

Article

Pesticides, Drinking Water and Cancer Risk: A Portrait of Paraná Southwest, Brazil

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Abstract: A 2018 report from the Water Quality for Human Consumption Vigilance Information System (SIS  GUA, Brazil) showed the presence of 27 pesticides in Brazilian drinking water, of which 11 have carcinogenic potential. We assessed the data for 27 municipalities in Paran   state southwest, a rural landscape with high cancer rates. We selected data from the carcinogenic potential of 11 pesticides provided by international agencies (alachlor, aldrin-diheldrin, atrazine, chlordane, DDT, diuron, glyphosate, lindane, mancozeb, molinate, and trifluralin) and estimated the number of cancer cases attributable to drinking water contamination by pesticides. Also, we correlated such findings with incidence and mortality cancer rates for ten topographies obtained from the Brazilian National Cancer Institute (INCA) database. A total of 9 cities were selected, corresponding to about 81,000 people. All towns had all pesticides quantified in the drinking water. About ten cancer cases were attributed to drinking water contamination by pesticides in 2014–2017, mainly linked to diuron and mancozeb. Concerning the consolidated incidence of cancer cases reported by the INCA, significant correlations were found regarding aldrin-diheldrin, alachlor, and atrazine for breast cancer, atrazine for prostate cancer, and mancozeb and diuron for colon cancer, among others. Regarding the consolidated mortality rates, some correlations were found between DDT and trifluralin for the breast, DDT and lindane for the prostate, and glyphosate for lung cancer. Moderate correlations were found between the estimated and consolidated cancer cases for several topographies. Our findings highlight the correlation between drinking water contamination in Paran   state southwest and its increased incidence of cancers with poor prognosis.



Citation: Machado, M.G.; Orrut  a, J.F.G.; Panis, C. Pesticides, Drinking Water and Cancer Risk: A Portrait of Paran   Southwest, Brazil. *Pollutants* **2024**, *4*, 302–315. <https://doi.org/10.3390/pollutants4030020>

Academic Editor: Saddam Hussain

Received: 15 April 2024

Revised: 4 June 2024

Accepted: 11 June 2024

Published: 26 June 2024



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Keywords: pesticides; drinking water; cancer; cancer risk; Brazil; water contamination

1. Introduction

Pesticides are chemical products used to control pests that can cause diseases in plants and compromise their cultivation. They can be used not only in large-scale agriculture but also in domestic gardens and household infestation control. Most pesticides are considered harmful to human health and the environment, particularly when used in large quantities and without proper protective measures [1].

Pesticides can reach aquatic systems, contaminating them and reducing water potability, further spreading contamination [2] and, as a result, are frequently detected as contaminants in human drinking water. Additionally, pollution from these substances is prolonged due to their persistence in the environment [3,4]. For example, pesticides banned in Brazil for over twenty years are still found in water, such as aldrin-diheldrin, dichlorodiphenyltrichloroethane-dichlorodiphenyldichloroethylene-dichlorodiphenyldichloroethane (DDT-DDD-DDE), and lindane. This confirms their long-lasting presence as environmental contaminants [5].

The health damage resulting from constant and intense exposure to pesticides includes an increased risk of various neoplasms, such as thyroid, hematological, renal, Hodgkin and non-Hodgkin lymphomas, breast, prostate, lung, and liver tumors, among others [6–12] as

well as other systemic diseases [13–15]. Additionally, other systemic diseases are linked to pesticide exposure [13–15]. There is also evidence connecting specific pesticides to various cancers: glyphosate is linked to breast cancer [16]; dieldrin to lung, liver, uterine, thyroid, breast, and lymphoid tissue tumors [17]; and alkyl urea and amine compounds to brain tumors [18].

Brazil is one of the world's largest consumers of pesticides [3], with the state of Paraná among the leading regions for pesticide trade [19,20]. On average, each Brazilian consumes seven liters of pesticides annually, and approximately 70,000 cases of poisoning are reported each year, a rate thirteen times higher than that in the United States [12,21,22]. This is particularly alarming given that around 80% of the pesticides permitted in Brazil are banned in at least three Organization for Economic Cooperation and Development (OECD) countries in Europe [1].

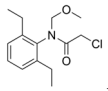
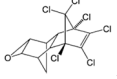
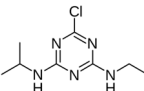
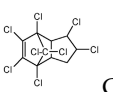
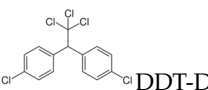
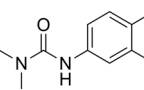
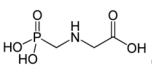
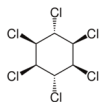
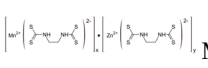
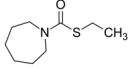
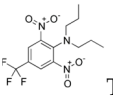
In a report published in 2018 by the Water Quality Surveillance Information System (SISÁGUA) [23], at least 1 of 27 pesticides was identified in the drinking water of 1 in every 4 Brazilian cities, and several of these have a significant carcinogenic potential [24,25]. The tracked pesticides were 2,4-dichlorophenoxyacetic acid-2,4,5-Trichlorophenoxyacetic acid (2,4D-2,4,5T), alachlor, aldicarb, aldrin, atrazine, carbendazim, carbofuran, chlordane, chlorpyrifos dichlorodiphenyltrichloroethane-dichlorodiphenyldichloroethylene-dichlorodiphenyldichloroethylene (DDT-DDD-DDE), diuron, endosulfan, endrin, glyphosate-aminomethylphosphonic acid (AMPA), lindane- γ -hexachlorocyclohexane (γ -HCH), mancozeb-ethylenethiourea (ETU), methamidophos, metolachlor, molinate, parathion, pendimethalin, permethrin, prophenofos, simazine, tebuconazole, terbufos, and trifluralin. For DDT, glyphosate, lindane, and mancozeb, by-product levels were also reported (DDD-DDE, AMPA, γ -HCH, and ETU, respectively). This is a matter of urgent concern, particularly when we consider that in Brazil, the acceptable concentration levels of permitted products, such as glyphosate-aminomethylphosphonic acid (AMPA), are 5000 times higher than in the European Union [26]. This underscores the country's failure in water monitoring and treatment, which could lead to severe health consequences for its inhabitants.

Pesticide contamination is a global issue, posing significant risks to human and environmental health, as reported in Thailand, Ethiopia, Malaysia, Japan, China, India, the Netherlands, and the United States, mostly by atrazine, glyphosate, diuron and 2,4-dichlorophenoxyacetic acid (2,4-D) [27–32]. Lifelong consumption of pesticide-contaminated drinking water has been linked to an increased cancer risk. Additionally, there are suggested correlations between pesticide exposure and various types of cancer, including breast, lung, thyroid, and bladder tumors [4].

According to the National Cancer Institute (INCA) (2020) [33], Paraná is among the five Brazilian states with the highest incidence of cancer, primarily of the colon, lung, breast, and oral cavity. A previous study from our group highlighted the high contamination rates of drinking water in this area, involving both currently permitted pesticides and those banned over two decades ago [4]. However, the link between this contamination and increased cancer risk remains under-documented in the country, particularly for individuals living in rural regions with significant pesticide use, such as the mesoregions of Paraná state, which are marked by elevated cancer rates [34,35]. This underscores the urgent need for further research and intervention in areas like Paraná state southwest.

In this context, the study delved into the profile of pesticide contamination reported by SISAGUA from 2014 to 2017 in the water consumed by the population residing in nine municipalities within the 8th Health Region of Paraná state. The number of cancer cases attributable to this contamination and its correlation to the consolidated incidence and mortality rates of ten cancer types were estimated. This analysis considered 11 pesticides with a defined benchmark cancer risk: alachlor, aldrin-dieldrin, atrazine, chlordane, DDT-DDD-DDE, diuron, glyphosate, lindane, mancozeb, molinate, and trifluralin.

Table 1. 11 pesticides identified as having a benchmark cancer risk index.

Pesticide	Benchmark Cancer Risk of 1 Case/10 ⁶ People (EPA/OEHAA)	Classification	Cancer Evidence
 Alachlor	0.4	Probably carcinogenic to humans (IARC. EPA)	Laryngeal cancer. lymphohematopoietic (IARC) Urinary tract (EPA)
 Aldrin-dieldrin	0.002	Probably carcinogenic to humans (IARC. EPA)	Breast (IARC) Liver (EPA)
 Atrazine	0.15	Not classifiable as to human carcinogenicity (IARC)	Thyroid (OEHAA)
 Chlordane	0.1	Possibly carcinogenic (IARC. EPA)	Liver (IARC and EPA) Thyroid (OEHAA)
 DDT-DDD-DDE	0.1	Possibly carcinogenic (IARC. EPA)	Testis. liver and lymphoma (IARC) Liver (EPA)
 Diuron	2	Probably carcinogenic to humans (IARC. EPA)	Kidney. lung (IARC) Urinary tract (EPA)
 Glyphosate-AMPA	56.45	Probably carcinogenic to humans (IARC) Not Classifiable as to Human Carcinogenicity (EPA)	Lymphoma (IARC. OEHAA)
 Lindane	0.032	Carcinogenic to humans (IARC. EPA)	Lymphoma (IARC) Liver (EPA and OEHAA)
 Mancozeb-ETU	0.06 (ETU)	No data (IARC) Probably carcinogenic (EPA for ETU)	Thyroid (IARC)
 Molinate	1	Not classifiable as to human carcinogenicity (IARC)	Urinary tract (OEHAA)
 Trifluralin	4	Not classifiable as to human carcinogenicity (IARC) Possibly carcinogenic (EPA)	Lymphoma. thyroid. stomach. liver (IARC) Urinary tract (EPA)

Note 1: Benchmark cancer risk values of the pesticides selected for investigation based on the United States Environmental Protection Agency (U.S. EPA) or the California Office of Environmental Health Hazard Assessment (OEHHA) categorization. cancer classification group for each one based on data from the International Agency for Research on Cancer (IARC) or EPA and cancer evidence based on IARC. EPA. and OEHAA data. Note 2: Classification. Sources: 1. EPA: <https://www.epa.gov/sdwa/human-health-benchmarks>, accessed on 18 March 2024; and <https://www.epa.gov/sites/production/files/2015-10/documents/hh-benchmarks-techdoc.pdf>, accessed on 18 March 2024. 2. EPA (DDT): https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=147, accessed on 18 March 2024; 3. IARC: <https://monographs.iarc.fr/agents-classified-by-the-iarc/>, accessed on 18 March 2024; 4. OEHHA: <https://oehha.ca.gov/>, accessed on 18 March 2024. EU Drinking Water Directive 98/83/EC: Drinking water legislation in Europe is derived from the EU Drinking Water Directive which sets minimum standards for various substances in water. For any individual pesticide the maximum allowed at any time is 0.1 ppb (parts per billion) and the total for all pesticides must not exceed 0.5 ppb.

This research's focus was on nine municipalities within the 8th Health Regional of Paraná (Figure 1). These locations were chosen because they showed contamination by at least one quantified pesticide, which were: Capanema (#1), Cruzeiro do Iguaçu (#2), Pérola d'Oeste (#3), Pinhal de São Bento (#4), Planalto (#5), Pranchita (#6), Salgado Filho

(#7), Salto do Lontra (#8), and Verê (#9). The inhabitant number for each locality was extracted from the 2022 Demographic Census of the Brazilian Institute of Geography and Statistics (IBGE) [36]. Thus, the population coverage of this study was about 81,000 people. Consumption data for each pesticide by the analyzed municipalities were extracted from the Pesticide Commercialization Report of the Brazilian Institute of Environment and Renewable Natural Resources (IBAMA) (2019) [19].

Based on this, the number of cancer cases attributable to the contamination of drinking water for each pesticide was calculated using the following formula [4]:

$$\frac{\text{Average pesticide (ppb)} \times \text{number of individuals at risk}}{10^6 \text{ Benchmark cancer risk}}$$

where ‘average pesticide (ppb)’ refers to the average contamination value of the drinking water in each of the analyzed municipalities by the respective substance; ‘number of individuals at risk’ refers to the population of each locality; and ‘ 10^6 Benchmark cancer risk’ is the value defined by the Office of Environmental Health Hazard Assessment (OEHHA) (2009) [37]. Thus, it represents the probability of a resident developing cancer during their lifetime due to pesticide exposure through ingesting contaminated water.

To assess the correlation between water contamination by the eleven pesticides and the consolidated number of documented cancer cases in the municipalities included, data related to the ten most incident neoplasms in this population were collected (breast, prostate, colon, and rectum; lung, trachea, and bronchi; uterine cervix; stomach; thyroid; oral cavity—lip, tongue, gum, and floor of mouth; esophagus; and bladder) and were available in the database Information from the Hospital Cancer Registry (IRHC)—Hospital Tabulator, State Database of Paraná, from the National Cancer Institute (INCA) [38], corresponding to the same period as the SISÁGUA report [23]. The mentioned primary locations were chosen for having the highest prevalence nationwide. The mortality values for the selected neoplasms were taken from the Cancer Mortality Atlas, from INCA [39], for each primary location and mentioned city in the same period.

Finally, using GraphPad Prism software 9.0, the Spearman correlations between drinking water contamination and the incidence of neoplasms and mortality were analyzed. Also, the estimated cancer cases attributable to drinking water contamination and the consolidated cancer incidence provided by the INCA for the same period were correlated considering a $p < 0.05$ as significant.

3. Results

Table 2 shows the mean pesticide contamination levels in the water for each of the nine municipalities included in Paraná state southwest. Residues of the persistent organic pollutants (POPs) aldrin-dieldrin (average 0.006 parts per billion—ppb), chlordane (average 1.67 ppb), dichlorodiphenyltrichloroethane-dichlorodiphenyldichloroethylene-dichlorodi-phenyldichloroethane (DDT-DDD-DDE) (average 0.035 ppb), and lindane (average 20.03 ppb) were found in all the mentioned localities. Aldrin-dieldrin in municipality 6 (0.03 ppb) is on the Brazilian maximum allowed limit (0.03 ppb) and it should not be found in the European Union’s (EU) drinking water. Chlordane has a maximum allowed limit of 0.2 ppb in Brazil and 0.01 ppb in the EU, above both in municipalities 6 (0.05) and 7 (15 ppb). DDT-DDD-DDE was not over the Brazilian limit (1 ppb) in any locality but was above the EU limit (0.01 ppb) in municipality 6 (0.05 ppb). Lindane, a proven carcinogen, presented significantly over the EU limit (0.1 ppb) in municipality 6 (0.3 ppb). The other municipalities showed values below both the Brazilian and EU limits, demonstrating the persistence of these substances in the environment for a long time and their possible extensive use in the past.

Regarding the pesticides currently permitted in the country, alachlor (20 ppb), atrazine (2 ppb), glyphosate-aminomethylphosphonic acid (AMPA) (500 ppb), molinate (6 ppb), and trifluralin (20 ppb) were below the Brazilian limit in the analyzed municipalities. Above the European limit, alachlor (0.1 ppb) was present in municipalities 1, 2, 3, 5, 7, and

9 (0.2 ppb each) as well as in municipality 6 (0.3 ppb). Atrazine (0.1 ppb) was above the EU limit in municipalities 2 (0.198 ppb) and 6 (1 ppb). Glyphosate-AMPA (0.1 ppb) showed a value above in all the municipalities with a minimum of 45 ppb and a maximum of 200 ppb. Molinate and trifluralin are prohibited in European drinking water, so they were above the limit in all the municipalities. Borderline concentrations to the Brazilian allowed limits were evidenced for diuron (90 ppb) and mancozeb-ethylene thiourea (ETU) (180 ppb) in municipalities 1, 2, 3, 5, 7, and 9. Municipality 6 showed an elevation only concerning the EU limit (0.1 ppb for both), with values of 10 and 100 ppb, respectively.

Table 2. Pesticide levels in ppb for all studied municipalities based on SISAGUA 2014–2017 report.

	Alachlor	Aldrin-diheldrin	Atrazine	Chlordane	DDT- DDD- DDE	Diuron	Glyphosate- AMPA	Lindane	Mancozeb- ETU	Molinate	Trifluraline
Capanema (#1)	0.2	0.004	0.01	0.002	0.002	90	65	0.002	180	0.5	0.02
Cruzeiro do Iguaçu (#2)	0.2	0.004	0.198	0.002	0.002	90	65	0.002	180	0.5	0.02
Pérola D'Oeste (#3)	0.2	0.004	0.01	0.002	0.002	90	65	0.002	180	0.3	0.02
Pinhal de São Bento (#4)	0.01	0.001	0.01	0.001	0.002	0.0007	65	0.002	0.027	0.1	0.02
Planalto (#5)	0.2	0.004	0.01	0.002	0.002	90	65	180	180	0.5	0.02
Pranchita (#6)	0.3	0.03	1	0.05	0.3	10	200	0.3	100	3	0.3
Salgado Filho (#7)	0.2	0.008	0.01	15	0.002	90	65	0.002	180	0.5	0.02
Salto do Lontra (#8)	0.01	0.001	0.01	0.001	0.002	0.0007	65	0.002	0.027	0.1	0.02
Verê (#9)	0.2	0.004	0.01	0.002	0.002	90	45	0.002	180	0.5	0.02
Maximum allowed in Brazil	20	0.03	2	0.2	1	90	500	2	180	6	20
Maximum allowed in the European Union	0.1	0	0.1	0.01	0.01	0.1	0.1	0.1	0.1	0	0

Regarding the benchmark cancer risk assigned to each substance, for example, glyphosate-AMPA had the lowest estimated risk by the previously mentioned equation, at a value of 56.45. It has a probable carcinogenic potential, mainly related to the occurrence of lymphomas, while aldrin-diheldrin had the highest index and is linked to breast and liver cancer (Table 2).

The number of cancer cases attributable to drinking water contamination for each municipality is shown in Table 3, with a total of ten cases. Mancozeb-ETU was responsible for six cases, mainly in municipality 1. Two cases were calculated for diuron contamination. The other cases represent the sum of all the pesticide residues in all the cities.

Table 4 shows the results of Spearman correlations regarding drinking water contamination by pesticides and the consolidated incidences for the ten most incident cancer topographies in the Brazilian population. The incidence of breast cancer showed a positive correlation with contamination by aldrin-diheldrin, atrazine, chlordane, and molinate as well as prostate cancer and atrazine. Colon neoplasia presented a significant positive correlation with diuron and mancozeb-ETU. For lung cancer, there was a positive correlation with atrazine. Diuron and mancozeb-ETU correlated to gastric neoplasm and alachlor, aldrin-diheldrin, and chlordane contamination. Ultimately a positive correlation was observed between esophageal cancer and glyphosate-AMPA contamination.

Concerning the mortality rates (Table 5), significant correlations were observed between breast cancer and DDT-DDD-DDE and trifluralin; prostate cancer and lindane, DDT-DDD-DDE, and trifluralin; lung cancer and glyphosate-AMPA; and, finally, esophageal cancer and glyphosate-AMPA and lindane.

Table 3. Estimated cancer cases for each pesticide based on its levels in ppb and benchmark cancer risk index according to IARC/EPA.

	Alachlor	Aldrin-diheldrin	Atrazine	Chlordane	DDT- DDD- DDE	Diuron	Glyphosate- AMPA	Lindane	Mancozebe- ETU	Molinate	Trifluraline
Capanema (#1)	0.009562	0.038248	0.001275	0.000382	0.000382	0.86058	0.001381	0.001195	5.7372	0.009562	0.0000956
Cruzeiro do Iguaçu (#2)	0.002126	0.0000068	0.005613	0.000000068	0.00008504	0.19134	0.000307	0.000266	0.09567	0.002126	0.00002126
Pérola D'Oeste (#3)	0.003174	0.012694	0.000423	0.000127	0.000127	0.285615	0.000458	0.000397	0.142808	0.001904	0.0000317
Pinhal de São Bento (#4)	0.0000683	0.001366	0.000182	0.0000273	0.0000546	0.000000956	0.000197	0.000171	0.00000922	0.000273	0.0000137
Planalto (#5)	0.00674	0.026958	0.000899	0.00027	0.00027	0.606555	0.000973	0.000842	0.303278	0.00674	0.0000674
Pranchita (#6)	0.002579	0.010314	0.000344	0.000103	0.000103	0.232065	0.000372	29.00813	0.116033	0.002579	0.0000258
Salgado Filho (#7)	0.00179	0.01432	0.000239	0.537	0.0000716	0.1611	0.000259	0.000224	0.08055	0.00179	0.0000179
Salto do Lontra (#8)	0.00037	0.007393	0.000986	0.000148	0.000296	0.00000517	0.001068	0.000924	0.0000499	0.001479	0.0000739
Verê (#9)	0.003939	0.015756	0.000525	0.000158	0.000158	0.35451	0.000394	0.000492	0.177255	0.003939	0.0000394
SUM	0.030348	0.1270558	0.010486	0.538215	0.00154724	2.691771	0.005409	29.01264	6.65285312	0.030392	0.0003867
Total estimated cancer cases: 39											

Table 4. Spearman's correlation between cancer incidence and drinking water contamination in ppb for 2014–2017.

	Alachlor	Aldrin-diheldrin	Atrazine	Chlordane	DDT- DDD- DDE	Diuron	Glyphosate- AMPA	Lindane	Mancozeb- ETU	Molinate	Trifluraline
Spearman R (BREAST CANCER)	0.6169	0.7396 *	0.6786 *	0.7525 *	0.6228	0.3701	0.4549	0.5145	0.3701	0.7006*	0.6228
Spearman R (PROSTATE CANCER)	0.5209	0.5968	0.6487 *	0.6228	0.4671	0.4661	0.2759	0.1715	0.4661	0.5060	0.4671
Spearman R (COLON CANCER)	0.3907	0.4671	0.2162	0.5709	0.07785	0.8431 **	−0.02237	0.1715	0.8431 **	0.4671	0.07785
Spearman R (LUNG CANCER)	0.6037	0.4138	0.7473 *	0.3218	0.5517	0.3539	0.5058	0.6114	0.3539	0.5320	0.5517
Spearman R (UTERINE CANCER)	−0.01388	−0.1839	−0.02265	−0.1839	0.000	0.3469	−0.09813	−0.03774	0.3469	−0.1576	0.000
Spearman R (STOMACH CANCER)	0.6360*	0.6670*	0.2319	0.7191 *	0.2733	0.8285 **	0.000	0.09723	0.8285 **	0.5759	0.2733
Spearman R (THYROID CANCER)	0.1316	0.2699	−0.1989	0.3668	0.000	0.4387	−0.1193	0.2784	0.4387	0.2699	0.000
Spearman R (ORAL CANCER)	0.4899	0.3668	0.3579	0.2699	0.5813	0.08043	0.6443	0.6443	0.08043	0.3114	0.5813
Spearman R (ESOPHAGUS CANCER)	0.2706	0.1379	0.5058	0.04597	0.5517	−0.06245	0.6869*	0.5360	−0.06245	0.2561	0.5517
Spearman R (BLADDER CANCER)	−0.3677	−0.4552	−0.2308	−0.4552	0.000	−0.1414	−0.1077	−0.03847	−0.1414	−0.3815	0.000

* $p < 0.05$. ** $p < 0.01$.

Table 5. Spearman’s correlation between cancer-related deaths and drinking water contamination in ppb for 2014–2017.

	Alachlor	Aldrin-diheldrin	Atrazine	Chlordane	DDT- DDD- DDE	Diuron	Glyphosate- AMPA	Lindane	Mancozeb- ETU	Molinate	Trifluraline
Spearman R (BREAST CANCER)	0.1891	0.06507	0.4862	−0.04555	0.6637 *	−0.2716	0.5385	0.6208	−0.2716	0.2343	0.6637 *
Spearman R (PROSTATE CANCER)	0.2810	0.2790	0.4549	0.2141	0.7006 *	−0.1576	0.5742	0.7233 *	−0.1576	0.2919	0.7006 *
Spearman R (COLON CANCER)	0.2193	0.2206	−0.007457	0.2725	0.1557	0.5209	0.03728	0.4549	0.5209	0.1168	0.1557
Spearman R (LUNG CANCER)	0.4524	0.4476	0.3206	0.4087	0.6228	0.1645	0.6935 *	0.5891	0.1645	0.2530	0.6228
Spearman R (UTERINE CANCER)	0.1901	0.02768	0.1829	0.02768	0.000	0.5118	−0.05568	0.1989	0.5118	0.04152	0.000
Spearman R (STOM- ACH CANCER)	0.3261	0.2627	0.2642	0.1970	0.5517	0.006939	0.2038	0.4605	0.006939	0.4335	0.5517
Spearman R (THYROID CANCER)	Not cal- culated	Not cal- culated	Not cal- culated	Not calculated	Not calculated	Not cal- culated	Not calculated	Not cal- culated	Not calculated	Not cal- culated	Not calculated
Spearman R (ORAL CANCER)	−0.2348	−0.2639	−0.1064	−0.2639	0.000	−0.1467	−0.2767	−0.1064	−0.1467	−0.1806	0.000
Spearman R (ESOPHA- GUS CANCER)	0.3128	0.2408	0.5161	0.1887	0.5076	0.09969	0.6881*	0.6507*	0.09969	0.2733	0.5076
Spearman R (BLADDER CANCER)	−0.1414	−0.08702	−0.2308	−0.02677	0.000	0.1414	−0.1077	0.2693	0.1414	0.000	0.000

* $p < 0.05$. ** $p < 0.01$.

The correlation between the estimated number of cases resulting from each pesticide detected in the drinking water for each municipality and the consolidated number of cases registered by the National Cancer Institute (INCA) [38,39] for each topography in the study period (2014–2017) is shown in Figure 2. For breast cancer, a moderate positive correlation was noted. Atrazine presented a weak correlation with prostate cancer, and colon cancer showed a moderate correlation with most pesticides. A similar pattern was observed for lung cancer, which had positive correlations with nine of the eleven pesticides (($R > 0.30$)—alachlor, diuron, and mancozeb-ETU ($R = 0.4233$ each), atrazine ($R = 0.6197$, the highest), DDT-DDD-DDE and trifluralin (both $R = 0.3620$), glyphosate-AMPA ($R = 0.3865$), lindane ($R = 0.5461$), molinate ($R = 0.4847$)), and the sum of the cases ($R = 0.3754$). A uterine neoplasm correlation was observed with alachlor, diuron, and mancozeb-ETU ($R = 0.3497$ each, being the highest value). For stomach cancer, positive correlations were also evidenced with most substances (($R > 0.30$)—alachlor, diuron, and mancozeb-ETU ($R = 0.5957$ each), aldrin-diheldrin ($R = 0.6018$, the maximum value), chlordane ($R = 0.5897$), DDT-DDD-DDE and trifluralin (both $R = 0.3040$), mancozeb-ETU ($R = 0.5957$), molinate ($R = 0.5350$)) and the sum of the cases ($R = 0.5244$). Thyroid neoplasia had the highest correlation in the study with chlordane ($R = 0.8599$) in addition to alachlor, diuron, mancozeb-ETU, and molinate ($R = 0.3426$ each), DDT-DDD-DDE and trifluralin ($R = 0.4202$ for both), aldrin-diheldrin ($R = 0.6659$), glyphosate-AMPA ($R = 0.3556$), and the sum of the cases ($R = 0.3696$). Oral cavity cancer also presented several significant correlations with alachlor, diuron, and mancozeb-ETU ($R = 0.4332$), aldrin-diheldrin ($R = 0.3168$), DDT-DDD-DDE and trifluralin ($R = 0.5107$ for both), glyphosate-AMPA ($R = 0.5883$), lindane ($R = 0.7306$, being the highest value), molinate ($R = 0.3685$), and the sum of the cases

($R = 0.5382$). Positive correlations were noted for esophageal cancer, with the highest being with lindane ($R = 0.3620$), in addition to alachlor, diuron, and mancozeb-ETU ($R = 0.2147$ each), molinate ($R = 0.2761$), and the sum of the estimates ($R = 0.2523$). Finally, bladder neoplasm correlated significantly with DDT-DDD-DDE, trifluralin (with $R = 0.4127$), and glyphosate-AMPA ($R = 0.3877$).

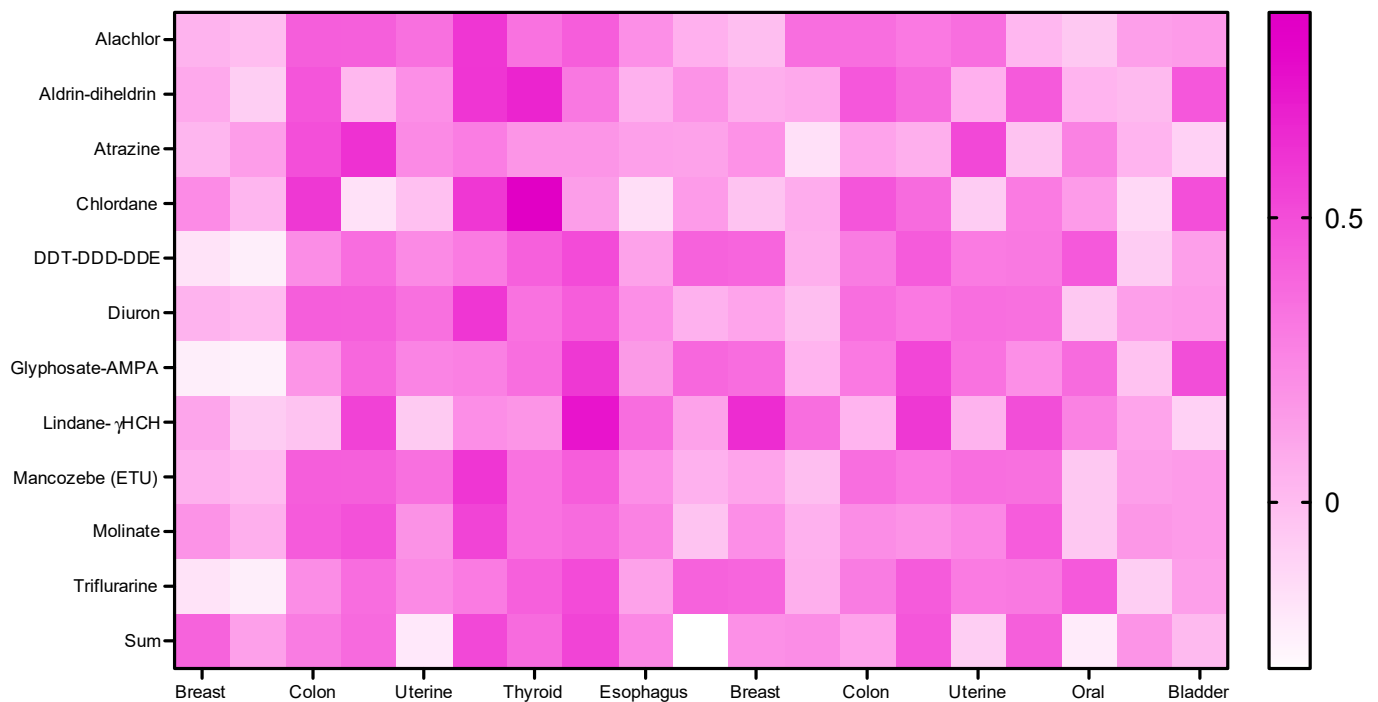


Figure 2. Spearman correlation matrix between the estimated cancer cases versus the number of cancer cases reported by INCA for the municipalities included in the study (2014–2017).

4. Discussion

Paraná state, known as one of the largest food producers in the world, is characterized by the extensive use of pesticides. Consequently, environmental pollution has been reported, including in drinking water [4]. In the present study, the focus was on the contamination of Paraná state southwest, a mesoregion composed of 27 municipalities responsible for most of its pesticide trade. Extensive defilement of drinking water by current and legacy pesticides in this territory was discovered. Furthermore, the number of cancer cases attributable to this contamination was calculated, which was correlated with consolidated rates for incidence and mortality concerning the ten main topographies reported in the country. Only towns with at least one quantified pesticide were included, covering 81,000 people living in 9 cities. Therefore, these findings cover a relevant public health issue in a significant pesticide trade area.

Water treatment in Paraná state is entirely automated and runs continuously, 24 h a day, 7 days a week. The water is extracted directly from the rivers and undergoes a series of processes at the treatment facility, including coagulation, flocculation, sedimentation, and filtration along with the introduction of fluoride and chlorine. Following these procedures, the water is transferred to reservoirs before being distributed to homes. However, to our knowledge, none of these processes have the capability to eliminate pesticides from drinking water anywhere in the world. This situation makes contamination by these substances a global public health concern.

In breaking down the complacent Brazilian legislation about pesticide contamination in drinking water, significant discrepancies between the maximum allowed limits in the European Union (EU) and Brazil became apparent. The EU allows a maximum of 0.1 parts per billion (ppb) for specific pesticides in drinking water and a total of 0.5 ppb for all

detected pesticides. In contrast, Brazilian legislation authorized outstanding amounts of pesticides in drinking water, which are increased compared to the EU limits. The range varies from 10 to 5000 times more pesticides permitted in Brazilian drinking water than in the EU.

Both current and legacy pesticides as contaminants of drinking water were detected. For example, remaining pollutants banned for decades from Brazil, such as aldrin-dieldrin, exhibited concentrations above the Brazilian maximum limit of 0.03 ppb. Considering its benchmark cancer risk value of 0.002 [24,37], even minimal concentrations of this substance are enough to contribute to a higher cancer risk in exposed populations. This pesticide is an organochlorine, and it should not be observed in European drinking water.

The detection of such persistent organic pollutants (POPs) in the analyzed municipalities draws attention because it indicates that pesticides banned in the past are persisting in the environment. Dichlorodiphenyltrichloroethane (DDT), a component of the pesticide dichlorodiphenyltrichloroethane-dichlorodiphenyldichloroethane-dichlorodiphenyldichloroethylene (DDT-DDD-DDE), has poor water solubility and a half-life estimated in 150 years, which leads to its accumulation in both aquatic environments and the human body, progressively increasing the concentration in tissues and consequently the risk of cancer [40,41]. Therefore, its cumulative effects through time and the risk that it poses to chronic onset pathologies such as cancer and neurodegenerative diseases must be considered. Furthermore, according to the EU, the sum of pesticide concentrations should not exceed 0.5 ppb. Still, in Brazil, this parameter has no defined maximum value, which considerably maximizes the population risk.

The Water Quality Surveillance Information System (SISAGUA) document reported 27 pesticides detected in Brazilian drinking water, and 11 have some carcinogenic classification according to the International Agency for Research on Cancer (IARC) (2021) [25] and/or the United States Environmental Protection Agency (U.S. EPA) (2005) [24], which were this study's aim. The pesticides analyzed included proven carcinogens, such as lindane; probable carcinogenic substances, such as alachlor, aldrin-dieldrin, diuron, glyphosate-aminomethylphosphonic acid (AMPA), and mancozeb-ethylene thiourea (ETU); possible carcinogenic substances, such as chlordane and DDT-DDD-DDE; or even endocrine disruptors, such as atrazine, mancozeb, and glyphosate-AMPA [24,25,42–47]. This categorization is assessed in conjunction with the benchmark cancer risk [24,37], which is the concentration required to generate one case of cancer for every 10^4 or 10^6 individuals over a 70-year exposure period [4]. Among the pesticides evaluated, aldrin-dieldrin had the lowest value (0.002), while glyphosate-AMPA had the highest (56.45). Therefore, a concentration of 0.002 ppb of aldrin-dieldrin over 70 years is needed to cause one case of cancer. Only two of the eleven analyzed municipalities had lower concentrations than this.

We found significant correlations between the consolidated incidence and cancer deaths documented by the INCA for the study period (2014–2027) and drinking water contamination by the SISAGUA reported for the studied municipalities. Stomach and breast cancer were those that exhibited more significant correlations for incidence (five and four, respectively) and breast, prostate, and esophagus exhibited more significant correlations for mortality (two each).

Concerning the correlations regarding cancer incidence, mancozeb-ETU and diuron had the highest estimates for related cases, showing significant correlations with colon and stomach cancers. However, despite the literature pointing out that such pesticides are linked to thyroid cancer risk, no significant relationships were found [48,49]. Breast cancer, the most prevalent female malignancy during the study period, was associated with aldrin-dieldrin, atrazine, chlordane, and molinate. Exposure to aldrin-dieldrin is linked to an increased risk of breast cancer in young women [50], including triple-negative breast cancer [51]. There is also evidence supporting the association of atrazine [52] and chlordane [53] with breast cancer risk. Such findings reinforce previous studies and highlight the contribution of pesticide exposure to female breast cancer, beyond occupational/householding contact [54].

Glyphosate is the main pesticide traded in the world, and the only association of glyphosate-AMPA estimated cancer cases and the consolidated cases by the National Cancer Institute (INCA) was found with esophageal cancer. Dysplastic lesions were reported in the esophagus and large intestine of rats after glyphosate exposure [55], and significant esophagus abnormalities were presented after acute glyphosate poisoning [56], including esophageal perforation and death [57].

There is limited information on pesticide exposure and cancer mortality, primarily because it is challenging to attribute cancer deaths to specific substances. Our data suggest that higher contamination of drinking water by pesticides such as DDT-DDD-DDE, lindane, trifluralin, and glyphosate correlates with increased mortality rates from breast, prostate, and esophagus cancers in the selected areas. The existing literature often addresses general population contamination by pesticides without considering specific sources like drinking water, which underscores the relevance of our study.

A Brazilian study from Santa Catarina, a state near Paraná southwest, suggests that high pesticide consumption correlates with breast cancer mortality [58]. However, this study did not provide information on drinking water contamination by pesticides and its contribution to this scenario. It is suggested that fungicides and insecticides contribute to an increased age-standardized mortality rate (ASMR) in Brazil. Herbicides raise the ASMR in the Northeast and Midwest regions, while insecticides increase the ASMR in the Northeast, Southeast, and Midwest regions [59], but there has been no mention of drinking water or specific cancers. In another study, a recent survey in the U.S. linked the presence of urinary glyphosate to increased mortality in the overall adult population, regardless of the cause of death [60]. Similarly, long-term occupational exposure to dust and pesticides was linked to shorter disease-free survival and higher mortality rates in healthy older adults living in Australia [61]. Interestingly, a study found that the bladder cancer risk significantly increases with increased water intake, but no specific substance was linked to this. The scarce literature available that correlates pesticides in drinking water and cancer mortality strengthens the suitability of our findings. It highlights the complexity of health research and how seemingly straightforward factors like water intake can have unexpected associations with health outcomes. The link between water intake and cancer risk without a specific substance identified raises questions about the potential mechanisms at play. And the correlation between pesticides in drinking water and cancer mortality underscores the importance of understanding environmental factors in disease development. It sounds like an area ripe for further investigation to unravel the underlying connections.

These findings reinforce the importance of drinking water contamination as a presumed source for cancer cases beyond occupational submission or direct contact with high doses of such pesticides. Concerning the impact of pesticide mixtures, little is known about human exposure. *In vitro* data [62] investigating the potential interactions among 15 pesticides showed that 60% of mixtures exhibit synergism, 27% display antagonism, and 13% have addictive effects, even at low concentrations, suggesting the underestimation of their putative interactions. Despite some researchers pointing out the fact of evaluating pesticide mixture exposure, they do not measure their levels or provide details about which type of substances are being assessed. Also, experimental data point out that such low-dose mixtures have adverse effects on cancer behavior [63].

5. Conclusions

This study reveals widespread contamination of drinking water in rural areas of Brazil such as the Paraná southwest municipalities, encompassing both permitted and banned pesticides with potential carcinogenic properties. The estimation of cancer cases resulting from low-dose exposure is noteworthy, especially considering the significant correlations observed among drinking water contamination, cancer incidence, and mortality rates. A limitation of the study is its relatively short four-year timeframe, which limited the analysis of the long-term effects of pesticides on cancer development. The lack of knowledge to estimate the cancer risk attributable to pesticide mixtures present in drinking water is

another substantial flaw. Despite this, these findings aim to disseminate knowledge to both academic and local communities regarding water contamination and its potential link to cancer, aiming to enhance governmental oversight and reduce allowable pesticide levels. Similar investigations should be extended to other rural regions of Paraná and Brazil, incorporating additional pesticides and types of cancer to gain deeper insights into the relationships between cancer incidence and mortality.

Author Contributions: All the authors contributed to the study conception and design, material preparation, and data collection and analysis. All authors have read and agreed to the published version of the manuscript.

Funding: Programa de Bolsas de Iniciação Científica da Unioeste, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Call number 01/2019), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq grants number 444333/2023-1 and 305335/2021-9).

Data Availability Statement: All the data are available in the manuscript tables.

Conflicts of Interest: The authors declare no conflicts of interest.

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