Supplementary Materials

Table S1. 54 Carcinogenic binary chemical combinations collected from publications.

Species		Chemical 1	Chemical 2	Sources
Rat	liver	Diethylnitrosamine (DEN)	4-dimethylaminoazobenzene	Habs & Schmähl, 1980[1]
			4-dimethylaminostilbene	
	liver	Diethylnitrosamine (DEN)	phenobarbital	Nishizumi, 1976[2]
	liver	Dimethylnitrosamine (DMN)	4-dimethylaminoazobenzene (DAB)	Takayama & Imaizumi, 1969[3]
	liver	Aflatoxin B_1	Fumonisin B_1	Qian et al, 2016[4]
	liver	Diethylnitrosamine (DEN)	Aflatoxin B_1	Sekijima et al, 1999[5]
		Microcystin-LR		
	liver	Diethylnitrosamine (DEN)	Nodularin (NOD)	Song et al, 1999[6]
	Liver	n-bis(2-hyrdoxypropyl) nitrosamine (DHPN)	Phenobarbital (PB)	Shimo et al, 1994[7]
			Thiourea (TU)	
	Liver	Sterigmatocystin (STG)	Nitrosodimethylamine (NDMA)	Terao et al, 1978[8]
	Liver	Diethylnitrosamine (DEN)	Fumonisin B_1	Gelderblom et al, 1996[9]
	liver	N-2-fluorenylacetamide (2-FAA)	Methapyrilene (MP)	Furuya & Williams, 1984[10]
			Diethylnitrosamine (DEN)	
	liver	Diethylnitrosamine (DEN)	Clofibrate	Mochizuki et al, 1983[11]
	liver	N-nitrosomorphine (NNM)	Phenobarbital	Schwarz et al, 1983[12]
	liver	Diethylnitrosamine (DEN)	Carbon tetrachloride	Cho & Jang, 1993[13]
	liver and kidney	Dimethylnitrosamine (DMN)	carbon tetrachloride	Pound et al, 1973[14]
	Liver and squamous cell	Dimethylnitrosamine (DMNA)	disulfiram (DSF)	Schmähl et al, 1976[15]
		Diethylnitrosamine (DEN)	disulfiram (DSF)	
	lung	Dimethylnitrosamine (DMN)	3-methylcholanthrene (MCA)	Hoch-Ligeti et al, 1968[16]
	Lung and heart	Methyl-acetoxymethyl-nitrosamine	disulfiram (DSF)	Habs & Schmähl, 1980[1]

	urinary bladder	N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)	N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT)	Tsuda et al, 1977[17]
		N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)	N-2-fluorenylacetamide (2-FAA)	
		N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)	3, 3'-dichlorobenzidine (3, 3'-DCB)	
		N-2-fluorenylacetamide (2-FAA)	N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT)	
	Urinary bladder	Sodium o-phenylphenate (OPP-Na)	Thiabendazole (TBZ)	Fujii et al, 1986[18]
	Urinary bladder	n-butyl-n-(4-hydroxybutyl) nitrosamine(BBN)	diphenyl	Kurata et al, 1986[19]
	Mammary	Methylnitrosourea (MNU)	Estrone (E1)	Bigsby, 2002[20]
	mammary	N-methyl-N-nitrosourea (MNU)	7,12-dimethylbenz[α]anthracene (DMBA)	Shirai et al, 1997[21]
	mammary	N-nitrosomethylurea (NMU)	reserpine	Verdeal et al, 1983[22]
	mammary	N-nitrosomethylurea (NMU)	ketoconazole	Van Cauteren et al, 1984[23]
	Pancreatic	Azaserine	Linoleic acid (LA)	Appel et al, 1994[24]
	Prostate	3,2'-dimethyl-4-aminobiphenyl (DMAB)	Testosterone propionate (TP)	Yaono et al, 2000[25]
	prostate	N-mthyl-N-nitrosourea (MNU)	Testosterone propionate (TP)	Pollard & Luckert, 1987[26]
	Colon	di(2-ethylhexyl)phthalate (DEHP)	1,2-dimethylhydrazine (DMH)	Chen et al, 2017[27]
Mouse	skin	4-nitroquinolone n-oxide	20-methylcholanthrene	Nakahara & Fukuoka, 1960[28]
	skin	7,12-dimethylbenz[α]anthracene (DMBA)	1α,25-dihydroxyvitamin D3	Wood et al, 1985[29]
	lung	Dimethylnitrosamine (DMN)	Diethylnitrosamine (DEN)	Cardesa et al, 1974[30]
	liver	Polychlorinated terphenyl (PCT)	Hexachlorobenzene (HCB)	Shirai et al, 1978[31]
Hamster	Squamous cell	Diethylnitrosamine (DEN)	Benzo[a]pyrene (BaP)	Montesano et al, 1974[32]
	Squamous cell	N-methyl-N-nitrosourea (MNU)	Benzo[a]pyrene (BaP)	Kaufman & Madison, 1974[33]

	Squamous cell	N-nitrosonornicotine (NNN)	7,12 dimethylbenz[α]anthracene (DMBA)	Altuwairgi et al, 1995[34]
			4-nitroquinolone n-oxide	
Fish	liver	N-methyl-N'-nitro-nitrosoguanidine (MNNG)	Fumonisin B1	Carlson et al, 2001[35]
	liver	Aflatoxin B_1	Tocopheryl acetate	Adams & Whitten, 2018[36]
	Histopathological Analysis	Benzo[b]fluoranthene (BBF)	Phenanthrene	Martins et al, 2015[37]
HepG2 Cells	DNA adduct formation	Benzo[a]pyrene (BaP)	Dibenzo[a,h]anthracene (DB[a,h]A)	Staal et al, 2007[38]
			Benzo[b]fluoranthene (B[b]F)	
			Fluoranthene (FA)	
			1-methylphenanthrene (1-MPA)	
			Dibenzo[a,l]pyrene (DB[a,l]P)	
HepG2/WB-F344 liver cell lines	DNA adduct formation	Benzo[a]pyrene (BaP)	7H-dibenzo[c,g]carbazole (DBC)	Gábelova et al, 2013[39]
Balb/c 3T3 cells	Cell transformation frequency	Diethylnitrosamine (DEN)	2,3,7,8-Tetracholorodibenzo-p-dioxin (TCDD)	Zhang et al, 2013[40]

Table S2. 25 non-carcinogenic binary drug and chemical combinations collected from publications.

Species		**Chemical 1**	**Chemical 2**	**Sources**
Rat	liver	Curcumin	Piperine	Patial et al, 2015[41]
	liver	Combretastatin A-4 phosphate (CA4-P)	Vincristine	Aboubakr et al, 2017[42]
	colon	Umbelliferone (UMB)	5-fluorouracil (5-FU)	Muthu & Vaiyapuri, 2013[43]
	colon	(-)-Epigallocatechin gallate (EGCG)	Sulindac	Ohishi et al, 2002[44]
	colon	morin	esculetin	Sharma et al, 2017[45]
	oesophageal	Celecoxib	S,S'-1,4-phenylene-bis(1,2-ethanediyl)bis-isothiourea (PBIT)	Shi et al, 2016[46]
	mammary	Melatonin	Tamoxifen	Kothari et al, 1997[47]
	Mammary	Fish oil (Maxepa)	1α,25-dihydroxyvitamin D_3	Chatterjee et al, 2010[48]
mouse	Breast cancer	Thymoquinone (TQ)	Resveratrol (RES)	Alobaedi et al, 2017[49]

hamster	Pancreatic cancer	Celecoxib	capecitabine	Arjona-Sánchez et al, 2010[50]
Cell line	Breast cancer	Doxorubicin	Quercetin	Qureshi et al, 2016[51]
	Breast cancer	All-trans retinoic acid (ATRA)	Docetaxel (Taxotere)	Wang & Wieder, 2004[52]
	Breast cancer	All-trans retinoic acid (ATRA)	Tamoxifen	Wang et al, 2007[53]
	Breast cancer	All-trans retinoic acid (ATRA)	Doxorubicin	Sun et al, 2015[54]
	Breast cancer	All-trans retinoic acid (ATRA)	Cisplatin (CDDP)	Grunt et al, 1998[55]
	Breast cancer	Valproic acid	Hydroxyurea (HU)	Tian et al, 2017[56]
	Hepatocellular carcinoma	Curcumin	Sorafenib	Hu et al, 2015[57]
	Prostate cancer	Suramin	Cisplatin (CDDP)	Lopez Lopez et al, 1994[58]
	Prostate cancer	Naringin	Atorvastatin	Wu et al, 2019[59]
	Head and neck squamous cell	13-cis retinoic acid	Curcumin	Spingarn et al, 1998[60]
			phenidone	
			Nordihydroguaiaretic acid (NDGA)	
			5,8,11,14-eicosatetraynoic acid (ETYA)	
	Ovary and endometrial cancer	Cisplatin (CDDP)	Quercetin	Scambia et al, 1992[61]
	Lung cancer	Cisplatin (CDDP)	Cisatracurium besylate	Yabasin et al, 2014[62]

Table S3. Change in % accuracy for distinct training and test sets of virtual mixtures for the binary classification of carcinogenicity of chemical mixtures.

Classification		Accuracy %		% change
		Train/Test Not Separated	Train/Test Separated	
Binary	HNN	98.86	72.91	26.25
	RF	98.71	88	10.85
	Bag	98.3	87.39	11.10
	Ada	99.78	98.16	1.62

Table S4. Change in % accuracy for distinct training and test sets of virtual mixtures for the multiclass classification of carcinogenicity of chemical mixtures.

Classification		Accuracy %		% change
		Train/Test Not Separated	Train/Test Separated	
Multiclass	HNN	96.03	54.65	43.09
	RF	91.39	62.22	31.92
	Bag	91.74	58.17	36.59
	Ada	80.21	51.25	36.11

Table S5. Change in coefficient of determination (R^2) for distinct training and test sets of virtual mixtures for the regression classification of carcinogenicity of chemical mixtures.

Classification		Coefficient of determination (R^2)		% change
		Train/Test Not Separated	Train/Test Separated	
Regression	HNN	0.962	0.383	60.18
	RF	0.903	0.285	68.44
	SVM	0.777	-0.147	118.92
	GB	0.942	0.251	73.35
	KR	0.961	0.036	96.25
	DTBoost	0.961	0.202	78.98
	NN	0.97	-0.448	146.19
	Consensus	0.959	0.229	76.12

Equation S1. Equations to calculate the evaluation metrics for binary & multiclass classification.

$$Accuracy = \frac{TP + TN}{TP + TN + FN + FP} \times 100$$

$$Sensitivity(truepositiverate) = \frac{TP}{TP + FN} \times 100$$

$$Specificity(truenegativerate) = \frac{TN}{TN + FP} \times 100$$

Where, TP = True Positive, TN = True Negative, FP = False Positive, and FN = False Negative.

Equation S2. Equations to calculate the evaluation metrics for regression models.

$$R^2 = \frac{ESS}{TSS} = \frac{\sum_{i=1}^{n}(\hat{y}_i - \bar{y})^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2}$$

$$MSE = \frac{\sum_{i=1}^{n} |\hat{y}_i - y_i|^2}{n}$$

$$MAE = \frac{\sum_{i=1}^{n} |\hat{y}_i - y_i|}{n}$$

Where, ESS is explained sum of squares and TSS is the total sum of squares, $\hat{y}_i$ is the predicted value of the i^{th} dependent variable, y_i is the i^{th} observed dependent variable, and $\bar{y}$ is the mean of the observed data.

The number of unique simulations were run is 30 and average is taken for each statistical metrics such as AUC, accuracy, selectivity, sensitivity and precision.

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