



## REVIEW ARTICLE

## SECONDARY DATA ANALYSIS ON PESTICIDE-GENE-DISEASE RELATIONS

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## ABSTRACT

Chemical pesticides can present toxic effects to human beings, and they are classified based on chemical characterization, presenting 300 active substances and more than 2000 different formulations. Their overuse can represent a significant risk factor to human health. Therefore, it is essential to investigate the putative association between health harms and pesticides because this information can be helpful for monitoring and controlling pesticide exposure. This study aims to analyze secondary data about pesticides and their effects on genes and disease phenotypes leading to health harm. For this, we used information about pesticides available on the Ministry of Agriculture, Livestock Breeding, and Supply documents. We also use the Set Analyzer tool available on the Comparative Toxicogenomics Database (CTD) to verify a putative association between pesticides and their specific chemical groups to human diseases. Finally, we use variance analysis to evaluate them for statistical purposes. Results showed that 127 chemical groups could be found in food, and they are classified into eight functional classes of pesticides used against pests in food crops. These functional classes are acaricides, bactericides, fungicides, herbicides, insecticides, molluscicides, nematocides, and plant growth regulators. Furthermore, data obtained from the CTD showed a predominance of digestive, nervous, respiratory, and skin diseases as the significant harms caused by pesticide exposure. Results also showed that all the pesticides' functional classes affect genes associated with cancer development. Considering all the 127 chemical groups, we identified 145321 genes affected by these substances: 49733 genes affected by acaricides, 26832 genes affected by fungicides, 22687 genes affected by herbicides, 42681 genes affected by insecticides, 15842 genes affected by molluscicides, 15842 genes affected by nematocides, and 17217 genes affected by plant growth regulators. Organophosphates are the primary chemical group responsible for genetic effects, mainly leading to cancer and nervous system diseases. So, we conclude that seven different chemical groups can affect genes associated with cancer development and also concluded pesticide use could be related to genes effects and diseases development which can lead to health harms.

## KEYWORDS

Pesticides, cancer, human health, Comparative Toxicogenomics Database (CTD), Ministry of Agriculture, Livestock Breeding, and Supply.

### 1. INTRODUCTION

Pesticides have different levels of toxicity to human beings. These substances are used to control pests on crops and, according to their action, can be insecticides, acaricides, nematocides, fungicides, and herbicides. Pesticides are classified according to their chemical classes based on chemical components. Pesticides classes present 300 active substances and more than 2000 different formulations, of which the most used are organophosphates, organochlorines, carbamates, and pyrethroids (Adad et al., 2015). As pesticides have been used in indiscriminate and inappropriate ways, it is essential to understand their chemical characterization and effects on human health. Pesticides can represent a significant risk factor to human health, and it should be investigated the putative association between health harms and pesticide use. This information can be helpful for monitoring and controlling pesticide exposure.

People who work with these substances in industry or crops are more exposed to the toxicity, especially without personal protective equipment.

Contact of rural workers with pesticides mainly occurs through the skin, inhalator way, and ocular mucosa (Ahmad and Ahmad, 2017). A study with two groups of farmworkers exposed to different pesticides, for example, showed a significant increase in micronuclei, karyorrhexis, karyolysis, and binucleated cells frequencies in exposed people compared to the control group (Arteaga-Gomez et al., 2016). Non-occupational pesticide exposure, during the human embryonic period, for instance, can lead to chronic diseases, which will evolve in adult life (Ayaz et al., 2017). Some non-transmissible diseases such as type 2 diabetes and obesity, infertility and reproductive problems as attention deficit hyperactivity disorder and autism have been associated with pesticides exposure (Cardoso, 2020; Chawla et al., 2018; Datta et al., 2016; Davis et al., 2018; Dusman et al., 2012).

Since 2008, Brazil is one of the largest pesticide consumers globally, consuming one million tons from 2011 to now. This consumption level makes Brazil responsible for 86% of all pesticide consumption in Latin America (Eleftheriadou et al., 2019). Thus, more effective control of pesticide use is necessary and should be based on scientific data.

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Considering this background information, we aim to analyze data about pesticides and their effects on genes and phenotypes leading to health harm.

## 2. MATERIALS AND METHODS

### 2.1 Pesticide data search

Data from the Ministry of Agriculture, Livestock Breeding, and Supply (MAPA) database were used to define the most used pesticides in Brazil in November 2020. We used this list to search for information about pesticides' chemical groups and chemical structures. Based on this, we classified the pesticides according to the chemical groups identified as carbamates, organophosphates, organochlorides, and others.

### 2.2 Association between pesticides and human diseases genotypes and phenotypes

We used the Set Analyzer tool available in the Comparative Toxicogenomics Database to verify a putative association between pesticides and their specific chemical groups to human diseases. Comparative Toxicogenomics Database is an open-access database that selects scientific literature to provide content about molecular mechanisms of substances on genes leading to specific phenotype alterations (Georgiadis et al., 2018). Search in this base was performed between November 2020 and February 2021 and was used as search parameters for pesticides' names from the list obtained in the 2.1 Pesticide data search. Analysis of data obtained in this search was limited to cancer, digestive system diseases, nervous system diseases, respiratory system, and skin diseases.

### 2.3 Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test. The statistical threshold was set at  $p < 0.05$ .

## 3. RESULTS

### 3.1 Pesticides functional classes and chemical groups

According to the Ministry of Agriculture, Livestock Breeding, and Supply database, we identified pesticides' chemical groups most used in Brazil. This information was analyzed compared to those found in the Comparative Toxicogenomics Database to associate pesticides and human diseases (Table 1). Results showed that 127 chemical groups (Table 1) represent eight functional classes of pesticides used against pests in food crops, such as acaricides, bactericides, fungicides, herbicides, insecticides, molluscicides, nematocides, and plant growth regulators. In addition, data obtained from the Comparative Toxicogenomics Database showed a predominance of digestive, nervous, respiratory, and skin diseases (Table 1) as the significant harms caused by pesticide exposure.

**Table 1:** Pesticides chemical groups numbers related to human diseases.

Diseases	Chemical groups numbers
Digestive	35
Nervous	27
Respiratory	32
Skin	33

Digestive diseases are related to at least 35 pesticides chemical groups referring to pesticide residues ingestion risk. Respiratory harms were associated with 32 pesticides (Table 1), and 33 other pesticides' chemical groups (Table 1) were related to skin diseases. These results refer to pulmonary and cutaneous ways of pesticide residues absorption, which are primarily related to the lack of personal protective equipment. Regarding nervous system diseases, we found 27 pesticides' chemical groups (Table 1) which present a chemical structure that causes damage to this system. Considering all these 127 chemical groups and the associated diseases, we identified 145321 genes (Table 2) affected by these substances, which are correlated to these health harms. As it is known that pesticides can be toxic or even genotoxic, it is essential to analyze in a specific way the putative association between pesticides' chemical groups and human diseases. For this, we verified the number of genes affected by each chemical group to identify which chemical groups are more harmful to human health in a general way.

The following chemical groups were described for the acaricide functional class: alkyl sulfite, avermectin, benzilate, benzoylurea, carbamates, chlorocyclodiene, chlorodiphenylsulfone, keto-enol, organochlorine,

organophosphate, oxime methylcarbamate, phenyl methylcarbamate, pyrazole, pyrazole analog, pyrethroids, pyridazine, and urea (Table 2). Nevertheless, it was described only two pesticides' chemical groups, each for bactericide (dicarboximide and strobilurin) and plant growth regulator functional classes (triazole and urea) (Table 2). It was reported that only four pesticides' chemical groups each for molluscicide (neonicotinoid, organophosphate, oxime methylcarbamate, and phenyl methylcarbamate) and nematocide (benzofuranyl methylcarbamate, carbamates, organophosphate, and oxime methylcarbamate) (Table 2).

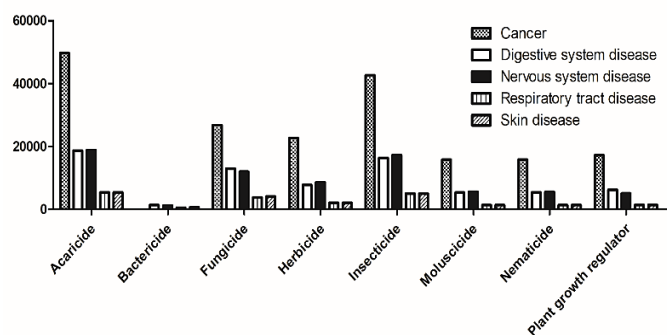
Table 2 showed ten different pesticides' chemical groups for herbicides: chloroacetanilide, dinitroaniline, diphenyl ether, methyl isothiocyanate, oxime cyclohexanodione, pyridine carboxylic acid, thiocarbamate, triazine, triazinone, and urea. Fungicides presented 23 different chemical groups: acetamide, anilopyrimidine, benzamide, benzimidazole, benzothiadiazole, carbamates, chloroaromatic, dicarboximide, hydroxyanilides, imidazole, imidazolinone, imidazolylcarboxamide, isophthalonitrile, methyl isothiocyanate, morpholine, organophosphate, oxazolidinedione, phenylpyrazoles, phenylurea, pyrimidines, strobilurin, sulfamides, and triazole (Table 2).

As the most numerous functional class, Table 2 described 25 different chemical groups related to insecticides: avermectin, benzodioxol methylcarbamate, benzofuranyl methylcarbamate, benzohidrazila, benzothiadiazole, benzoylurea, carbamates, chlorocyclodiene, chlorodiphenylsulfone, dimethyl carbamate, diphenyl ether, keto-enol, methyl isothiocyanate, neonicotinoid, organochlorine, organophosphate, oxadiazine, oxime methylcarbamate, phenyl methylcarbamate, pyrazole, pyrethroids, pyridazine, pyridyloxypropyl ether, tetraoic acid, and triazinamine.

### 3.2 Pesticides affecting human diseases related genes

Figure 1 shows the number of genes affected by pesticides and the diseases associated with them. Results showed that all the pesticides' functional classes affect genes associated with cancer development. These cancer-causing genes are affected by acaricides (49733 genes), fungicides (26832 genes), herbicides (22687 genes), insecticides (42681 genes), molluscicides (15842 genes), nematocides (15842 genes), and plant growth regulators (17217 genes). Regarding the cancer-causing genes, acaricides affect many more genes than bactericides, fungicides, herbicides, molluscicides, nematocides, and plant growth regulators (in all comparisons,  $p < 0.05$ ). Results also showed that cancer-causing genes are more affected by insecticides than bactericides, molluscicides, nematocides, and plant growth regulators (in all comparisons,  $p < 0.05$ ). We also identified that organophosphates and organochlorides acaricides are responsible for most of the affected cancer-causing genes (14476 and 15842, respectively; Figure 1). About bactericides, we observed this chemical group is the least related to cancer development until now, with no cancer-causing gene affected by them.

Figure 1 reports genes related to digestive system diseases are affected by acaricides (18652 genes), bactericides (1389 genes), fungicides (12947 genes), herbicides (7769 genes), insecticides (16398 genes), molluscicides (5371 genes), nematocides (5411 genes) and plant growth regulator (6220 genes). In addition, it became clear that organophosphates (5246 genes), triazines (4664 genes), organochlorides (4007 genes), and triazoles (3427 genes) are the chemical groups mainly responsible for genotypic alterations that can cause digestive system diseases. Regarding digestive system disease-causing genes, it was observed that acaricides and insecticides have high genotoxic potential (18652 and 16398 genes, respectively) when compared to other functional classes (bactericides, fungicides, herbicides, molluscicides, nematocides, and plant growth regulators) (for all comparisons,  $p < 0.05$ ).



**Figure 1:** Pesticides' chemical groups associated to affected genes causing human diseases

**Table 2: Number of human diseases related genes affected by pesticides classified according to functional classes and chemical groups.**

Functional classes	Chemical groups	Cancer	Digestive system disease	Nervous system disease	Respiratory tract disease	Skin disease
Acaricide	Alkyl sulphite	62	33		5	5
	Avermectin		24	19	12	14
	Benzylate		24	19	12	14
	Benzoylurea		8		5	5
	Carbamates		145	121	54	62
	Chlorocyclodiene		1017	805	387	470
	Chlorodiphenylsulfone		1017	805	387	470
	Ketoenol				3	3
	Organochlorine	14476	4007	4934	1329	1267
	Organophosphate	15842	5246	5450	1314	1326
	Oxima methylcarbamate		15	22	11	11
	Phenyl methylcarbamate,		18	19	8	14
	Pyrazole	2812	1098	910	229	217
	Pyrazole analog		24	15		13
	Pyrethroids	8556	2924	3476	923	776
	Pyridazinone	705	259	205	69	74
Urea	7280	2793	2099	660	665	
Bactericide	Dicarboximide		1065	969	431	500
	Strobilurin		324	231	112	158
Fungicide	Acetamide		13	18	11	11
	Anilinopyrimidine		34	26	20	22
	Benzamide		24	19	12	14
	Benzimidazole		81	51	48	48
	Benzothiadiazole		145	121	54	62
	Carbamates		145	121	54	62
	Chloroaromatic		1017	805	387	470
	Dicarboximide		1065	969	431	500
	Hydroxyanilides		31	22	19	20
	Imidazole		79	46	33	44
	Imidazolinone		233	216	99	124
	Imidazolylcarboxamide		233	216	99	124
	Isophthalonitrile		233	216	99	124
	Methyl isothiocyanate			8	5	6
	Morpholine		10		5	6
	Organophosphate	15842	5246	5450	1314	1326
	Oxazolinedione	286	162	167	80	46
	Phenylpyrazoles		147	98	90	99
	Phenylurea		6			
	Pyrimidines	705	259	205	69	74
Strobilurin		324	231	112	158	
Sulfamides	62	33		5	5	
Triazo	9937	3427	2990	777	763	
Herbicide	Chloroacetanilide		79	64	40	46
	Dinitroaniline		21	20	10	18
	Diphenylether		16		7	9
	Methyl isothiocyanate			8	5	6
	Oxima cyclohexanodione	286	162	167	80	46
	Pyridinecarboxylic acid		13	18	11	11
	Tiocarbamate	21	10			
	Triazine	15096	4664	6230	1303	1294
	Triazinone	4	11			9

	Urea	7280	2793	2099	660	665	
Insecticide	Avermectin		24	19	12	14	
	Benzodioxol methylcarbamate			8	5	6	
	Benzofuranyl methylcarbamate		5				
	Benzohidrazila		8		5	5	
	Benzothiadiazole		145	121	54	62	
	Benzoylurea		8		5	5	
	Carbamates		145	121	54	62	
	Chlorocyclodiene		1017	805	387	470	
	Chlorodiphenylsulfone		1017	805	387	470	
	Dimethylcarbamate		21	20	10	18	
	Diphenylether		16		7	9	
	Ketoenol				3	3	
	Methyl isothiocyanate				8	5	6
	Neonicotinoid			92	87	37	
	Organochlorine	14476	4007	4934	1329	1267	
	Organophosphate	15842	5246	5450	1314	1326	
	Oxadiazine	286	162	167	80	46	
	Oxima methylcarbamate		15	22	11	11	
	Phenyl methylcarbamate		18	19	8	14	
	Pyrazole	2812	1098	910	229	217	
Pyrethroids	8556	2924	3476	923	776		
Pyridazinone	705	259	205	69	74		
Pyridyloxypropyl ether		147	98	90	99		
Tetranic acid		13	18	11	11		
Triazinamine	4	11			9		
Molluscicide	Neonicotinoid		92	87	37		
	Organophosphate	15842	5246	5450	1314	1326	
	Oxima methylcarbamate		15	22	11	11	
	Phenyl methylcarbamate		18	19	8	14	
Nematicide	Benzofuranyl methylcarbamate		5				
	Carbamates		145	121	54	62	
	Organophosphate	15842	5246	5450	1314	1326	
	Oxima methylcarbamate		15	22	11	11	
Plant growth regulator	Triazo	9937	3427	2990	777	763	
	Urea	7280	2793	2099	660	665	

Figure 1 also describes genes related to nervous system diseases are affected by acaricides (18899 genes), bactericides (1200 genes), fungicides (11995 genes), herbicides (8606 genes), insecticides (17293 genes), molluscicides (5578 genes), nematocides (5593 genes) and plant growth regulator (5089 genes). In this sense, we observed that the most genotoxic chemical groups regarding nervous system disease-causing genes are triazines (6230 genes), organophosphates (5450 genes), organochlorides (4934 genes), and pyrethroids (3476 genes). In addition, organophosphates, one of the most responsible for gene alterations leading to nervous system diseases, are also found in acaricides, fungicides, insecticides, molluscicides, and nematocides formulations.

Acaricides significantly affect nervous system disease-causing genes ( $p < 0.05$ , compared to other functional classes). Insecticides also have high genotoxic potential affecting more nervous system disease-causing genes than bactericides, molluscicides, nematocides, and plant growth regulators ( $p < 0.05$  for all comparisons). Results showed genes associated with respiratory system diseases are affected by acaricides (5408 genes), bactericides (543 genes), fungicides (3823 genes), herbicides (2116 genes), insecticides (5035 genes), molluscicides (1370 genes), nematocides (1379 genes) and plant growth regulator (1437 genes) (Figure 1). Organophosphates (1314 genes), organochlorides (1329 genes), and triazines (1303 genes) are the major chemical groups affecting

respiratory system disease-causing genes.

It was also found that genes related to skin diseases are affected by acaricides (5046 genes), bactericides (658 genes), fungicides (4108 genes), herbicides (2104 genes), insecticides (4980 genes), molluscicides (1351 genes), nematocides (1399 genes) and plant growth regulator (1428 genes) (Figure 1). Organophosphates (1326 genes), organochlorides (1267 genes), and triazines (1294 genes) are the major chemical groups affecting respiratory system disease-causing genes. Results also showed organophosphates are the primary chemical group in all pesticides' functional classes responsible for genetic effects, mainly leading to cancer and nervous system diseases. Furthermore, organochlorides are the primary chemical group responsible for genetic damage leading to nervous system diseases.

#### 4. DISCUSSION

The World Health Organization (WHO) establish pesticide toxicity is associated with function and other factors. Prolonged exposure and contact with pesticide high concentrations implicate chronic effects, including cancer and adverse effects on reproduction (Han et al., 2018). Pesticides are also capable of accumulation in consumers' bodies in the food chain, causing health hazards (Hansen et al., 2017). Human beings are

more susceptible to exposure because of the wide use of pesticides. This significant susceptibility occurs because some pesticides can produce genomic alterations, leading to the development of cancer and other neurological and reproductive health issues (He et al., 2017). Work exposure and diet are the most significant sources of carcinogenic exposure due to the prolonged exposure at work, and the composition, prepare and contaminants present in food (Huang et al., 2015).

Results showed pesticides could induce genotypic alterations leading to disease development, but the way of each substance act on organisms can lead to different alterations in genes. Organophosphates and organochlorides cause the most significant genotypic damage favoring cancer development, digestive system, nervous system, respiratory system, and skin diseases. Results also showed that triazines could cause genotypic alterations related to digestive, nervous, and respiratory diseases. Regarding triazoles and pyrethroids, we observed they can cause gene damage leading to digestive and nervous system diseases, respectively. Thus, the way through the substance act and its permanence in organisms define its genotoxicity. Besides, we observed that acaricides and insecticides based on organophosphates and organochlorides could cause a more significant number of genetic alterations for all disease categories.

Human beings have a high capacity for pesticide absorption through inhalation, ingestion, and dermal ways (Hansen et al., 2017). Thus, due to this easy pesticide absorption in the human body, people are more susceptible to diseases development since these substances can lead to genetic alterations. Organophosphates can irreversibly inhibit acetylcholinesterase, causing the accumulation of acetylcholine in the synaptic cleft and consequently the neuron's persistent depolarization (Jacobsen-Pereira et al., 2018). In this sense, when organophosphate pesticides inhibit acetylcholinesterase, they bound to serine residues producing reactive oxygen species and causing DNA damage (Kapeleka et al., 2021). An example of organophosphate widely used in agriculture is malathion that is genotoxic, mutagenic, and carcinogenic. Malathion causes oxidative stress, and it has been associated with the development of blood cancer since, after malathion exposure, lymphocytes presented DNA damage as a consequence of oxidative stress by free radicals (Lekei et al., 2017). Permethrin and malathion have genotoxic potential once they induce DNA breaks, chromosome aberrations, and micronuclei. Because of that, permethrin and malathion can also be related to blood cancer and lymphoma (Nandipati and Litvan, 2016).

Therefore, organophosphate intoxication affects different body systems. From chemical reactions with cells, enzymes, and amino acids, pesticides can generate mutagenic substances, inducing apoptosis. Besides, we noticed that organochlorides are also related to many different genetic alterations. This association is caused by the fact that organochlorides can persist through the food chains and be related to prolonged human exposure, most affecting genes related to cancer and nervous system diseases. Dieldrin and hexachlorocyclohexane, lipophilic organochlorides, showed quick and easy absorption and accumulation in adipose tissue. It was also noted that these organochlorides penetrate the blood-brain barrier, and because of that and other epidemiological studies have been related to Parkinson's disease (Nascimento and Melnyk, 2016).

It has been reported that organochloride metabolites and interference with cytochrome P450 enzymes lead to genotoxic effects. They have been pointed out as a risk factor for breast cancer due to their effects on the estrogen receptor (Navarrete-Meneses et al., 2017). Thus, organochlorides can act on essential enzymes and hormones as described, and the prolonged exposure and bioaccumulation on organisms can deregulate chemical processes and trigger genotypic alterations (Olakkaran et al., 2020). Acaricides and insecticides based on organophosphates and organochloride formulations, for example, are the most associated with genetic alterations correlated to cancer. As acaricides and insecticides are widely used in agriculture, there is a linear relationship between this wide use and high exposure causing health hazards (Hansen et al., 2017). In this sense, we observed that the organochloride acaricide Dicofof could cause nocive effects to humans, being highly cytotoxic and genotoxic to the RBCs (red blood cells) and lymphocytes when inhaled (Othmene et al., 2021).

Organophosphates and organochlorides act in a specific way against certain biologic targets in the human body, which can trigger reactions that lead to molecule breaks, enzyme inhibition, oxidative stress, and apoptosis. When organophosphates and organochlorides are combined or used in high concentrations, it can lead to DNA damage, creating free radicals that react with cell membranes (Santos and Leite, 2016). Although organophosphates and organochlorides cause genotypic alterations leading to digestive system diseases, triazines induce the most damage on genes related to these diseases, which occurs due to the formation of

reactive metabolites that affects DNA (Silva et al., 2021). Tebucophenol, an example of triazole, can also cause oxidative damage and apoptosis in intestinal cells (Singh et al., 2016).

Atrazine, an example of triazine, is also related to nervous system diseases besides being considered an endocrine disruptor (Skinner et al., 2016). Pyrethroids can also inhibit nervous impulses by interfering with the function of voltage-gated sodium channels and adversely affecting the nervous system in the long term (Taghavi et al., 2020). Regarding respiratory system and skin diseases, results showed organophosphates, organochlorides, and triazines acting on genes related to these diseases, which may be due to the high exposure through the respiratory and dermic ways. When these compounds have the potential for skin irritation, this can increase dermal permeation and increase exposure risk (WHO, 2020). A study showed that organophosphates in lower concentrations reduced cell viability and induced cell death in higher concentrations (Zeljezic et al., 2018).

On the other hand, neonicotinoids are molluscicides considered low toxicity to humans. Nevertheless, neonicotinoids can penetrate vegetable tissues and remain long, causing bioaccumulation through the food chain. Thus, food intake of neonicotinoids is responsible for neurotoxicity, genotoxicity, hepatotoxicity, endocrine system deregulation, and immunosuppressive potential (Zimmet et al., 2007). Carbofuran, a carbamate nematocide applied to different crops, is highly toxic and is embryotoxic, mutagenic, and teratogenic. Pesticides use and management bad practices, the management of pesticides packaging, and the absence of individual protection devices can contribute to greater exposure to these compounds. Thus, farmworkers are more vulnerable to contamination by dermic and oral exposure. Finally, in general, the population is also exposed to these substances by pesticides residues present in food (Santos and Leite, 2016). Pesticides are related to public health matters since prolonged exposure to these substances can trigger off genetic problems. Thus, this issue has to be discussed based on reliable scientific information.

## 5. CONCLUSION

From the above, we conclude that all chemical groups of pesticides cause genotypic alterations and contribute to diseases. We also conclude that acaricides and insecticides are responsible for causing the most significant number of genetic alterations related to the appearance of cancers. As widely used in agriculture, acaricides and insecticides are related to bioaccumulation and prolonged exposure. It was also noted that organophosphates and organochlorides are highly genotoxic and capable of promoting enzymatic, metabolic, and hormonal disturbances, facilitating genetic alterations. Thus, these substances are directly related to all disease categories studied in this work. Because of the high genotoxic potential attributed to pesticides, their uncontrol use can be considered a public health problem. Thus, wide use and prolonged exposure through diet or work exposure have to be investigated, clearing the relation with growing cancer cases and other diseases in different areas. Furthermore, more studies elucidating pesticides' effects on the human body are necessary because these results about health damage caused by pesticides can be helpful to the health authorities to the regulation and control use measures.

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