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Widespread pesticide contamination of drinking water and impact on cancer risk in Brazil

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ABSTRACT

Pesticides, which are associated with endocrine dysfunction, immunological dysregulation, and cancer, are widespread sources of drinking water contamination. The state of Paraná has a population of 11 million, is the second largest grain producer in Brazil and is a leading consumer of pesticides. In this study, we analyzed the extent of drinking water contamination from 11 proven, probable, or potentially carcinogenic pesticides (alachlor, aldrin-dieldrin, atrazine, chlordane, DDT-DDD-DDE, diuron, glyphosate-AMPA, lindane-γ-HCH, mancozeb-ETU, molinate, and trifluralin) in 127 grain-producing municipalities in the state of Paraná. Extensive contamination of drinking water was found, including legacy pesticides such as aldrin-dieldrin (mean 0.047 ppb), DDT-DDD-DDE (mean: 0.07), chlordane (mean: 0.181), and lindane-HCH (mean: 2.17). Most of the municipalities were significantly above the maximum limits for each one of the currently allowed pesticides (67% for alachlor, 9.44% for atrazine, 96.85% for diuron, 100% for glyphosate-AMPA, 80.31% for mancozeb-ETU, 91.33% for molinate, and 12.6% for trifluralin). Ninety-seven percent of municipalities presented a sum of all pesticides at levels significantly above (189.84 ppb) the European Union preconized limits ($<$0.5 ppb). Using the mean pesticide concentration in water (ppb), the exposed population for each municipality, and the benchmark cancer risk for pesticides, we estimated the minimum number of cancer cases attributable to pesticide-contaminated drinking water during the period (total of 542 cases). More than 80% were attributed to mancozeb-ETU and diuron. Glyphosate-AMPA and diuron-attributable cases strongly correlated with the total cancer cases in the same period ($R = 0.8117$ and 0.8138, respectively) as well as with breast cancer cases ($R = 0.7695$ and 0.7551, respectively). Water contamination was significantly correlated with the sum of the estimated cancer cases for all 11 pesticides detected in each city ($R = 0.58$ and $p < 0.0001$). These findings reveal extensive contamination of drinking water in the state of Paraná and suggest that contamination may increase the risk of cancer in this region.

1. Introduction

Environmental pesticide contamination is a global health concern, especially in Brazil, given its status as one of the largest pesticide consumers in the world as well as its permissive regulatory control. The country consumes more than 500 thousand tons of these substances per year, resulting in an annual pesticide consumption of 7 L per capita. Moreover, approximately 80% of the pesticides authorized for commercialization in Brazil are prohibited in at least three countries of the Organization for Economic Cooperation and Development (OECD) of the European community and have resulted in more than 70,000 intoxications (Panis et al., 2022a).

Uncontrolled pesticide use may cause large-scale environmental contamination, including the contamination of water, soil, air, plants,

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animals, food products, and humans. These substances can reach aquatic systems through runoff from pulverized crops, reducing the potability of water for human consumption (Aydinalp and Porca, 2004). In addition, the soil matrix acts as pesticide storage because of its high capacity to interact with such substances (Syafrudin et al., 2021). Despite their loss by microbial degradation and soil adsorption, pesticides are frequently reported as contaminants in drinking water.

The European Union (EU) standards of drinking water safety levels follow the precautionary principle in environmental science (Kriebel et al., 2001), and are considered a reference for human health and environmental protection. According to the EU Drinking Water Directive, the sum of the maximum allowable concentration of pesticides in drinking water is 0.1 μg/L (Dolan et al., 2013). Despite this, pesticide levels in drinking water are commonly above the EU preconized limits because of their capacity for persistence in the environment.

For example, legacy pesticide residues have been reported as drinking water contaminants worldwide (EPA, 2021). Organochlorine pesticides, such as aldrin-dieldrin, DDT-DDE, and HCH isomers, are among the major persistent organic pollutants (POPs) owing to their high toxicity and persistence (Hung and Thiemann, 2002; Kaushik et al., 2010; Aydin et al., 2013; Agarwal et al., 2015; Rodríguez et al., 2017). Similar results have been reported for currently allowed pesticides, such as glyphosate (Van Stempvoort et al., 2016; Tang et al., 2015), with acceptable levels in drinking water being 5000 times higher in Brazil than in the European Union (EU) (Bombardi, 2019).

The consequences of lifetime human exposure to pesticides have been drawing increased attention because of their potential impact on health, and the risks to human health have been documented (Yi et al., 2019; Zhang et al., 2020; Pizzatti et al., 2020; Zhang et al., 2021; Panis et al., 2022b). For instance, the Agricultural Health Study, a consortium focused on understanding the impact of human exposure to mixed pesticides, documented health outcomes associated with chronic pesticide exposure (AHS, 2021). The consequences of exposure include increased risk for thyroid dysfunction, including cancer (Hoffmann et al., 2021, Shrestha et al., 2018), risk of hematological cancers and their precursor conditions (Lerro et al., 2021; Andreotti et al., 2018), altered kidney function and risk of renal carcinoma (Shearer et al., 2021; Andreotti et al., 2020), high Parkinson's disease incidence (Shrestha et al., 2020), female hormone disruption (Farr et al., 2004) and evidence of immune disorder occurrence (Parks et al., 2019; Cooper et al., 2004).

Human health benchmarks for pesticides have been proposed as a strategy to ensure that pesticide concentrations in drinking water remain at a safe level and to protect the public against their carcinogenic potential (U.S. EPA, 2017). Therefore, regardless of their concentration in drinking water at any given time, pesticides are considered a potential risk for cancer development due to their continuous ingestion.

In this context, a technical report published in 2018 by the Brazilian Water Quality Surveillance Information System for Human Consumption (SISÁGUA, 2021), the official agency responsible for water quality monitoring in Brazil, identified the presence of at least one of 27 different pesticides in the drinking water of one in four Brazilian cities. Five of these pesticides are categorized as probably carcinogenic to humans, indicating that these agents have strong carcinogenic potential, according to the cancer classification proposed by both the United States Environmental Protection Agency (U.S. EPA, 2005) and the International Agency for Research on Cancer (IARC, 2019). POPs DDT-DDD-DDE and lindane, along with currently allowed pesticides such as glyphosate, diuron and mancozeb, are amongst the residues detected.

Some high-producing agricultural regions consume a large share of the pesticides used in Brazil and may display substantially higher drinking water contamination. The state of Paraná is among the top three food producing and pesticide consumers in Brazil (IBAMA, 2019; Brovini et al., 2021; FAO, 2021). Given the permissive regulation of pesticide use in Brazil, it is possible that drinking water contamination would be substantial and likely high above the regulatory thresholds used in other regions of the world.

According to the National Cancer Institute (INCA), Paraná is among the top five states with the highest cancer incidence in the country, particularly for certain types such as colon, lung, breast, and oral cancers (INCA, 2020). Contamination of drinking water by pesticides has been extensively documented worldwide. However, results regarding pesticide consumption (or exposure) and their association with cancer risk are inconclusive (Oller-Arlandis and Sanz-Valero, 2012; Inoue-Choi et al., 2016) or divergent (Wong et al., 1989; Van Leeuwen et al., 1999; Buczyńska and Szadkowska-Stańczyk, 2005; McElroy et al, 2007) Most of these studies investigated populations with a small group of exposed individuals, which may be a relevant limitation in research concerning the relationship between pesticides in drinking water and cancer risk.

Here, we evaluated evidence regarding pesticide contamination in the drinking water of municipalities in the state of Paraná. We estimated the cancer risk for approximately 5 million people exposed to pesticides found as contaminants in drinking water that present some carcinogenic potential according to the IARC classification. We also investigated the correlation between drinking water contamination, cancer cases reported by INCA during the same period, and pesticide trade for the chemicals currently allowed in the state.

2. Methods

This study was based on the SISÁGUA Report for drinking water quality in Paraná from 2014 to 2017 (available at https://dados.gov.br/dataset; SISÁGUA, 2021). The complete supporting database extracted from SISÁGUA is shown in Supplementary Table 1. SISÁGUA is a report of the National Program for the Monitoring of the Quality of Water for Human Consumption (VIGIÁGUA), which consists of a set of actions that aim to guarantee safe drinking water for population consumption, compatible with the standards preconized by Brazilian legislation (Candiotto et al., 2017). As part of VIGIÁGUA, 27 pesticides were monitored in drinking water, including those currently traded in the country, as well as some banned pesticides that are classified as persistent organic pollutants. 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-dichlorodiphenyldichloro ethylene-dichlorodiphenyldichloroethylene (DDT-DDD-DDE), diuron, endosulfan, endrin, glyphosate-aminomethylphosphonic acid (AMPA), lindane-gamma-hexachlorocyclohexane (γ-HCH), mancozeb-ethyleneth iourea (ETU), methamidophos, metolachlor, molinate, parathion, pendimenthalin, permethrin, prophenofos, simazine, tebuconazole, terbufos, and trifluraline. For DDT, glyphosate, lindane, and mancozeb, by-product levels have also been reported (DDD-DDE, AMPA, γ-HCH, and ETU, respectively).

The study design is illustrated in Fig. 1. Based on data available in the SISÁGUA report (from samples collected and analyzed between 2014 and 2017) for Paraná, we included 127 municipalities, corresponding to approximately 5.5 million people and a coverage rate of 50% of the state population. Paraná contains 399 municipalities, 326 of which had their drinking water analyzed and reported by SISÁGUA. Among these, 127 (here analyzed) presented the quantification of at least one of the 11 pesticides listed by the International Agency for Research on Cancer (IARC, 2019) and the United States Environmental Protection Agency (U.S EPA, 2005) as probably or possibly carcinogens to humans: alachlor, aldrin-dieldrin, atrazine, chlordane, DDT-DDD-DDE, diuron, glyphosate-AMPA, mancozeb-ETU, molinate, and trifluralin, along with the proven carcinogenic pesticide lindane.

We calculated the cancer risk level by estimating the number of cancer cases attributable to each pesticide according to the following formula:

[(Observed average pesticide ppb × number of individuals at risk)/ 10^6 benchmark cancer risk]

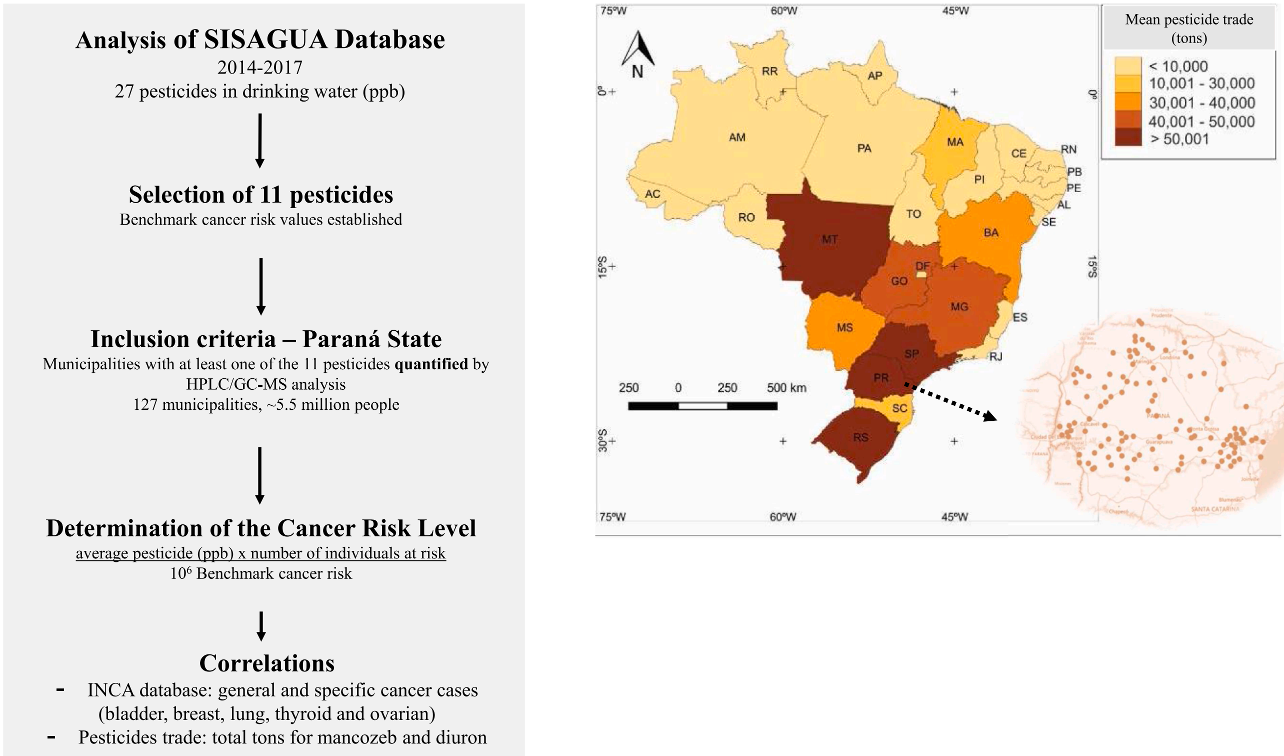

Fig. 1. Design of the study. From 2014 to 2017 the main water regulatory agency in Brazil (SISAGUA, http://sisagua.saude.gov.br/sisagua) tracked the contamination of 27 pesticides in public drinking water. Out of these, 16 pesticides are putatively carcinogenic and 11 have a known benchmark cancer risk. From this data, we excluded unquantifiable values and possible typos to calculated the average municipality contamination. Based on this information and demographic information, we applied the benchmark concept to estimate the number of cancer-associated with drinking water contamination by pesticides in municipalities from Paraná State. In the map, the mean pesticide trade of the 27 Brazilian States:Acre - AC; Alagoas - AL; Amapá - AP; Amazonas - AM; Bahia - BA; Ceará - CE; Distrito Federal - DF; Espírito Santo - ES; Goiás - GO; Maranhão - MA; Mato Grosso - MT; Mato Grosso do Sul - MS; Minas Gerais - MG; Pará - PA; Paraíba - PB; Paraná - PR; Pernambuco - PE; Piauí - PI; Roraima - RR; Rondônia - RO; Rio de Janeiro - RJ; Rio Grande do Norte - RN; Rio Grande do Sul - RS; Santa Catarina - SC; São Paulo - SP; Sergipe - SE; Tocantins - TO. Paraná is among the top 5 pesticide traders of the country. The highlight shows the 127 cities of the state included in the study.

Where: (i) the observed average pesticide ppb = average drinking water contamination level in ppb for each chosen pesticide reported to each selected municipality, (ii) the number of individuals at risk = number of individuals registered as residents for each municipality, and (iii) 106 Benchmark cancer risk = value estimated by the Office of Environmental Health, Hazard Assessment, California Environmental Protection Agency, Office of Environmental Health Hazard Assessment Air Toxicology and Epidemiology Branch (OEHAA, 2009). This represents the probability that an individual exposed to a determined pesticide will develop cancer over a lifetime.

As aldrin-dieldrin, diuron, lindane-γ-HCH, and mancozeb-ETU together were responsible for almost 98% of the estimated cancer cases, further analyses considered only these pesticides. Diuron and mancozeb are currently allowed in Brazil, whereas aldrin-dieldrin and lindane-γ-HCH are banned.

Aiming to investigate putative associations between the estimated cancer cases related to drinking water contamination by the 11 selected pesticides and the number of consolidated cancer cases registered in Paraná, we obtained the total number of cancer cases registered in the same period as the SISÁGUA report (2014–2017) from the National Hospital Cancer Registry Information Hospital Tabulator (INCA, 2021). The data included five specific cancers (bladder, breast, lung, thyroid, and ovarian) by year, municipality of origin, and primary tumor localization. The 2014–2017 average was calculated for each cancer type. We selected these five cancer types based on the literature. Diuron and mancozeb have been reported to be associated with bladder and thyroid cancer, respectively. Lung cancer (second most common among males) and breast cancer (most common among females) were selected due to their high incidence in the Brazilian population. Ovarian cancer was selected because it is likely to be less affected by drinking water contamination than genetic factors.

Statistical analyses were conducted using GraphPad Prism software (version 7.0; GraphPad, San Diego, CA, USA). Spearman correlations were performed among ppb levels in drinking water for aldrin-dieldrin, diuron, lindane-γ-HCH, and mancozeb-ETU; the volume of pesticide currently traded for each municipality; and the mean number of cancer cases reported by INCA. Statistical significance was set at p value < 0.05.

3. Results

Pesticide contamination in drinking water was evaluated relative to the maximum limits allowed by Brazilian and European Union (EU) agencies as well as the benchmark cancer risk according to EPA/OEHAA and the IARC/EPA cancer classification for the 11 selected pesticides (Table 1). Data concerning drinking water contamination for each pesticide and municipality were tabulated for the 2014–2017 period (Supplementary Table 1; SISÁGUA, 2021). We calculated the average municipality contamination, including only the values reported as equal to or greater than the limit of quantification established for each substance. Data are reported in comparison to the maximum allowable limit in drinking water set by regulatory agencies in Brazil and the EU (Table 1). Pesticide contamination in drinking water varies across 127 municipalities in Paraná State (Figs. 2 and 3). Three persistent organic pollutants (POPs), namely aldrin-dieldrin, chlordane, and DDT-DDD-DDE, along with lindane-γ-HCH, are not currently allowed in Brazil, but remain present at concerning levels in some municipalities (Fig. 2). Aldrin-dieldrin levels ranged from 0.001 ppb to 3 ppb, with a mean concentration of 0.047 ppb. Seven municipalities (7.21%) had values

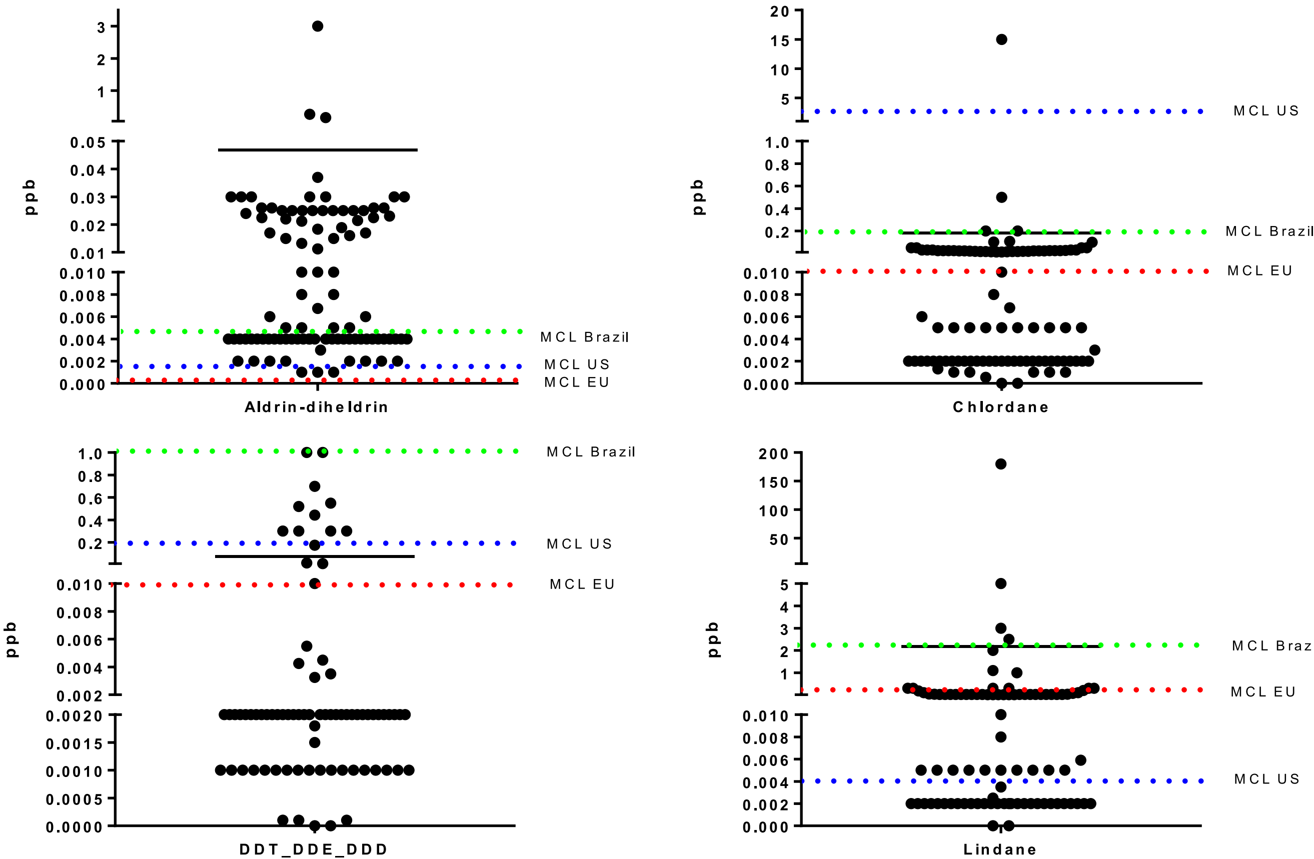

Fig. 2. Pesticide levels (ppb) in drinking water from 127 municipalities located at Paraná State, data for the persistent organic pollutants (POPs). Pesticide concentration is expressed in ppb, as informed in the SISÁGUA report. The graphs represent the mean ppb reported by SISAGUA 2014–2017 document for quantified pesticides, and each dot represent one specific municipality. The lines indicate the maximum concentration allowed for each pesticide in Brazil (green line), US (blue line) and Europe (red line).

equal to or higher than the maximum limit allowed in Brazil. All municipalities exceeded the maximum limit established by the EU. The mean concentration of chlordane was 0.181 ppb and four municipalities had values equal to or higher than the Brazilian maximum allowed limit. Approximately 44% of the 127 cities had chlordane levels above EU limits. Despite DDT-DDD-DDE being banned from Brazil in 1985, it was detected in the drinking water from almost all municipalities analyzed with a mean concentration of 0.07 ppb – almost 7-fold the maximum EU limit. Two municipalities presented DDT-DDD-DDE water contamination over the maximum limit allowed for Brazilian law (1 ppb). For lindane-γ-HCH, values ranged from 0 to 180 ppb (1,800 times over the EU limit of 0.1 ppb), with a mean concentration of 2.17 ppb (21.7 times over the EU limit). Approximately 16% of municipalities had lindane-γ-HCH concentrations over the EU limit. A total of 64 municipalities (50.4%) had all four POPs concomitantly measured in drinking water, while only 18 (14.2%) did not have any POP detected. Furthermore, 8.66% of municipalities were at or above the maximum limits for aldrin-dieldrin (range 0.03–11 ppb), 3.15% for chlordane (range 0.2–15 ppb), 1.6% for DDT-DDD-DDE (range 1–2 ppb) and 3.94% for lindane-γ-HCH (2–180 ppb). When considering the sum of all POPs studied, 32.3% of the municipalities presented levels over the limit of 0.5 ppb recommended by the EU for drinking water safety.

Regarding the pesticides that are currently allowed (Fig. 3), alachlor concentrations ranged from 0 to 20 ppb (200 times over the EU limit of 0.1 ppb), with a mean concentration of 0.7 ppb. Values over the Brazilian maximum limit were found in three municipalities. Most of the analyzed samples were above the EU maximum limits. For atrazine, the values ranged from 0 to 2.5 ppb (25 times over EU limits), with a mean concentration of 0.16 ppb. A total of 12 municipalities showed levels equal to or over the EU limits; three municipalities showed levels equal to or greater than the Brazilian maximum limits. In the case of diuron, drinking water contamination ranged from 0.0007 to 90.05 ppb, and the mean concentration was 73.53 ppb (735.3 times over EU limits). Only four municipalities were under the EU recommended limits; the 75th percentile showed a mean concentration of approximately 90 ppm, which is the maximum limit allowed in Brazil (900 times over EU limits). Glyphosate-AMPA was the only residue that had values below the maximum limits allowed by Brazilian regulators in all municipalities analyzed by SISÁGUA. Values ranged from 0.12 to 282.5 ppb, with a mean concentration of 74.79 ppb (747.9 times over EU limits). According to Brazilian regulations, the maximum glyphosate-AMPA limit allowed for drinking water is 500 ppb, which is 5000-fold higher than the EU recommended limit.

Almost 50% of the municipalities had all currently allowed pesticides concomitantly detected in their drinking water, while only 18.9% did not show any of these pesticides. Diuron and mancozeb-ETU were the main contaminants detected at the Brazilian maximum allowed concentrations (90 ppb for diuron and 180 ppb for mancozeb-ETU) in almost 52% of all municipalities studied, representing values 900 and 1800 times above the European limit, respectively. Furthermore, 97% of the included municipalities presented a sum of all pesticides at levels above the EU recommended limits (sum over 0.5 ppb limit, mean of 189.84 ppb). Considering the EU limits, most municipalities were significantly above the maximum limits for each of the currently allowed pesticides (67% for alachlor, 9.44% for atrazine, 96.85% for diuron, 100% for glyphosate-AMPA, 80.31% for mancozeb-ETU, 91.33% for molinate, and 12.6% for trifluralin).

Mancozeb-ETU contamination was found in several municipalities,

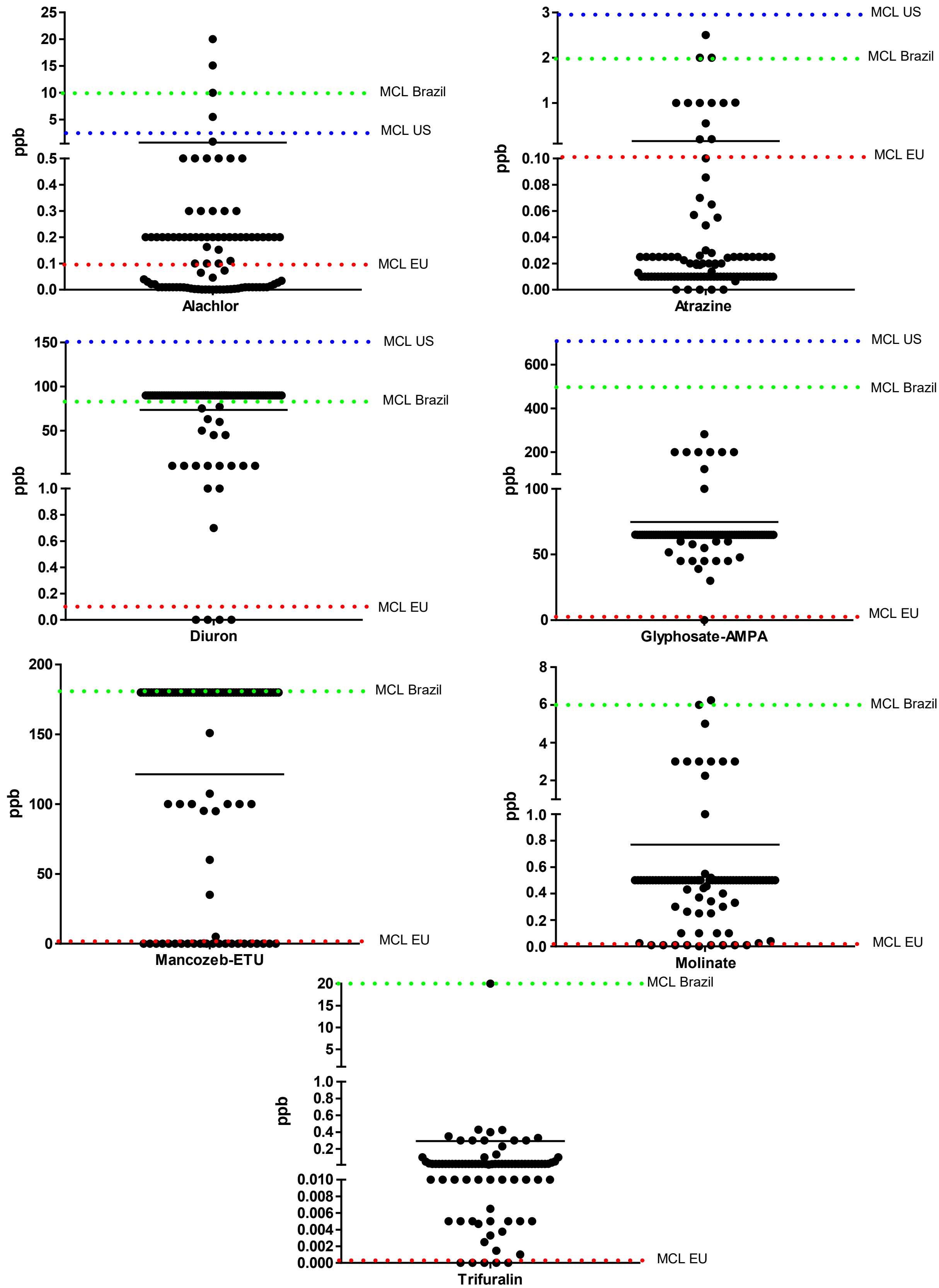

Fig. 3. Pesticide levels (ppb) in drinking water from 127 municipalities located at Paraná State, data for the currently allowed. Pesticide concentration is expressed in ppb, as informed in the SISÁGUA report. The graphs represent the mean ppb reported by SISAGUA (2014–2017) for quantified pesticides, and each dot represent one specific municipality. The lines indicate the maximum concentration allowed for each pesticide in Brazil (green line), US (blue line) and Europe (red line). For some pesticides, the US allowed limit was not found.

ranging from 0 to 180 ppb (1,800 times over the EU limit of 0.1 ppb), with a mean concentration of 121.4 ppb. The mean mancozeb level for the 75th percentile was 180 ppb, showing that most of the cities included in the study presented the maximum limits allowed by Brazilian law. For molinate, the concentrations ranged from 0 to 6.25 ppb (mean 0.77 ppb, 7.7 times over EU limits), and two municipalities exhibited values equal to or higher than the allowable limits recommended by Brazilian law. Trifluralin levels varied from 0 to 20 ppb (200 times the EU limits), and one municipality had a concentration at the upper limit allowed by Brazilian law (São João do Ivaí, 20 ppb).

Based on the average drinking water contamination and the benchmark cancer risk according to EPA/OEHAA and the IARC/EPA cancer classification for the 11 selected pesticides (Table 1), we estimated 542 cancer cases per million people collectively attributable to the 11 pesticides analyzed, across all municipalities (Fig. 4). Approximately 50% of cases were attributable to mancozeb-ETU contamination (273 cases per million), followed by diuron (178 cases), aldrin-dieldrin (43 cases), and lindane-γ-HCH (38 cases).

Significant correlations between drinking water contamination (ppb) and pesticide trade in tons were found in diuron and mancozeb (Table 2). Data about the 11 selected pesticides and their specific associated cancers are shown in Table 3. Cancer cases attributable to diuron and glyphosate-AMPA were strongly correlated with cancer cases reported by INCA, particularly for the total number of cases ($R = 0.8117$ and 0.8138, respectively) and breast cancer ($R = 0.7695$ and 0.7551, respectively) (Fig. 5 and Supplementary Table 2). Negative or weak correlations were observed for ovarian cancer (R-values varying from −0.2454 to 0.04030). Strong correlations were observed between aldrin-dieldrin and glyphosate-AMPA levels. Mancozeb-ETU showed the weakest correlation with most cancers. Overall, ovarian cancers showed weak correlations with all pesticides, whereas breast cancers showed the strongest correlations. Significant positive correlations between the sum of lung, breast, thyroid, bladder, and ovarian cancer cases reported by INCA (total cases) and pesticide-attributable cancer cases were found for 10 out of the 11 pesticides, excluding alachlor. Lung, thyroid, and bladder cancers showed significant correlations with pesticide-attributable cancer cases (8 out of 11 pesticides), whereas for breast cancer, this significance was observed in 9 out of 11 pesticides. Regarding each pesticide, alachlor- and mancozeb-attributable cancer

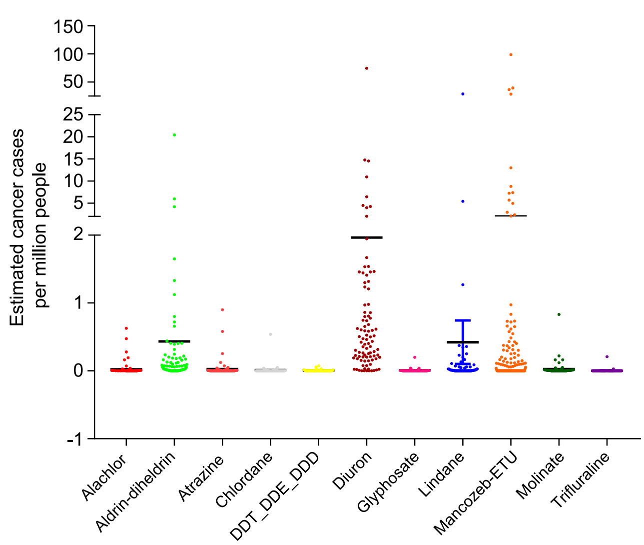

Fig. 4. Total estimated cancer cases attributed to the contamination of drinking water for the 11 included pesticides evaluated in 127 municipalities from Paraná State. The estimative was performed based on the mean concentration of the pesticide in drinking water reported by SISÁGUA in the period from 2014 to 2017, considering its benchmark cancer risk and the number of exposed people.

Table 1
Cancer risk-associated 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, maximum limits of pesticides in drinking water allowed by Brazilian and European Union regulatory agencies, and cancer classification group for each one based on data from the International Agency for Research on Cancer (IARC) or EPA.

Pesticide	Maximum limit allowed - Brazil (ppb)	Maximum limit allowed – European Union (ppb)	Benchmark cancer risk of 1 case/ 10^6 people (EPA/ OEHAA)	Carcinogenicity evidence classification
Alachlor	20	0.1	0.4	Probably carcinogenic to humans (IARC, EPA)
Aldrin_dieldrin	0.03	0	0.002	Probably carcinogenic to humans (IARC, EPA)
Atrazine	2	0.1	0.15	Not classifiable as to human carcinogenicity (IARC)
Chlordane	0.2	0.01	0.1	Possibly carcinogenic (IARC, EPA)
DDT_DDD_DDE	1	0.01	0.1	Possibly carcinogenic (IARC, EPA)
Diuron	90	0.1	2	Probably carcinogenic to humans (IARC, EPA)
Glyphosate + AMPA	500	0.1	56.45	Probably carcinogenic to humans(IARC) Not Classifiable as to Human Carcinogenicity (EPA)
Lindane - HCH	2	0.1	0.032	Carcinogenic to humans (IARC, EPA)
Mancozeb/ ETU	180	0.1	0.06 (ETU)	No data (IARC) Probably carcinogenic (EPA for ETU)
Molinate	6	0	1	Not classifiable as to human carcinogenicity (IARC)
Trifluralin	20	0	4	Not classifiable as to human carcinogenicity (IARC) Possibly carcinogenic (EPA)

Notes: Classification. Source(s):1.EPA: https://www.epa.gov/sites/production/files/2018–03/documents/dwtable2018.pdf; and https://www.epa.gov/sites/production/files/2015–10/documents/hh-benchmarks-techdoc.pdf2. EPA(DDT): https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr = 147; 3.IARC: https://monographs.iarc.fr/agents-classified-by-the-iarc/; 4.OEHHA: https://oehha.ca.gov/. 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. AMPA = aminomethylphosphonic acid; ETU = ethylenethiourea.

Table 2
Correlations between the levels of pesticides in drinking water (ppb) versus the average trade of Mancozeb and Diuron, in the 127 municipalities in the state of Paraná in the analyzed period (2014–2017).

Correlation	Spearman r value (CI 95)%	P value
Diuron in drinking water (ppb) × Diuron trade (tons)	0.07268 (−0.1413 to 0.2802)	0.4935
Mancozeb/ETU in drinking water (ppb) × Mancozeb trade (tons)	0.2221 (0.01434 to 0.4115)	0.0314*

* $p < 0.05$.

Table 3
Mean pesticide levels in drinking water (ppb), the main use in Brazil, and cancer association according to IARC, EPA, and OEHAA agencies.

Pesticide	Mean concentration indentified (ppb, min–max)	Main use in Brazil[a]	Cancer association
Alachlor	0.69 (0–20)	Herbicide Sugar cane and corn crops	Laryngeal cancer, lymphohematopoietic (IARC) Urinary tract (EPA)
Aldrin_dieldrin	0.047 (0.001–3)	Insecticide Banished	Breast (IARC) Liver (EPA)
Atrazine	0.16 (0–2.5)	Herbicide Sugar cane and corn crops	Thyroid (OEHAA)
Chlordane	0.18 (0–15)	Inseticide Banished	Liver (IARC and EPA) Thyroid (OEHAA)
DDT_DDD_DDE	0.07 (0–1)	Inseticide Banished	Testis, liver and lymphoma (IARC) Liver (EPA)
Diuron	73.53 (0.001–90.05)	Herbicide Sugar cane and other crops	Kidney, lung (IARC) Urinary tract (EPA)
Glyphosate-AMPA	74.79 (0.12–282.5)	Herbicide soy, weat and corn crops	Lymphoma (IARC, OEHAA)
Lindane-γHCH	2.17 (0–180)	Inseticide Banished	Lymphoma (IARC) Liver (EPA and OEHAA)
Mancozeb-ETU	121.4 (0–180)	Fungicide Rice, soy and other crops	Thyroid (IARC)
Molinate	0.77 (0–6.25)	Herbicide Rice	Urinary tract (OEHAA)
Trifluraline	0.29 (0–20)	Herbicide Cotton, rice, sugar cane	Lymphoma, thyroid, stomach, liver (IARC) Urinary tract (EPA)

Notes: [a] Source: ADAPAR – Agência Paranaense de Defesa Agropecuária. For all municipalities included, the sum of the total pesticide content is over the EU limits (0.5 ppb).

cases had less correlation with consolidated cancer cases than the other pesticides (one out of five correlations was significant). Aldrin-dieldrin, atrazine, chlordane, DDT-DDD-DDE, diuron, glyphosate-AMPA, lindane, and trifluralin-attributable cancer cases showed significant correlations with consolidated cancer cases in four out of five topographies.

Concerning the impact of the 11 pesticide mixtures on cancer cases, a significant correlation was found between the sum of the estimated cancer cases attributable to all 11 pesticides and the sum of the consolidated cancer cases reported by INCA in the same period ($R = 0.58$ and $p < 0.0001$, Supplementary Table 3).

4. Discussion

Studies have investigated the cancer risk associated with pesticide exposure in contaminated water worldwide (Pawlak et al., 2021). Some of the pesticides identified here are proven carcinogens (e.g., lindane-γ-HCH), probable carcinogens (e.g., alachlor, aldrin-dieldrin, diuron, glyphosate-AMPA, mancozeb-ETU), or endocrine disruptors (EDCs, such as atrazine, mancozeb, and glyphosate), and cause significant changes in DNA, including mutations and epigenetic modifications (Kucka et al., 2012; Axelstad et al., 2011; Lesseur et al., 2021; Kumar et al., 2020). Brazil has relatively high maximum limits compared to those established for the EU, ranging from 20-fold higher for atrazine and alachlor to 5000-fold higher for glyphosate levels. The POPs aldrin-dieldrin and lindane-γ-HCH presented the greatest benchmark cancer risk (0.002 and 0.032, respectively), which means that very small concentrations of these substances in drinking water are enough to contribute to increased cancer risk. According to the IARC/EPA cancer classification, lindane-γ-HCH is the only substance described as a proven carcinogen, whereas chlordane and DDT-DDD-DDE were classified as possibly carcinogenic. Finally, the EU allows a total sum of 0.5 ppb for all pesticides detected in drinking water, while in Brazil, there is no regulation for the maximum allowed when all pesticides are considered together.

Our findings indicate that pesticides currently sold and those banned decades ago are widely detected as contaminants in the state's water system. It was also observed that the levels of individual pesticides were substantially above the safe limits recommended by the EU for practically all municipalities analyzed. Thus, considering pesticides in aggregate, all municipalities analyzed in the present study reached pesticide levels above this value. We estimated the impact of drinking water contamination on the number of cancer cases attributable to 11 pesticides with potential or proven carcinogenic activity, and the estimates were correlated with cancer cases registered in Paraná for the same period.

4.1. POPs

The water for human consumption in much of Brazil is contaminated by pesticides, which has permissive legislation regarding the maximum allowable limits compared to the EU. Desirable aldrin-dieldrin levels in aquatic environments are reported by WHO as less than 0.01 ppb (WHO, 2003); Brazil accepts 3 times higher levels as safe, whereas the EU sets the safe level at zero. All the samples analyzed in our study exhibited POP contamination. Aldrin-dieldrin has a half-life >5 years (EPA, 2003). Despite decades of global bans, aldrin-dieldrin has been documented in aquatic systems in heavy pesticide traders such as China, with maximum concentrations of 0.163 ppb for aldrin and 0.0233 ppb for dieldrin (Pan et al., 2019; Zhang et al., 2021). China and Brazil are among the top pesticide users, ranking first and third in the world, respectively (FAO, 2021). Comparatively, despite China's average pesticide use per hectare of cropland, which is twice that registered for Brazil, the highest level of aldrin-dieldrin reported by SISÁGUA was 18- to 128-fold higher than that documented for China. This indicates that the capacity of pesticides to reach drinking water systems in Brazil is considerable.

The same situation has been documented for other POPs, confirming that some regions in Brazil are probably among the most extensively contaminated places worldwide (Wu et al., 2014). The maximum value of DDT-DDD-DDE detected in our study was 1 ppb, which is the exact maximum limit allowed in Brazil, but 100 times the EU limit. DDT is poorly soluble in water, causing it to bioaccumulate in the human body, and it has an estimated half-life of about 150 years in aquatic environments (Callahan et al., 1979). For lindane-γ-HCH, the maximum observed contamination value corresponds to 1,800 times the EU limit. Historically, the state of Paraná has been a significant supplier of wood for export (Berger et al., 2007), and lindane was largely employed as a preservative in the past, before the institution of restrictive measures against the use of this substance (IBAMA, 2006). Interestingly, lindane residue is not ordinarily detected in surface water, where it is generally removed by evaporation, and has an estimated half-life of approximately two weeks (ABRAF, 2005; CDC, 2021). Therefore, its detection in analyzed drinking water samples may reflect its leaching from

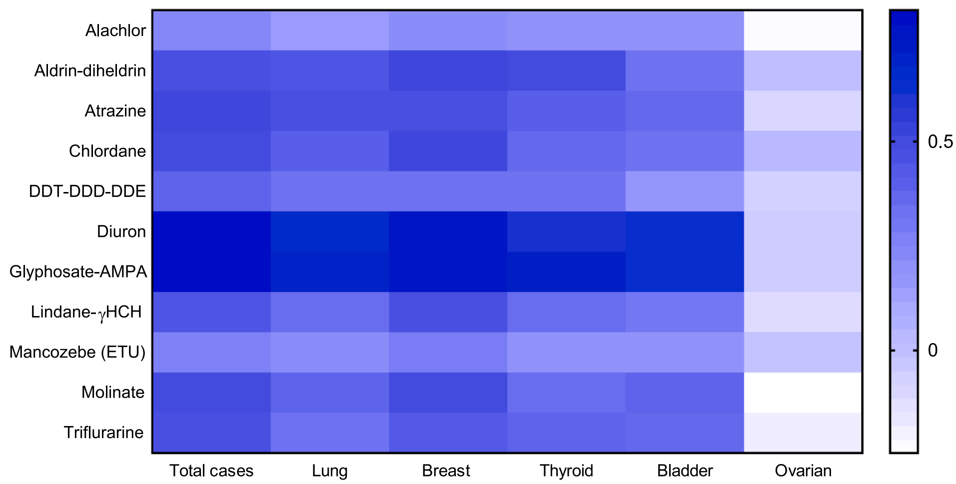

Fig. 5. Spearman correlation matrix between the estimated cancer cases versus the number of cancer cases reported by INCA for the 127 municipalities in Paraná state in the period 2014–2017.

extensively contaminated soil, where its half-life and stability increase considerably. Furthermore, its detection in drinking water should be viewed with concern, since this compound is considered to be quite toxic. Studies worldwide have reported very low levels of DDT-DDD-DDE and lindane-γ-HCH residues in drinking water in several countries (Kuba et al., 2015; Aydin et al., 2013; Buczyńska and Szadkowska-Stańczyk, 2005; Fatoki and Awofolu, 2004; Hung and Thiemann, 2002; Kalajzic et al., 1998), highlighting the extent of water system contamination by harmful legacy pesticides.

4.2. Current use pesticides

Regarding pesticides that are currently allowed in Brazil, all except for atrazine and alachlor were detected at levels significantly higher than the recommended EU limits for practically all examined municipalities. The observed levels of glyphosate-AMPA, mancozeb-ETU, and diuron were very high, reaching mean concentrations of >70 ppb each.

Glyphosate is the most widely used pesticide in Brazil (IBAMA, 2019), with glyphosate-AMPA safe levels in Brazil set at 5,000 times above the safe levels recommended by the EU (Bombardi, 2019). Paraná State, one of the largest producers of corn and soy in the world, stands out as the second main consumer of glyphosate in the country. Glyphosate accounts for almost 50% of pesticide trade in the state (Gaboardi et al., 2019). This chemical has an estimated half-life of six hours (Connolly et al., 2019), and despite being complexed with organic matrices present in aquatic systems, it has been detected at considerable levels in water samples worldwide, in association with its breakdown byproduct AMPA (Geng et al., 2021; Reynoso et al., 2020; Close et al., 2021). Most of these studies have reported lower levels of glyphosate contamination than those found in the present study. Considering the short half-life of glyphosate, it is possible that its levels oscillate substantially in water over time.

Our results also showed that diuron and mancozeb-ETU could be significant drinking water contaminants in Paraná. Data concerning aquatic diuron contamination have indicated low levels in several countries worldwide despite continuous recommendations to avoid its use (EU, 2000). Contamination has been reported at very low levels, which may be related to its low water solubility. Mancozeb-ETU is the fifth most traded pesticide in the state (ADAPAR 2021). Mancozeb is chemically unstable in aqueous systems, degrades quickly, and yields the final product ETU (López-Fernández et al., 2017). Little information is available regarding mancozeb-ETU as a contaminant of drinking water; its detection has been reported at very low levels in banana plantation areas in Costa Rica (van Wendel de Joode et al. 2016). We found a significant positive correlation between the mancozeb trade and its levels in the drinking water of Paraná. Considering its high persistence in the environment over 250 days (Rocha et al., 2013), and the high levels observed in more than 90% of the studied municipalities, our findings suggest that Paraná drinking water has been severely contaminated by multiple sources of mancozeb-ETU, such as polluted soil and direct entry into aquatic systems by careless manipulation and application of this product.

4.3. Pesticide exposure and cancer risk

Three of the pesticides examined here (glyphosate-AMPA, diuron, and mancozeb-ETU) are classified by the IARC as probable human carcinogens (IARC, 2015, 2021). We observed that more than 80% of the municipalities had levels above the EU limit for at least one of these three pesticides, and all of them were above the EU limits for glyphosate-AMPA. The benchmark cancer risk is calculated for each substance based on the pesticide concentration needed to yield one case of cancer for every 10^4 or 10^6 people over a 70-year interval of exposure. Aldrin-dieldrin offers the biggest carcinogenic risk (benchmark cancer risk of 0.002), as compared to glyphosate-AMPA (benchmark cancer risk of 56.45).

Diuron, maconzeb-ETU, lindane-γ-HCH, and aldrin-dieldrin accounted for almost 90% of the total estimated cancer cases attributable to pesticide consumption via contaminated drinking water. Approximately 20% of cancer cases were credited to POPs contamination. According to the EPA, aldrin-dieldrin is a probable carcinogen linked to breast and liver cancers (EPA, 2003). Experimental evidence demonstrates that aldrin-dieldrin bioaccumulates in mammary tissue (Gautam et al., 2020), and is positively associated with breast cancer risk among environmentally exposed populations because of its xenoestrogen potential (Boada et al., 2012), especially in association with other organochlorines (Jm et al., 2004). We found a significant correlation between aldrin-dieldrin-estimated cancer cases and the number of breast cancer cases reported by the National Cancer Institute in the same period. Coincidentally, Paraná State registered higher rates of breast cancer cases during the study period, with estimates above 25% of the national rates.

Lindane-γ-HCH is a proven carcinogen, and its ingestion in contaminated water and food increases the risk of cancer development in both children and adults (Odewale et al., 2021; Woldetsadik et al., 2021). We obtained a significant positive correlation between lindane-γ-HCH estimated cancer cases and the consolidated incidence of total cancer cases reported for Paraná State in the same period. The small number of cases attributed to lindane contamination agrees with the low incidence of cancer types associated with this substance in Paraná State, especially lymphoma cases. Despite this, lymphomas are aggressive and lethal tumors, with a considerable contribution of environmental risk factors, which incidence has increased over the years (INCA, 2020).

Diuron and Mancozeb-ETU contributed to most of the estimated cancer cases. Diuron has been linked by EPA/IARC as a probable carcinogen for several cancer types, such as kidney, urinary tract, and lung tumors. Previous studies have reported the occurrence of acute lymphoblastic leukemia following maternal exposure to diuron (Park et al., 2020), indicating that it can be transferred by the human placenta to the fetus (Mohammed et al., 2018). A strong correlation was found between the calculated cancer cases due to diuron and the total number of cancer cases reported by the INCA. The same was found for bladder cancer, which is the sixth most common cancer in men in the state of Paraná.

Finally, a significant correlation was found between the sum of the 11 pesticide-attributable cancer cases and consolidated cancer cases reported by INCA in the same period. Although it is difficult to estimate the impact of pesticide mixtures on human cancer development, our analysis indicated that benchmark cancer risk estimation can be a reasonable way to assess this situation.

5. Conclusions

This study highlights the extent of drinking water contamination in Paraná State, an important agricultural region in Brazil. Contamination includes current and legacy pesticides that have been linked to environmentally induced carcinogenesis, reaching significantly higher levels than those prescribed by EU limits. Estimates of putative cancer cases linked to water contamination by single pesticides highlight a considerable number of individuals at risk, especially for diuron, mancozeb, and lindane contamination. The profile of these water pollutants also raises concerns regarding potential additive or synergistic interactions among pesticides, as most individuals are exposed to an ensemble of several pesticides. Finally, estimates of pesticide-induced cancers are correlated with the number of cancer cases registered in the same period and show a strong positive correlation with breast cancer consolidated cases for glyphosate and diuron-attributable cases. Additional studies that include other Brazilian states and other agricultural regions with high pesticide concentrations are urgently needed and may strengthen and clarify our findings. Funding: Research in the Lemos lab is supported by grant 5R01ES027981. JC was supported by a Lemann Foundation Fellowship. Carolina Panis was supported by grants from Conselho Nacional de Desemvolvimento Científico e Tecnológico (CNPq Chamada CNPq/MCTI/FNDCT Nº 18/2021 and Chamada CNPq Nº 4/2021 - Bolsas de Produtividade em Pesquisa - PQ) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Professor Visitante no Exterior Júnior - Edital nº 01/2019 - Seleção 2019).

CRediT authorship contribution statement

Carolina Panis: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Luciano Zanetti Pessôa Candiotto:** Resources, Data curation, Methodology, Software, Formal analysis. **Shaiane Carla Gaboardi:** Resources, Data curation, Methodology, Software, Formal analysis. **Susie Gurzenda:** Resources, Data curation, Methodology, Software, Formal analysis. **Jurandir Cruz:** Resources, Data curation, Methodology, Software, Formal analysis. **Marcia Castro:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Supervision. **Bernardo Lemos:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107321.

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