducts [82]. Cigarette smoke was reported to induce *CYP1A1* and *CYP1B1* expressions in lung tissue of smokers and of lung cancer patients (both smokers and non-smokers) [83–85], which correlates with increased levels of BPDE and DNA adducts [86–90]. Bulky BaP-like DNA adducts were also detected in breast cancer patients [91, 92]. PAHs reactive metabolites are known to cause point mutations in RAS proto-oncogenes, such as codon 13 and codon 61 of the HRAS gene (reviewed in [93]). These observations suggest that the AHR/CYP450-dependent DNA adducts formation is a likely pathway to be affected by exposure to hydrocarbons mixture in the development of breast and lung cancers.

Several mechanisms by which AHR modulates the cell cycle have been proposed to account for the pro-/anti-proliferative action of AHR agonists observed with tumor cells in vitro [67, 68, 78]. One of the proposed ligand-activated mechanisms involved transcriptional upregulation of the *CDKN1B* gene by agonist-activated AHR binding to the gene's promoter region [94, 95]. However, this mechanism has not been demonstrated in the development and progression of either breast or lung cancer. Being an inhibitor of cyclin-dependent kinase activity,

increased CDKN1B activity limits phosphorylation of retinoblastoma protein (Rb), resulting in restriction of E2F-dependent gene expression and progression through the cell cycle [70]. In the absence of ligand, AHR complexed with cyclin D and the cyclin-dependent kinases CDK4/6 to promote cell cycle progression in human breast cancer cells [96]. TCDD, the atypical AHR agonist, dissociates the AHR/cyclinD/CDK complex to induce cell cycle arrest [96]. This contradictory role of AHR may reflect the impact of exposure to hydrocarbon mixtures on cell proliferation, as most of the investigated hydrocarbons are AHR agonists with different affinity to the receptor [70]. Similar contradictory effects of AHR on cell cycle progression were also observed in human lung cancer cells [97]. The impact of exposure to mixtures of 2-methyl-1,3-butadiene, carbon tetrachloride, TCDD, and BaP on this pathway may contribute to the development of breast and or lung cancer as these hydrocarbons interacted with *CDKN1B* gene (Suppl Table 2).

The mechanisms by which AHR shapes the tumor microenvironment are unclear, but it has been proposed that systemic and tumor-localized generation of endogenous AHR ligands heightened AHR expression/activity, which may establish a pro-inflammatory yet immune-suppressive tumor micro-environment. This favors tumor survival and escapes from immune surveillance, which results in tumor progression [70]. Indeed, AHR overexpression that is correlated with elevated expression of inflammatory markers, including interleukin-8 (IL-8), has been observed in human breast tumors [98]. *IL-8* has been identified as a critical gene that mediates breast cancer invasion and metastasis to the lungs [99]. The involvement of *IL1B*—one of the 16 common genes identified in this study—in this mechanism has not been elucidated in both breast and lung cancer development and progression. Our mapping, however, showed *IL1B* is involved in modulating the IL-17 signaling pathway, lipid and atherosclerosis pathway, and fluid shear stress and atherosclerosis pathway in both breast and lung cancer development. It is plausible that the impact of PAHs mixture on these pathways may involve AHR activation, as fluid shear stress in endothelial cells has been shown to modulate CYP1A-dependent AHR activation [100, 101], but the mechanism of activation remains unclear [67, 68].

Adaptive responses to cellular damage

AHR activation has also been shown to be associated with the oxidative stress response pathway. For example, exposure of estrogen receptor (ER) positive breast cancer cells to low doses of PAHs mixture activated AHR and overexpressed CYP1 isoforms, which correlated with increased expression of antiapoptotic and antioxidant proteins [102].

Besides catalyzing the biotransformation of PAHs to DNA damaging reactive metabolites, CYP1A1 and CYP1B1 catalyze the oxidation of estradiol (E2) to 2-hydroxyestradiol and 4-hydroxyestradiol, which subsequently undergo one-electron oxidation to produce unstable semiquinones (SQs) intermediates [103], potential mutagens that can damage DNA [104, 105]. Additionally, redox cycling can occur, where the SQs can pass their unpaired electron to molecular oxygen, forming a superoxide anion and restoring the catechol. Superoxide anion can then be metabolized to other reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2) [103, 105]. Another contributor of ROS in breast cancer cells is the expression of *CYP2E1*, which increased significantly in breast tumors and adjacent tissues [106]. CYP2E1 also regulates autophagy, stimulates stress in the endoplasmic reticulum, and suppresses the metastatic potential of breast cancer cells [107], indicative of the protective role of CYP2E1.

Excessive ROS can cause DNA damage, as well as lipid and protein oxidation, which triggers an oxidative stress response that involves activation of the NRF2-KEAP1 signaling pathway. This pathway modulates the expression of genes encoding antioxidant proteins, such as superoxide dismutase and HMOX1. The latter is involved in the maintenance of cellular homeostasis by catalyzing the oxidation of heme to carbon monoxide, biliverdin, and ferrous iron. These biologically active compounds participate in cellular protection by reducing oxidative injury, attenuating the inflammatory response, inhibiting cell apoptosis, and regulating cell proliferation [108]. In mouse, HMOX1 activity increased tumor growth and angiogenic potential, as well as decreased apoptosis in lung cancer progression [109], whilst in rat and human breast cancer cells, HMOX1 activity inhibits proliferation [110].

Notably, the NRF2-KEAP1 signaling pathway is linked to ferroptosis, one of the common pathways in the development of breast and lung cancer mapped out in this study.

Ferroptosis

Ferroptosis is a non-apoptotic programmed cell death, which has gained traction as a new target for treating tumors [111]. It is regulated by a complex signaling pathway that is dependent on lipid peroxidation and iron accumulation [111, 112]. Evidence that supports the potential physiological roles of ferroptosis in tumorigenesis resides in the way it is induced in cancer cells. This includes activation of the RAS–RAF–MEK–ERK pathway and induction in cancer cells with mutant RAS, as well as dependency on iron, which is known to be important for cancer cell proliferation (reviewed in [112]). Induction of ferroptosis has been shown to suppress

tumor growth, but ferroptotic damage favors tumor growth by triggering inflammation-associated immunosuppression in the tumor microenvironment [112]. Therefore, the three key features of ferroptosis: iron accumulation, increased lipid peroxidation and inability to efficiently reduce lipid peroxidases, must be well regulated to strike the delicate balance of survival and damage in tumorigenesis.

Little is known about ferroptosis role in breast and lung cancer progression, and the impact of exposure to hydrocarbons mixture on such association. However, several studies have found important correlations between mutations in tumor suppressor gene and proto-oncogene, *TP53* and *RAS*, and in genes encoding proteins involved in stress response pathways. One of these pathways is the NRF2 signaling pathway [112], which is one of the common molecular pathways identified in this study.

Depending on the pathological condition, the transcription factor NRF2 serves as either an anti- or pro-ferroptotic activator. Under oxidative stress conditions, NRF2 complexed with its chaperon protein to bind to the ARE (Antioxidant Response Element) on the promoter region of its target genes with anti- or pro-ferroptotic functions. An example of iron-related NRF2 target gene that promotes ferroptotic cascade is HMOX1, which catalyzes the cleavage of heme to form biliverdin, carbon monoxide, and ferrous iron (Fe^{2+}) [113]. Chemical-induced ferroptotic cell death driven by increased HMOX1 expression was observed in HT-1080, neuroblastoma and glioblastoma cell lines [114–116]. An example of NRF2 acting as anti-ferroptotic activator is in its regulating the expression of enzymes responsible for glutathione synthesis, as well as preventing lipid peroxidation and reducing oxidized CoQ10, a key membrane antioxidant (GPX4 and FSP1) [113]. Notably, GSTP1 has been shown to be involved in tumor development through the ferroptosis pathway [117] and was suggested to be a novel negative regulator of ferroptosis that may play an important role in lung cancer radiotherapy by inhibiting ferroptosis [118]. Crosstalk mechanisms between the RAS–RAF–MEK–ERK pathway and the NRF2 signaling pathway, with the involvement of GSTP1 in ferroptosis during tumorigenesis in breast and lung cells, and impact of exposure to halogenated and polyaromatic hydrocarbons on the crosstalk mechanisms have yet to be explored.

The role of AHR and NRF2 in regulating ferroptosis in breast and lung cancer cells is unclear, but AHR has been shown to promote the development of non-small cell lung cancer (NSCLC) by inducing the expression of *SLC7A11*, a key regulator of ferroptosis [119].

In sum, as most hydrocarbons are AHR ligands, the impact of inhalation exposure to hydrocarbons mixture on these physiological functions is complex, given the distinct classes of AHR ligands: agonist, antagonist and selective AHR modulators [70]. However, this study revealed an important role of AHR in being the bridge linking the development and progression of breast and lung cancers as it is involved (directly and or indirectly) in the regulation of biological pathways mapped out in this study. Notably, the mechanism by which IL1B regulates *IL-8*—a critical gene that mediates breast cancer invasion and metastasis to the lungs [99]—and the role of AHR in such mechanism, is worth pursuing.

Conclusion

Within the inherent limitations of in silico toxicogenomics associated tools, we were able to elucidate the molecular pathways of breast and lung cancer development potentially affected by exposure to hydrocarbons mixture. In silicon data-mining depends on the online sources and the quality of the interactions present in them. Complex molecular pathways were obtained by drawing statistical associations between chemical-gene-disease relationships. Therefore, dose-response relationship, interaction profile of hydrocarbons mixture, route and duration of exposure to the investigated hydrocarbons mixture, along with individual sensitivity of exposed subjects, cannot be drawn from this study. In conclusion, our findings should be regarded as insights into future in vivo and in vitr laboratory investigations that focus on inhalation exposure to the hydrocarbons mixture.

Abbreviations

A2M	Alpha-2-macroglobulin
ABCA8	ATP binding cassette subfamily A member 8
ABCB1	ATP binding cassette subfamily B member 1
ABCB1B	ATP-binding cassette, sub-family B
ABCC1	ATP binding cassette subfamily C member 1
ABCG2	ATP binding cassette subfamily G member 2
ABL1	Abl tyrosine kinase proto-oncogene 1
ACACB	Acetyl-CoA carboxylase beta
ACE	Angiotensin I converting enzyme
ACHE	Acetylcholinesterase
ACSM1	Acyl-CoA synthetase medium chain family member 1
ACTA2	Actin alpha 2
ACTB	Actinβ
ACVR1	Activin A receptor type 1
ADA	Adenosine deaminase
ADAR	Adenosine deaminase RNA specific
ADAM10	ADAM metallopeptidase domain 10
ADAM28	ADAM metallopeptidase domain 28
ADAM33	ADAM metallopeptidase domain 33
ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif 1
AFP	Alpha fetoprotein
AGR2	Anterior gradient 2
AHR	Aryl hydrocarbon receptor
AKAP12	A-kinase anchoring protein 12
AKT1	Akt kinase
AKT2	AKT serine/threonine kinase 2
ALDOA	Aldolase, fructose-bisphosphate A
ALK	ALK receptor tyrosine kinase
ALKBH8	AlkB homolog 8
ALX4	ALX homeobox 4
ANGPTL4	Angiopoietin like 4

ANK3	Ankyrin 3
ANKRD18A	Ankyrin repeat domain 18 A
ANKRD20A2P	Ankyrin repeat domain 20 family member A2
ANKRD34A	Ankyrin repeat domain 34 A
ANXA2	Annexin A2
AOC4P	Amine oxidase copper containing 4,pseudogene
APC	APC regulator of WNT signaling pathway
APC2	APC regulator of WNT signaling pathway 2
APOA1	Apolipoprotein A1
APOBEC3A	Apolipoprotein B mRNA editing enzyme catalytic subunit 3 A
APOBEC3B	Apolipoprotein B mRNA editing enzyme catalytic subunit 3B
APOC3	Apolipoprotein C3
APOE	Apolipoprotein E
APRT	Adenine phosphoribosyltransferase
AR	Androgen receptor
ARAF	A-Raf proto-oncogene
AREG	Amphiregulin
ARF1	ADP ribosylation factor 1
ARHGDIA	Rho GDP dissociation inhibitorα
ARHGEF5	Rho guanine nucleotide exchange factor 5
ARID1A	AT-rich interaction domain 1 A
ARRDC3	Arrestin domain containing 3
ARTN	Artemin
AS3MT	Arsenite methyltransferase
ATG10	Autophagy related 10
ATG101	Autophagy related 101
ATM	ATM serine/threonine kinase
ATOX1	Antioxidant 1 copper chaperone
ATP6AP1L	ATPase H + transporting accessory protein 1 like (pseudogene)
ATP7B	ATPase copper transportingβ
ATSDR	Agency for Toxic Substances and Disease Registry
AURKA	Aurora kinase A
AVPI1	Arginine vasopressin induced 1
AZGP1	α-2-glycoprotein 1,zinc-binding
B4GAT1	Beta-1,4-glucuronyltransferase 1
BAG1	BAG cochaperone 1
BAP1	BRCA1 associated protein 1
BARD1	BRCA1 associated RING domain 1
BAX	CL2 associated X
BCAR3	BCAR3 adaptor protein
BCHE	Butyrylcholinesterase
BCL2	BCL2 apoptosis regulator
BCL2A1	BCL2 related protein A1
BCL2L1	BCL2 like 1
BECN1	Beclin 1
BGN	Biglycan
BHLHE41	Basic helix-loop-helix family member e41
BIRC2	Baculoviral IAP repeat containing 2
BIRC5	Baculoviral IAP repeat containing 5
BMP2	Bone morphogenetic protein 2
BMP4	Bone morphogenetic protein 4
BMPR2	Bone morphogenetic protein receptor type 2
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRCA1	BRCA1 DNA repair associated
BRCA2	BRCA2 DNA repair associated
BRF1	BRF1 RNA polymerase III transcription initiation factor subunit
BRIP1	BRCA1 interacting helicase 1
BTN3A2	Butyrophilin subfamily 3 member A2
C1QBP	Complement C1q binding protein
CA12	Carbonic anhydrase 12
CADM1	Cell adhesion molecule 1
CALEPA	California Environmental Protection Agency
CALML3	Calmodulin like 3
CAS	Chemical Abstract Service
CASP7	Caspase 7
CASP8	Caspase 8
CAT	Catalase
CAV1	Caveolin 1
CBR2	Carbonyl reductase 2
CCL18	C-C motif chemokine ligand 18
CCL20	C-C motif chemokine ligand 20
CCN1	Cellular communication network factor 1
CCN2	Cellular communication network factor 2
CCND1	Cyclin D1
CCNE1	Cyclin E1
CCNG1	Cyclin G1
CCNH	Cyclin H
CCT5	Chaperonin containing TCP1 subunit 5
CD109	CD109 molecule
CD274	CD274 molecule
CD40	CD40 molecule
CD74	CD74 molecule
CDA	Cytidine deaminase
CDH1	Cadherin 1
CDH13	Cadherin 13
CDH2	Cadherin 2
CDH5	Cadherin 5
CDKN1A	Cyclin dependent kinase inhibitor 1 A
CDKN1B	Cyclin dependent kinase inhibitor 1B
CDKN1C	Cyclin dependent kinase inhibitor 1 C
CDKN2A	Cyclin dependent kinase inhibitor 2 A
CEACAM1	CEA cell adhesion molecule 1
CENPF	Centromere protein F
CES1	Carboxylesterase 1
CES1F	Carboxylesterase 1 F
CFL1	Cofilin 1
CHD4	Chromodomain helicase
DNA	Binding protein 4
CHEK1	Checkpoint kinase 1
CHEK2	Checkpoint kinase 2
CHRNA2	Cholinergic receptor nicotinic α 2 subunits
CHRNA3	Cholinergic receptor nicotinic α 3 subunits
CHRNA5	Cholinergic receptor nicotinic α 5 subunits
CHRNA7	Cholinergic receptor nicotinic α 7 subunits
CHRNB4	Cholinergic receptor nicotinic β 4 subunits
CHST15	Carbohydrate sulfotransferase 15
CLCA2	Chloride channel accessory 2
CLDN1	Claudin 1
CLDN4	Claudin 4
CLIC1	Chloride intracellular channel 1
CLPTM1L	Cleft lip and palate associated transmembrane protein 1
CLTB	Clathrin light chain B
CLUL1	Clusterin like 1
CNR2	Cannabinoid receptor 2
COL6A1	Collagen type VI α 1 chain
COL7A1	Collagen type VII α 1 chain
COMT	Catechol-O-methyltransferase
COTL1	Coactosin like F-actin binding protein 1
COX17	Cytochrome c oxidase copper chaperone COX17
CPE	Carboxypeptidase E
CPT1A	Carnitine palmitoyltransferase 1 A
CRHR1	Corticotropin releasing hormone receptor 1
CRP	C-reactive protein
CSF1	Colony stimulating factor 1
CSF1R	Colony stimulating factor 1 receptor
CSF2	Colony stimulating factor 2
CSF3	Colony stimulating factor 3
CST6	Cystatin E/M
CTD	Comparative Toxicogenomic Database
CTNNB1	Catenin beta 1
CTU1	Cytosolic thiouridylase subunit 1
CTU2	Cytosolic thiouridylase subunit 2
CUL5	Cullin 5
CWH43	Cell wall biogenesis 43 C-terminal homolog
CXCL1	C-X-C motif chemokine ligand 1
CXCL12	C-X-C motif chemokine ligand 12
CXCL14	C-X-C motif chemokine ligand 14
CXCL2	C-X-C motif chemokine ligand 2
CXCL3	C-X-C motif chemokine ligand 3
CXCL8	C-X-C motif chemokine ligand 8
CXCL9	C-X-C motif chemokine ligand 9

CXCR4	C-X-C motif chemokine receptor 4
CYP17A1	Cytochrome P450 family 17 subfamily A member 1
CYP19A1	Cytochrome P450 family 19 subfamily A member 1
CYP1A1	Cytochrome P450 family 1 subfamily A member 1
CYP1A2	Cytochrome P450 family 1 subfamily A member 2
CYP1B1	Cytochrome P450 family 1 subfamily B member 1
CYP24A1	Cytochrome P450 family 24 subfamily A member 1
CYP2A6	Cytochrome P450 family 2 subfamily A member 6
CYP2B1	Cytochrome P450 family 2 subfamily B member 1
CYP2D6	Cytochrome P450 family 2 subfamily D member 6
CYP2E1	Cytochrome P450 family 2 subfamily E member 1
CYP3A4	Cytochrome P450 family 3 subfamily A member 4
DAB2IP	DAB2 interacting protein
DAP3	Death associated protein 3
DAPK1	Death associated protein kinase 1
DDIT3	DNA damage inducible transcript 3
DDR1	Discoidin domain receptor tyrosine kinase 1
DEK	DEK proto-oncogene
DEPP1	DEPP autophagy regulator 1
DES	Desmin
DHFR	Dihydrofolate reductase
DIO3	iodothyronine deiodinase 3
DKK1	Dickkopf WNT signaling pathway inhibitor 1
DLL1	Delta like canonical Notch ligand 1
DLL4	Delta like canonical Notch ligand 4
DLL4	Delta like canonical Notch ligand 4
DNAI7	Dynein axonemal intermediate chain 7
DNASE1L3	Deoxyribonuclease 1 like 3
DNMT1	DNA methyltransferase 1
DNMT3A	DNA methyltransferase 3α
DNMT3B	DNA methyltransferase 3β
DOK1	Docking protein 1
DOK2	Docking protein 2
DOK3	Docking protein 3
DPYD	Dihydropyrimidine dehydrogenase
DSC3	Desmocollin 3
DTX3	Deltex E3 ubiquitin ligase 3
DYNC2H1	Dynein cytoplasmic 2 heavy chain 1
E2F1	E2F transcription factor 1
EAF2	ELL associated factor 2
ECHA	European Chemicals Agency
EDNRB	Endothelin receptor type B
EEF1B2	Eukaryotic translation elongation factor 1 beta 2
EEF2	Eukaryotic translation elongation factor 2
EFEMP1	EGF containing fibulin extracellular matrix protein 1
EFNA1	Ephrin A1
EFNB2	Ephrin B2
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EGR1	Early growth response 1
EHMT2	Euchromatic histone lysine methyltransferase 2
EIF2S2	Eukaryotic translation initiation factor 2 subunitβ
EIF6	Eukaryotic translation initiation factor 6
ELK3	ETS transcription factor ELK3
ELP1	Elongator acetyltransferase complex subunit 1
ELP3	Elongator acetyltransferase complex subunit 3
EMSY	EMSY transcriptional repressor, BRCA2 interacting
EMX2	Empty spiracles homeobox 2
ENO1	Enolase 1
EP300	E1A binding protein p300
EPA/RPF	USEPA relative potency factor applied
EPB41L3	Erythrocyte membrane protein band 4.1 like 3
EPHB4	EPH receptor B4
EPHX1	Epoxide hydrolase 1
EPOR	Erythropoietin receptor
ERBB2	Erb-b2 receptor tyrosine kinase 2
ERBB3	Erb-b2 receptor tyrosine kinase 3
ERCC1	ERCC excision repair 1,endonuclease non-catalytic subunit
ERCC6	ERCC excision repair 6,chromatin remodeling factor
ERGIC3	ERGIC and golgi 3
ESR1	Estrogen receptor 1
ESR2	Estrogen receptor 2
ESRRA	Estrogen related receptorα
ETS2	ETS proto-oncogene 2,transcription factor
ETV4	ETS variant transcription factor 4
EVL	Enah/Vasp-like
EU	European Union
EXO1	Exonuclease 1
EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit
F3	Coagulation factor III, tissue factor
FABP7	Fatty acid binding protein 7
FAS	Fas cell surface death receptor
FASLG	Fas ligand
FASN	Fatty acid synthase
FBL	Fibrillarin
FBXW7	F-box and WD repeat domain containing 7
FEN1	Flap structure-specific endonuclease 1
FGD5	FYVE, RhoGEF and PH domain containing 5
FGF10	Fibroblast growth factor 10
FGF3	Fibroblast growth factor 3
FGF4	Fibroblast growth factor 4
FGF9	Fibroblast growth factor 9
FGFR1	Fibroblast growth factor receptor 1
FGFR2	Fibroblast growth factor receptor 2
FHIT	Fragile histidine triad diadenosine triphosphatase
FHL2	Four and a half LIM domains 2
FKBPL	FKBP prolyl isomerase like
FLACC1	Flagellum associated containing coiled-coil domains 1
FLNA	Folliculin
FLT1	Fms related receptor tyrosine kinase 1
FN1	Fibronectin 1
FOS	Fos proto-oncogene, AP-1 transcription factor subunit
FOSB	FosB proto-oncogene, AP-1 transcription factor subunit
FOSL2	FOS like 2,AP-1 transcription factor subunit
FOXA1x	Forkhead box A1
FOXM1	Forkhead box M1
FOXP3	Forkhead box P3
FOXQ1	Forkhead box Q1
FST	Follistatin
FTO	FTO alpha-ketoglutarate dependent dioxygenase
FUBP1	Far upstream element binding protein 1
GALNT16	Polypeptide N-acetylgalactosaminyltransferase 16
GAST	Gastrin
GATA6	GATA binding protein 6
GC	GC vitamin D binding protein
GCLC	Glutamate-cysteine ligase catalytic subunit
GDF10	Growth differentiation factor 10
GEO	Gene Expression Omnibus
GJA1	Gap junction protein α 1
GJB1	Gap junction protein beta 1
GNAI2	G protein subunit α i2
GNMT	Glycine N-methyltransferase
GPER1	G protein-coupled estrogen receptor 1
GPI	Glucose-6-phosphate isomerase
GPNMB	Glycoprotein nmb
GPX1	Glutathione peroxidase 1
GPX2	Glutathione peroxidase 2
GPX3	Glutathione peroxidase 3
GPX4	Glutathione peroxidase 4
GRB7	Growth factor receptor bound protein 7
GRIK2	Glutamate ionotropic receptor kainate type subunit 2
GSK3B	Glycogen synthase kinase 3β
GSTM1	Glutathione S-transferase mu 1
GSTP1	Glutathione S-transferase pi 1
GSTP2	Glutathione S-transferase, pi 2
GSTT1	Glutathione S-transferase theta 1
GUCY1A2	Guanylate cyclase 1 soluble subunit α 2
GZMB	Granzyme B
H1-2	H1.2 linker histone, cluster member
H19	H19 imprinted maternally expressed transcript
H2AX	H2A.X variant histone
H2BC12	H2B clustered histone 12
H2BC4	H2B clustered histone 4

H6PD	Hexose-6-phosphate dehydrogenase/glucose 1-dehydrogenase
HADHB	Hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunitβ
HAPLN4	Hyaluronan and proteoglycan link protein 4
HES1	Hes family bHLH transcription factor 1
HEY1	Hes related family bHLH transcription factor with YRPW motif 1
HEY2	Hes related family bHLH transcription factor with YRPW motif 2
HEYL	Hes related family bHLH transcription factor with YRPW motif like
HHEX	Hematopoietically expressed homeobox
HIC1	HIC ZBTB transcriptional repressor 1
HIF1A	Hypoxia inducible factor 1 subunit alpha
HILPDA	Hypoxia inducible lipid droplet associated
HMMR	Hyaluronan mediated motility receptor
HMOX1	Heme oxygenase 1
HNRNPK	Heterogeneous nuclear ribonucleoprotein K
HNRNPL	Heterogeneous nuclear ribonucleoprotein L
HNRNPR	Heterogeneous nuclear ribonucleoprotein R
HOXB13	Homeobox B13
HOXB9	Homeobox B9
HOXD11	Homeobox D11
HP	Haptoglobin
HPSE	Heparinase
HRAS	HRas proto-oncogene, GTPase
HRG	Histidine rich glycoprotein
HSP90AA1	Heat shock protein 90 alpha family class A member 1
HSPA1B	Heat shock protein family A (Hsp70) member 1B
HTRA1	HtrA serine peptidase 1
IARC	International Agency for Research in Cancer
IIBSP	Integrin binding sialoprotein
ICAM5	Intercellular adhesion molecule 5
ID3	Inhibitor of DNA binding 3
IDO1	Indoleamine 2,3-dioxygenase 1
IDS	Iduronate 2-sulfatase
IER2	Immediate early response 2
IFNB1	Interferon β 1
IFNG	Interferon gamma
IGBP1	Immunoglobulin binding protein 1
IGF1	Insulin like growth factor 1
IGF1R	Insulin like growth factor 1 receptor
IGFBP5	Insulin like growth factor binding protein 5
IGFBP7	Insulin like growth factor binding protein 7
IKBKG	Inhibitor of nuclear factor kappa B kinase regulatory subunit gamma
IL10	Interleukin 10
IL1B	Interleukin 1β
IL1R2	Interleukin 1 receptor type 2
IL2	Interleukin 2
IL24	Interleukin 24
IL6	Interleukin 6
IQSEC1	IQ motif and Sect. 7 domain ArfGEF 1
IRF1	Interferon regulatory factor 1
IRF4	Interferon regulatory factor 4
ITSN2	Intersectin 2
JAG1	Jagged canonical Notch ligand 1
JAG2	Jagged canonical Notch ligand 2
JMJD6	Jumonji domain containing 6
JUN	Jun proto-oncogene
JUNB	JunB proto-oncogene
JUND	JunD proto-oncogene
KCNH1	Potassium voltage-gated channel subfamily H member 1
KDR	Kinase insert domain receptor
KIT	KIT proto-oncogene
KLHDC10	Kelch domain containing 10
KLHDC7A	Kelch domain containing 7 A
KLK10	Kallikrein related peptidase 10
KMT2D	Lysine methyltransferase 2D
KRAS	KRAS proto-oncogene
KRT14	Keratin 14
KRT18	Keratin 18
KRT5	Keratin 5
KRT8	Keratin 8
L3MBTL3	L3MBTL histone methyl-lysine binding protein 3
LAMTOR5	Late endosomal/lysosomal adaptor, MAPK and MTOR activator 5
LBX1	Ladybird homeobox 1
LDHAL6B	Lactate dehydrogenase A like 6B
LDHB	Lactate dehydrogenase B
LECT2	Leukocyte cell derived chemotaxin 2
LEF1	Lymphoid enhancer binding factor 1
LEP	Leptin
LEPR	Leptin receptor
LGR6	Leucine rich repeat containing G protein-coupled receptor 6
LIMD2	LIM domain containing 2
LINC00115	Long intergenic non-protein coding RNA 115
LINC00671	Long intergenic non-protein coding RNA 671
LLGL1	LLGL scribble cell polarity complex component 1
LLGL2	LLGL scribble cell polarity complex component 2
LMNTD1	Lamin tail domain containing 1
LOXL2	Lysyl oxidase like 2
LPAR1	Lysophosphatidic acid receptor 1
LRRC37A	Leucine rich repeat containing 37 A
LRRC3B	Leucine rich repeat containing 3B
LSP1	Lymphocyte specific protein 1
MACIR	macrophage immunometabolism regulator
MAL	Mal
MALAT1	Metastasis associated lung adenocarcinoma transcript 1
MAN2C1	Mannosidase alpha class 2 C member 1
MAP2K7	Mitogen-activated protein kinase kinase 7
MAP3K1	Mitogen-activated protein kinase kinase kinase 1
MAP3K8	Mitogen-activated protein kinase kinase kinase 8
MAP4K4	Mitogen-activated protein kinase kinase kinase kinase 4
MAPK1	Mitogen-activated protein kinase 1
MAPK14	Mitogen-activated protein kinase 14
MAPK3	Mitogen-activated protein kinase 3
MARCKS	Myristoylated alanine rich protein kinase C substrate
MCL1	MCL1 apoptosis regulator
MDM2	MDM2 proto-oncogene
MDM4	MDM4 regulator of p53
MECOM	MDS1 and EVI1 complex locus
MED12	Mediator complex subunit 12
MED28	Mediator complex subunit 28
MEIS1	Meis homeobox 1
MET	MET proto-oncogen
METTL6	Methyltransferase 6
MFGE8	Milk fat globule EGF and factor V/VIII domain containing
MIF	Macrophage migration inhibitory factor
MIR10A	MicroRNA 10a
MIR1246	MicroRNA 1246
MIR126	MicroRNA 126
MIR127	MicroRNA 127
MIR136	MicroRNA 136
MIR141	MicroRNA 141
MIR145	MicroRNA 145
MIR146A	MicroRNA 146a
MIR152	MicroRNA 152
MIR154	MicroRNA 154
MIR155	MicroRNA 155
MIR193A	MicroRNA 193a
MIR200B	MicroRNA 200b
MIR200C	MicroRNA 200c
MIR205	MicroRNA 205
MIR206	MicroRNA 206
MIR21	MicroRNA 21
MIR22	MicroRNA 22
MIR221	MicroRNA 221
MIR222	MicroRNA 222
MIR224	MicroRNA 224
MIR242	MicroRNA 242
MIR24-2	MicroRNA 24 – 2
MIR29A	MicroRNA 29a

MIR30	MicroRNA 30
MIR301A	MicroRNA 301a
MIR302D	MicroRNA 302d
MIR30A	MicroRNA 30a
MIR31	MicroRNA 31
MIR31HG	MIR31 host gene
MIR34B	MicroRNA 34b
MIR34C	MicroRNA 34c
MIR369	MicroRNA 369
MIR370	MicroRNA 370
MIR410	MicroRNA 410
MIR429	MicroRNA 429
MIR4435-2HG	MIR4435-2 host gene
MIR487B	MicroRNA 487b
MIR494	MicroRNA 494
MIR506	MicroRNA 506
MIR98	MicroRNA 98
MIRLET7BHG	MIRLET7B host gene
MKI67	Marker of proliferation Ki-67
MME	Membrane metalloendopeptidase
MMP1	Matrix metallopeptidase 1
MMP1	Matrix metallopeptidase 1
MMP10	Matrix metallopeptidase 10
MMP14	Matrix metallopeptidase 14
MMP1A	Matrix metallopeptidase 1a
MMP2	Matrix metallopeptidase 2
MMP3	Matrix metallopeptidase 3
MMP9	Matrix metallopeptidase 9
MOE	South Korea Ministry of Environment
MOL	South Korea Ministry of Labour
MPO	Myeloperoxidase
MPP1	MAGUK p55 scaffold protein 1
MRPL13	Mitochondrial ribosomal protein L13
MRPL19	Mitochondrial ribosomal protein L19
MRPL9	Mitochondrial ribosomal protein L9
MRPS22	Mitochondrial ribosomal protein S22
MRPS23	Mitochondrial ribosomal protein S23
MRPS28	Mitochondrial ribosomal protein S28
MRPS7	Mitochondrial ribosomal protein S7
MST1	Macrophage stimulating 1
MT3	Metallothionein 3
MTDH	Metadherin
MTHFR	Methylenetetrahydrofolate reductase
MTOR	Mechanistic target of rapamycin kinase
MTR	5-methyltetrahydrofolate-homocysteine methyltransferase
MUC12	Mucin 12
MUC16	Mucin 16
MYC	MYC proto-oncogene
MYH9	Myosin heavy chain 9
MYO18B	Myosin XVIIIB
NAT2	N-acetyltransferase 2
NCOA1	Nuclear receptor coactivator 1
NCOA2	Nuclear receptor coactivator 2
NCOA3	Nuclear receptor coactivator 3
NCOR1	Nuclear receptor corepressor 1
NDRG1	N-myc downstream regulated 1
NDUFS3	NADH: ubiquinone oxidoreductase core subunit S3
NECTIN2	Nectin cell adhesion molecule 2
NFE2L2	NFE2 like bZIP transcription factor 2
NFKBIA	NFKB inhibitorα
NFYA	Nuclear transcription factor Y subunitα
NISCH	Nischarin
NMBR	Neuromedin B receptor
NOP9	NOP9 nucleolar protein
NOS2	Nitric oxide synthase 2
NOS3	Nitric oxide synthase 3
NOTCH1	Notch receptor 1
NOTCH2	Notch receptor 2
NOTCH3	Notch receptor 3
NOTCH4	Notch receptor 4
NPPA	Natriuretic peptide A
NQO1	NAD(P)H quinone dehydrogenase 1
NQO1	NAD(P)H quinone dehydrogenase 1
NQO2	NAD(P)H quinone dehydrogenase 2
NR2F1	Nuclear receptor subfamily 2 group F member 1
NR2F6	Nuclear receptor subfamily 2 group F member 6
NR2F6	Nuclear receptor subfamily 2 group F member 6
NRCAM	Neuronal cell adhesion molecule
NRG1	Neuregulin 1
NRIP1	Nuclear receptor interacting protein 1
NSD2	Nuclear receptor binding SET domain protein 2
NSUN6	NOP2/Sun RNA methyltransferase 6
NUDT17	Nudix hydrolase 17
NUDT2	Nudix hydrolase 2
O&G	Oil and gas
OCLN	Occluding
OEHHA	Office of Environment Health Hazard Assessment
OGG1	8-oxoguanine DNA glycosylase
PABPC1	Poly(A) binding protein cytoplasmic 1
PAEP	Progestagen associated endometrial protein
PAK1	P21 (RAC1) activated kinase 1
PALB2	Partner and localizer of BRCA2
PARP1	Poly(ADP-ribose) polymerase 1
PCBP1	Poly(rC) binding protein 1
PCDHGB6	Protocadherin gamma subfamily B,6
PCNA	Proliferating cell nuclear antigen
PDCD1	Programmed cell death 1
PDCD4	Programmed cell death 4
PDE2A	Phosphodiesterase 2 A
PDGFA	Platelet derived growth factor subunit A
PDLIM4	PDZ and LIM domain 4
PDPK1	3-phosphoinositide dependent protein kinase 1
PDZK1	PDZ domain containing 1
PER3	Period circadian regulator 3
PGGT1B	Protein geranylgeranyltransferase type I subunit beta
PGR	Progesterone receptor
PHB1	Prohibitin 1
PHGDH	Phosphoglycerate dehydrogenase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunitα
PIM1	Pim-1 proto-oncogene, serine/threonine kinase
PIN1	Peptidylprolyl cis/trans isomerase, NIMA-interacting 1
PLA2G4A	Phospholipase A2 group IVA
PLEKHD1	Pleckstrin homology and coiled-coil domain containing D1
PON1	Paraoxonase 1
PPARGC1B	PPARG coactivator 1β
PPBP	Pro-platelet basic protein
PPM1D	Protein phosphatase, Mg2+/Mn2 + dependent 1D
PPP1R12B	Protein phosphatase 1 regulatory subunit 12B
PPP2R1B	Protein phosphatase 2 scaffold subunit 1β
PPRTV	USEPA Provisional Peer-Reviewed Toxicity Values
PRC1	Protein regulator of cytokinesis 1
PRDX1	Peroxiredoxin 1
PRDX6	Peroxiredoxin 6
PRKN	Parkin RBR E3 ubiquitin protein ligase
PRSS46	Protease, serine 46
PSMA4	Proteasome 20 S subunit α 4
PTEN	Phosphatase and tensin homolog
PTGIS	Prostaglandin I2 synthase
PTGS1	Prostaglandin-endoperoxide synthase 1
PTGS2	Prostaglandin-endoperoxide synthase 2
PTHLH	Parathyroid hormone like hormone
PTMA	Prothymosinα
PTPRD	Protein tyrosine phosphatase receptor type D
PYCARD	PYD and CARD domain containing
RAD51	RAD51 recombinase
RAD51B	RAD51 paralog B
RAD51C	RAD51 paralog C
RAD52	RAD52 homolog, DNA repair protein
RAD54L	RAD54 like
RAF1	Raf-1 proto-oncogene, serine/threonine kinase
RALYL	RALY RNA binding protein like
RAMP2	Receptor activity modifying protein 2
RARA	Retinoic acid receptorα

RARB	Retinoic acid receptorβ
RASSF1	Ras association domain family member 1
RB1	RB transcriptional corepressor 1
RB1CC1	RB1 inducible coiled-coil 1
RBM3	RNA binding motif protein 3
RBP4	Retinol binding protein 4
RCCD1	RCC1 domain containing 1
RCHY1	Ring finger and CHY zinc finger domain containing 1
RECQL	RecQ like helicase
RELA	RELA proto-oncogene, NF-kB subunit
REPS2	RALBP1 associated Eps domain containing 2
RGS2	Regulator of G protein signaling 2
RIBC2	RIB43A domain with coiled-coils 2
RIC8A	RIC8 guanine nucleotide exchange factor A
RIOX2	Ribosomal oxygenase 2
RMND1	Required for meiotic nuclear division 1 homolog
RNASET2	Ribonuclease T2
RNF115	Ring finger protein 115
RNF182	Ring finger protein 182
ROBO1	Roundabout guidance receptor 1
ROR1	Receptor tyrosine kinase like orphan receptor 1
RPL23A	Ribosomal protein L23a
RPL31	Ribosomal protein L31
RPLP2	Ribosomal protein lateral stalk subunit P2
RPS4X	Ribosomal protein S4 X-linked
RPS6	Ribosomal protein S6
RPS6KB2	Ribosomal protein S6 kinase B2
RPS7	Ribosomal protein S7
RPS8	Ribosomal protein S8
RRAD	Ras related glycolysis inhibitor and calcium channel regulator
RSPO3	R-spondin 3
RTEL1	Regulator of telomere elongation helicase 1
RUNX2	RUNX family transcription factor 2
RUNX3	RUNX family transcription factor 3
RXRB	Retinoid X receptorβ
SECISBP2L	SECIS binding protein 2 like
SELENBP1	Selenium binding protein 1
SELENOP	Selenoprotein P
SERPINA1	Serpin family A member 1
SERPINB2	Serpin family B member 2
SERPINB5	Serpin family B member 5
SERPING1	Serpin family G member 1
SETBP1	SET binding protein 1
SETD2	SET domain containing 2,histone lysine methyltransferase
SFRP1	Secreted frizzled related protein 1
SFRP2	Secreted frizzled related protein 2
SFRP5	Secreted frizzled related protein 5
SFTPB	Surfactant protein B
SFTPD	Surfactant protein D
SHMT1	Serine hydroxymethyltransferase 1
SIDT2	SID1 transmembrane family member 2
SIM1	SIM bHLH transcription factor 1
SIRT1	Sirtuin 1
SLC10A6	Solute carrier family 10 member 6
SLC16A3	Solute carrier family 16 member 3
SLC22A18	Solute carrier family 22 member 18
SLC28A1	Solute carrier family 28 member 1
SLC2A1	Solute carrier family 2 member 1
SLC2A10	Solute carrier family 2 member 10
SLC2A2	Solute carrier family 2 member 2
SLC2A5	Solute carrier family 2 member 5
SLC39A6	Solute carrier family 39 member 6
SLC3A2	Solute carrier family 3 member 2
SLC5A5	Solute carrier family 5 member 5
SLC7A5	Solute carrier family 7 member 5
SLCO1B1	Solute carrier organic anion transporter family member 1B1
SLCO1B3	Solute carrier organic anion transporter family member 1B3
SMARCC1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 1
SMC2	Structural maintenance of chromosomes 2
SNAI1	Snail family transcriptional repressor 1
SNAI2	Snail family transcriptional repressor 2
SNCG	Synuclein gamma
SND1	Staphylococcal nuclease and tudor domain containing 1
SNX32	Sorting nexin 32
SOD2	Superoxide dismutase 2
SOX2	SRY-box transcription factor 2
SOX30	SRY-box transcription factor 30
SOX9	SRY-box transcription factor 9
SPATA18	Spermatogenesis associated 18
SPP1	Secreted phosphoprotein 1
SPRY2	Sprouty RTK signaling antagonist 2
SRC	SRC proto-oncogene, non-receptor tyrosine kinase
SREBF2	Sterol regulatory element binding transcription factor 2
STARD8	StAR related lipid transfer domain containing 8
STAT3	Signal transducer and activator of transcription 3
STAT5A	Signal transducer and activator of transcription 5 A
STC2	Stanniocalcin 2
STIM1	Stromal interaction molecule 1
STK11	Serine/threonine kinase 11
STMN1	Stathmin 1
STN1	STN1 subunit of CST complex
STXBP4	Syntaxin binding protein 4
SULT1A1	Sulfotransferase family 1 A member 1
SYNE1	Spectrin repeat containing nuclear envelope protein 1
SYNJ2	Synaptojanin 2
TAFA4	TAFA chemokine like family member 4
TANK	TRAF family member associated NFKB activator
TBX3	T-box transcription factor
TCL1B	TCL1 family AKT coactivator B
TEP1	Telomerase associated protein 1
TERT	Telomerase reverse transcriptase
TFAP2A	Transcription factor AP-2α
TFPI2	Tissue factor pathway inhibitor 2
TFRC	Transferrin receptor
TGFB1	Transforming growth factor β 1
TGFBR2	Transforming growth factor beta receptor 2
TGM2	Transglutaminase 2
THBS1	Thrombospondin 1
THEMIS2	Thymocyte selection associated family member 2
TLE3	TLE family member 3
TLR4	Toll like receptor 4
TMEM25	Transmembrane protein 25
TMEM45A	Transmembrane protein 45 A
TNF	Tumor necrosis factor
TNFSF10	TNF superfamily member 10
TNIP1	TNFAIP3 interacting protein 1
TOP2A	DNA topoisomerase IIα
TOX3	TOX high mobility group box family member 3
TP53	Tumor protein p53
TP53BP1	Tumor protein p53 binding protein 1
TP53BP2	Tumor protein p53 binding protein 2
TP63	Tumor protein p63
TP73	Tumor protein p73
TRERF1	Transcriptional regulating factor 1
TRIM12A	Tripartite motif-containing 12 A
TRIM47	Tripartite motif containing 47
TRIO	Trio Rho guanine nucleotide exchange factor
TRMT11	TRNA methyltransferase 11 homolog
TRP53	Transformation related protein 53
TRP63	Transformation related protein 63
TSC2	TSC complex subunit 2
TSHR	Thyroid stimulating hormone receptor
TTR	Transthyretin
TUBB3	Tubulin beta 3 class III
TXN	Thioredoxin
TYMS	Thymidylate synthetase
TYRP1	Tyrosinase related protein 1
UBD	Ubiquitin D
UBE2C	Ubiquitin conjugating enzyme E2 C
UBLCP1	Ubiquitin like domain containing CTD phosphatase 1
UGT2B17	UDP glucuronosyltransferase family 2 member B17
UMPS	Uridine monophosphate synthetase

UN GHS	United Nations Globally Harmonized System of Classification and Labelling of Chemicals
UPK1B	Uroplakin 1B
USP18	Ubiquitin specific peptidase 18
VDR	Vitamin D receptor
VEGFB	Vascular endothelial growth factor B
VEGFC	Vascular endothelial growth factor C
VHL	Von Hippel-Lindau tumor suppressor
VIM	Vimentin
VPS39	VPS39 subunit of HOPS complex
WNT10B	Wnt family member 10B
WNT5A	Wnt family member 5 A
WT1	WT1 transcription factor
WWOX	WW domain containing oxidoreductase
XPC	XPC complex subunit
XRCC2	X-ray repair cross complementing 2
XRCC3	X-ray repair cross complementing 3
YAP1	Yes1 associated transcriptional regulator
YBX1	Y-box binding protein 1
ZC3H11A	Zinc finger CCCH-type containing 11 A
ZEB1	Zinc finger E-box binding homeobox 1
ZEB2	Zinc finger E-box binding homeobox 2
ZFP366	Zinc finger protein 366
ZNF365	Zinc finger protein 365
ZNF366	Zinc finger protein 366
ZNF404	Zinc finger protein 404
ZNF432	Zinc finger protein 432
ZNF595	Zinc finger protein 595
ZSCAN22	Zinc finger and SCAN domain containing 22
ZSWIM5	Zinc finger SWIM-type containing 5

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41021-024-00310-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Acknowledgements
Not applicable.

Author contributions
SHIH, AAB, and MI contributed to the direction of the paper. MZIZ and NIAS updated hazard classification of the chemicals under the supervision of MI. NASZ conducted CTD data-mining and compilation networks images under the supervision of SH & AAB. All authors contribute to the writing of the manuscript and provided feedback in finalizing the manuscript.

Funding
Not applicable.

Data availability
All data generated or analyzed during this study are included in this published article. Additional supplementary data are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Received: 20 November 2023 / Accepted: 7 June 2024
Published online: 09 July 2024

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