ORIGINAL ARTICLE

Factors Influencing the Presence of Glyphosate in Urine Among Populations in Agro-industrial Areas of Buenos Aires Province, Argentina

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ABSTRACT

Introduction: An increasing number of rural communities are raising concerns about potential health damage from agrochemicals. Understanding the presence of glyphosate in the human body makes it possible to develop, together with local stakeholders, a systemic model that reveals the socio-environmental determinants of health.

Materials and Methods: Participatory Action Research. Three-stage probabilistic sampling (city blocks, houses, family) in French (Partido de 9 de Julio; Buenos Aires Province) for measuring environmental factors and self-reporting of cancer. Analysis of glyphosate in urine by liquid chromatography coupled to tandem mass spectrometry. In-depth interviews with positive cases to determine the exposure pathway. Development of a conceptual model for analyzing systemic complexity.

Results: Out of the total of 46 blocks in French, we included 23 blocks with systematic sampling and, at 76 houses (50%), chose one subject randomly. In 21.8% of the households, there were reports of a history of cancer. In June 2023, 13% of the population (95% CI 6.5-23) showed quantifiable glyphosate in urine. Work exposure was ruled out in all cases, the primary self-reported sources being: "the discharge of agrochemicals in the nearby shed," "the grain silo," "drift," and "the mosquito trucks that pass by the street," variables belonging to economic and cultural determinants. A network of actors emerged, awaiting the socio-political problematization of the results mediated by the Honorable Deliberative Council and NGOs, which would balance the system with forces of care.

Discussion: Study with high external validity. There is a need to computerize community surveillance systems for both the suspicion of exposure and possible diseases related to agrochemicals, create referral circuits for samples to high-complexity laboratories, and design multiple strategies on the determinants to care for possible damages from chronic exposure.

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Conclusion: The presence of glyphosate in urine was due to environmental exposure; it expresses a passive, involuntary, and chronic absorption pathway of chemical pollutants resulting from the town's agricultural activity not counteracted by forces of care.

Key words: epidemiology, environmental health, complexity, glyphosate.

Condicionantes de la presencia de glifosato en orina en poblaciones de zonas agroindustriales de la provincia de Buenos Aires, Argentina

RESUMEN

Introducción: cada vez más comunidades rurales expresan preocupación por posible daño a la salud por los agroquímicos. A partir de conocer la presencia en el cuerpo humano de glifosato es posible confeccionar, junto a los actores locales, un modelo sistémico que evidencie los condicionantes socioambientales de la salud.

Materiales y métodos: Investigación-Acción Participativa. Muestreo probabilístico trietápico (manzanas, casas, familia) de French (Partido de 9 de Julio; Provincia Buenos Aires) para la medición de factores ambientales y autoinforme de enfermedad oncológica. Análisis de glifosato en orina por cromatografía líquida acoplada a espectrometría de masa en tándem. Entrevistas en profundidad a casos positivos para determinar la vía de exposición. Confección de un modelo conceptual para el análisis de la complejidad sistémica.

Resultados: del total de las 46 manzanas de French, 23 manzanas fueron incluidas con muestreo sistemático y en 76 casas (50%) una persona fue seleccionada al azar. En el 21,8% de los hogares refirieron antecedentes de enfermedad oncológica. El 13% de la población (IC 95%: 6,5-23) presentó glifosato cuantificable en orina en junio de 2023. La exposición laboral se descartó en todos los casos, siendo las principales fuentes autorreferidas: "la descarga de agroquímicos en el galpón cercano", "la cerealera", "la deriva" y "los camiones mosquito que pasan por la calle", variables pertenecientes a condicionantes económicos y culturales. Emergió una red de actores, a la espera de la problematización sociopolítica de los resultados mediada por el Honorable Concejo Deliberante (HCD) y las Organizaciones no Gubernamentales (ONG), que equilibren el sistema con fuerzas de cuidado.

Discusión: estudio de alta validez externa. Se requiere informatizar sistemas de vigilancia comunitarios tanto para la sospecha de exposición como de posibles enfermedades relacionadas con agroquímicos; crear circuitos de derivación de muestras a laboratorios de alta complejidad y diseñar estrategias múltiples sobre los condicionantes para cuidar de posibles daños por exposición crónica.

Conclusión: la presencia de glifosato en la orina se debió a exposición ambiental; expresa una vía de absorción pasiva, involuntaria y crónica de contaminantes ambientales que resulta de la actividad agropecuaria de French que no es antagonizada por fuerzas de cuidado.

Palabras clave: epidemiología, salud ambiental, complejidad, glifosato.

INTRODUCTION

Glyphosate (GLY) evolved in the 1970s as an herbicide, designed to inhibit the shikimate pathway, a metabolic pathway of aromatic amino acid synthesis exclusive to plants and bacteria. However, evidence of its effects on non-target organisms, such as humans and other mammals, is increasingly numerous and compelling. Recently, Chang et al.[1] have demonstrated a positive association between exposure to GLY and the presence of urinary biomarkers of oxidative stress in farmers. The induction of oxidative stress could be partially causal for both genotoxicity and the negative impact on the immune, nervous, and endocrine systems of GLY, as evidenced in experimental animal models exposed to this pesticide[2].

However, new mechanisms of action with consequences for humans have been described, which are difficult to attribute solely to GLY using the classical risk mode3. That is because such consequences can manifest without the exposure factor long after it has acted during embryogenesis or window periods[4,5].

In March 2015, the International Agency for Research on Cancer announced that GLY should be considered a probable carcinogen, a classification adopted by the National Cancer Institute in Argentina. Nevertheless, after this resolution, the amount of GLY applied per hectare in Argentina continued to increase, according to the consulted statistics.

Although new evidence has recently been published regarding the adverse effects of GLY on the health of

animals and humans[7-8], and the EFSA (European Food Safety Authority) was compelled to issue a statement extending the recommendation for the use of GLY for ten years, it also pointed out the lack of information necessary to define the safety of GLY, mentioning that the evidence is not sufficient to extend it to the usual 15 years. Therefore, in the face of controversies, a joint approach among regulatory agencies, civil society, and scientists is essential for making informed decisions under uncertainty. Additionally, research is ongoing to demonstrate the mechanism and damage caused by GLY[9-10]. In the recent SPRINT study, which covered 17 countries, the highest environmental and human biological matrix values for these pesticides were also observed in our country. In animals, cumulative toxicity from the daily load of pesticides entering with food has been documented, with synergistic interaction occurring at 'sub-threshold' doses of different pesticides present simultaneously[12].

These studies and the evidence that GLY is an endocrine disruptor[3,13,4], show that very little is known about the co-exposure to multiple pesticides and its long-term impact on reproductive health and human development. The highest level of consensus shows an association between GLY and non-Hodgkin lymphoma in humans[4,14,15].

Another increasingly pressing effect of pesticides is that they contribute to the emergence of multi-resistant bacteria[16]. Recently, the impact of GLY on the microbiome was demonstrated by selecting pathogenic bacteria that survive the minimum inhibitory concentration of beneficial ones[17]. GLY interferes with the production pathway of aromatic amino acids (shikimate pathway), which is also present in human gut bacteria, creating an additional form of harm to human health by affecting the gut microbiota, with ample evidence of our interdependence[18].

For this reason, more and more health professionals are hypothesizing an increase in environmental risks and diseases, which requires confirmation through epidemiological studies: the classical, descriptive, and analytical ones, integrated with new scientific designs that address systemic complexity[19,20], i.e., designs that analyze the forces acting on the kinetic state of the system (dissipative, autopoietic, or rigid), resulting from the tension between them[21]. The development of a systemic conceptual model allows, based on how these forces are expressed in historical, structural, and contextual variables of health determinants, to facilitate decision-making by governments, organized civil society, and individuals[22]. To build the framework, we systematize the available qualitative and quantitative data and investigate the missing data using a Participatory Action Research (in Spanish IAP: *Investigación de Acción Participativa*) design that involves all stakeholders, from the problem formulation to the interpretation of results and the discussion of solutions[23]. Since 2013, the Population Health Research Program (*Programa de Investigación en Salud Poblacional*, PISA) of the Hospital Italiano de Buenos Aires has been investigating environmental risk factors by integrating basic, clinical-epidemiological, and social science research to design public policies [5,24,26]. In June 2022, following the publication of the validation of the method for measuring GLY in urine[24], PISA was approached by researchers from 9 de Julio (Buenos Aires), concerned about the environmental risk in that locality, which prompted this investigation made possible through state funding (Grant Salud Investiga from Ministerio de Salud).

This study is a Participatory Action Research (IAP) that, based on the measurement of GLY in residents of areas adjacent to cultivated surfaces treated with pesticides and related activities, aimed to describe the determinants that influence the presence or absence of GLY in the human body. The purpose of this research is to provide scientific information to the community of French and the Honorable Deliberative Council (HCD, *Honorable Concejo Deliberante*) of 9 de Julio about the implications of the use of GLY in agricultural activities on the human body to facilitate a networked approach to health determinants.

MATERIALS AND METHODS

Design: IAP[23] with methodological triangulation[19]. The study was conducted in the town of French (Latitude: -35.51; Longitude: -61), within the Partido of 9 de Julio, with approximately 750 inhabitants.

We included respondents over 28 years of age present in the household at the survey and reported being residents and having spent the night in the town. We calculated a sample size of 58 cases based on the following parameters: a hypothesis of GLY prevalence in the urine of 20% according to previous experience from a study conducted in the locality of AviaTerai, Chaco province, where we found the presence of GLY in urine in 19.2% of the samples[24], a semi-precision amplitude of 10%, and a confidence level of 95% (OpenEpi® Software). The sample size was increased by 25% to account for a 75% response rate.

We conducted a probabilistic sampling in three stages: 1) simple random sampling of blocks using Google Maps®, 2) systematic sampling of households within the selected blocks, and 3) family/cohabitation group. Thus, we selected 23 blocks out of 46 (50%), recorded the number of households in each block, randomly chose one of the four corners, and visited the first household with residents, moving clockwise. We randomly recruited one person per household from among the cohabitants (using a die) and repeated the procedure until the sample was complete. We conducted the fieldwork over two days and required four groups (each consisting of 2 epidemiologists and a local citizen).

Data Collection: A 20 mL sample of the first morning urine was requested. The samples were divided into two tubes (for creatinine and GLY measurement) and kept on dry ice until their transfer within 24 hours to the laboratory. The housing, sociodemographic, environmental, occupational, and health characteristics

were evaluated using validated questions from the permanent household survey (INDEC, 2014. *Instituto Nacional de Estadística y Censos*) and the atmospheric exposure section of the medical history from the Ministry of Health of the Government of the City of Buenos Aires. The variables were integrated into a RedCap form and collected through telephone interviews. Our perception of environmental health came from in-depth interviews with positive cases and from dialogic devices of social encounters.

Analysis: The analysis of GLY in urine was conducted following the validated technique of liquid chromatography coupled with tandem mass spectrometry[24], reported in µmol/mol of creatinine in urine for quantification values greater than 0.5 µg/L.

STATA_v13® was used for statistical analysis. The results are presented as mean and standard deviation, median and interquartile range (25-75), or as percentage and 95% confidence interval (CI 95%), as appropriate. A p-value of less than 0.05 was considered statistically significant. Positive cases and reported environmental risk activities were geo-referenced. We analyzed the dimensions of the health determinants of Atlas-ti v23® and charted based on Pérodeau's model during stages of discussion/consensus of the collected qualitative and quantitative data[22].

We requested the signature of the informed consent form under the health research law of the province of Buenos Aires (Act 11044). The protocol was approved by the Ethics Committee of the Ministry of Health of the Province of Buenos Aires, ACTA2022-32658194-GDEBA-CECMSALGP; PRIISA 8103, and was conducted under the guidelines of the Declaration of Helsinki.

RESULTS

From the IAP Process: Three field trips were conducted:

1. March 2023: We held an in-person meeting with the mayor and the team from the Municipality of 9 de Julio. We decided to conduct the research in the locality of French. A mixed research team (MRT) was formed, including local actors and researchers from the involved institutions. We agreed on actions to determine the sampling framework, local dissemination, and field planning through a Problem-Based Participatory Management (PBPM) device validated in hospital management[27].

2. June 2023: Samples were collected. During an open meeting at the Senior Citizens' Center, attended by 50 people (ordinary citizens, Guardians of Ecology, the Italian Society, the Grandparents' Home, the Senior Citizens' Center, and journalists), various sources of environmental risk were discussed. Subsequently, the HCD officially requested the results, and the media raised the issue as a social concern. Both instances contributed to advancing the issue on the political decision-making agenda.

3. December 2023: The results were delivered to the HCD and presented in person to the participants, thanks to the dissemination and preparation of the Senior Citizens' Center by the local MRT.

Socio-demographic Profile

Of the total 46 blocks, we selected 23 (50%), a percentage that was maintained in the "houses" stratum (out of 152 existing houses in the 46 blocks, 76 houses belonging to the 23 blocks were selected).

All 76 selected individuals provided a urine sample (100%); the average age was 56.6 (16.2) years, with 67% women; 59 people (77.6%) completed the survey.

The socio-demographic profile and risk factors are shown in Table 1, with no significant differences by age and sex. Approximately half are employed, and the other half are retired. Some 21.8% of the households reported a history of oncologic disease, either in the surveyed individual or a cohabitant; 41.38% were covered by PAMI, and 28.8% perceived their health as fair or poor.

Glyphosate in Urine

13% (95% CI: 6.5-23) of the samples were quantifiable for GLY (median of 0.27 µmol/mol of creatinine; interquartile range 25-75: 0.22-0.36; minimum 0.18 and maximum 3.26) (Figures 1 and 2). Occupational exposure was dismissed in all cases. The occupations of those who tested positive included driver, textile worker, cook, office worker, and homemaker.

Georeferencing

Figure 3 shows the blocks included in the sample and the blocks with positive results. Three individuals who tested positive live near the school: on the same block, on a side block, and at an opposite corner.

The person with the highest value lives less than 50 meters from the agrochemical shed belonging to a grain company and 80 meters from the school. The value is nearly three standard deviations from the average of the results.

Self-perception of the Mode of Contamination

The interviews revealed a self-perception of the mode of environmental contamination, identifying specific sources of agrochemical exposure within the urban radius: storage of seeds in silos, grain companies, and agrochemical sheds.

Across the tracks, there is a shed where they keep the chemicals. We had to ask that company to please close the gate and put something up because we cannot even breathe inside the room. (Positive Patient 1).

I have a grain company one block away [...]. Every time a truck unloads, it releases a whole cloud of contaminated dust from the grain. (Positive Patient 2).

There seems to be a sense of resignation to enduring frequent smells of chemicals, dust, and others related to the agricultural activities of the town:

No, not every once in a while, you can smell it often, early in the morning; if they spray, the wind brings it, at night too, in the evening; there's also a lot of pig smell from the pig farm. (Citizen 12).

The mosquito trucks drive through the town, and the mechanic workshops are inside the village:

Table 1. Sociodemographic profile and classic risk factors of respondents in French. Year 2023

Feature	Categories	Indicator
What is/are your current occupation(s)? N (%)*		
*6 of the respondents have 2 occupations.		
2 respondents have 3 occupations		
	Work without salary (e.g., housewife	8 (13.6%)
	Studying	2 (3.4%)
	Retired	26 (44.1%)
	Pensioned	1 (1.7%)
	Unemployed (not working, but looking	2 (3.4%)
	for a job or would like to work)	
Time of residence in French, in years (standard deviation)		47.2 (23.7)
Self-perception of health, N (%)		5 (8.5%)
	Excellent	9 (15.2%)
	Good	28 (47.5%)
	Fair	15 (25.4%)
	Poor	2 (3.4%)
Health coverage, N (%)	Prepaid	5 (8.6%)
	Social Security	19 (32.8%)
	PAMI	24 (41.4%)
	Attended in the public system	10 (17.2%)
Smoking history, N (%)		30 (51.7%)
Current smoking, N (%)		15 (25.4%)
Weight, mean (standard deviation)		80.2 (14.5)
Height, mean (standard deviation)		1.66 (0.1)
Diabetes, N (%)		4 (6.8%)
Hypertension, N (%)		23 (39%)
Oncologic disease, N (%)		4 (6.8%)

They pass by here, all the "Mosquito trucks" right in front of my house (Mosquito

truck is a type of vehicle transporter truck, named after the old Argentine company El Mosquito S.A.). (Positive Patient 3).

However, since none of the individuals whose urine samples tested positive reported being specifically exposed to GLY or other pesticides, it is possible to argue that they are unaware of the specific circumstances of their own exposure. This suggests that the exposure is environmental rather than occupational, making it unfeasible to design preventive measures at the individual level, such as good practices for the use or handling of agrochemicals.

There is evidence of passive adaptation and helplessness in the face of environmental exposure:

"*This summer was so hot, for example, that you would open the windows in the evening. And I don't know about the chemicals or anything but the smell was so strong. It would come into the house, and you had to close the windows again*." (Citizen 6).

"*There are clandestine night-time sprayings, and if you call the police, they don't come*." (Senior Citizens' Center).

"*If we continue like this, the land will become sand dunes*." (Citizen 8)

Systemic Determinants of Health

The systemic model (Fig. 4) revealed structural and contextual variables that highlight a historical tension of systemic forces operating on French with minimal expression of care forces.

On the structural level:

A. The arsenic reduction plant does not undergo regular inspections. According to the UTNFTR laboratory report conducted by a private individual in 2021, the water is not fit for consumption (exceeding the accepted limit by seven times).

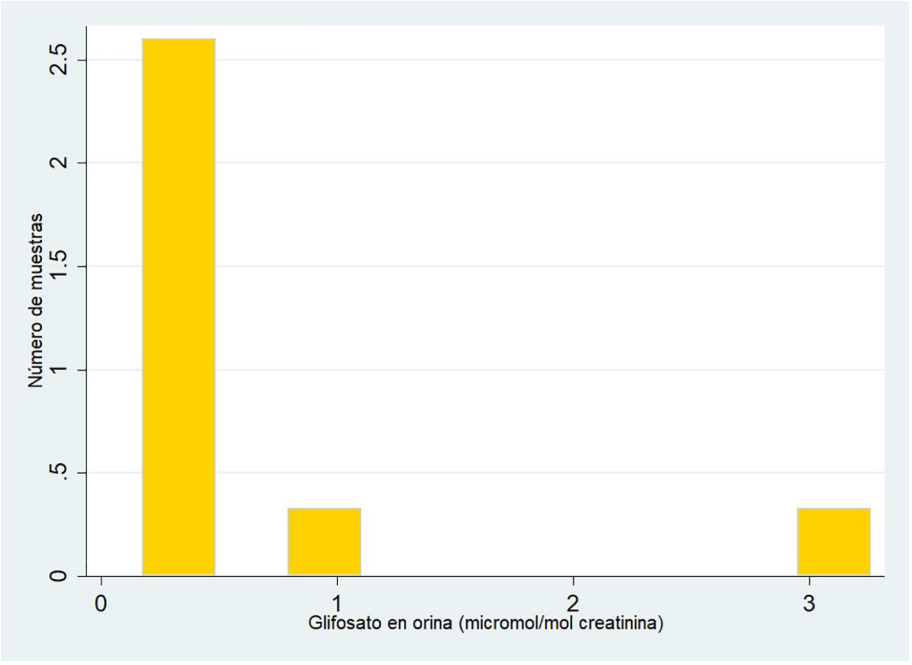

Figure 1. Distribution of glyphosate in urine among quantifiable samples (n=10). Town of French, Municipality of 9 de Julio, Buenos Aires Province, Argentina. Year 2023.

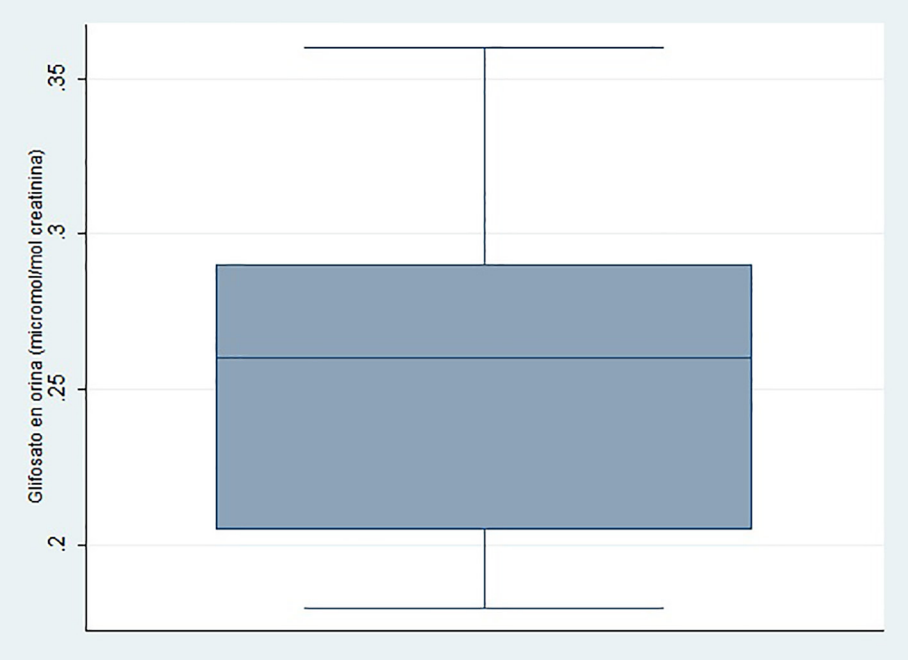

Figure 2. Box Plot of glyphosate values in urine in quantifiable samples (n 8, no extreme values) in the town of French, Municipality of 9 de Julio, Buenos Aires Province.

Figure 3. Systemic model of structural, contextual, and cultural determinants that directly or indirectly influence environmental contamination affecting people living in French.

B. It is observed and reported that the city falls behind in infrastructure planning. The city does not have public transportation. The train station is not active despite complaints.

C. The healthcare infrastructure, a health center, fails to cope with the needs of an aging population. There was no mention of preventive actions by the health system to address the socio-environmental issues that affect health.

D. The insufficient regulation of the productive model is reflected in existing laws due to their lack of effective implementation. An example of this is Provincial Law 10669, which prohibits the application of products without a mandatory agronomic prescription. According to the Chamber of Agricultural Health and Fertilizers (CASAFE), this provision is met in only 20% of cases[28].

At the contextual level:

E. The "culture of limited regulation and control" is also evident in the presence of storage facilities, grain silos, pig farms without waste treatment, and an open-air landfill within or adjacent to the town limits.

F. The care for environmental health is driven, in part, by the local school, young people, and new residents who promote culinary developments and rural tourism.

DISCUSSION

The population design of the study suggests that the implications of agricultural activity on the human body show up in 13% of the population of French through the presence of GLY in urine. Of the approximately 750 inhabitants residing in that town, 100 could have GLY

due to environmental exposure on days similar to the study's. We believe that the representativeness achieved by probabilistic sampling is a strength of the survey and allows the generalization of the results to other similar populations.

Thus, a person living in similar rural towns would have a 13% probability of having GLY in their urine (this includes 43 rural towns with a total of approximately 45,000 inhabitants, counting the 9 de Julio district and its six neighboring towns.)

Qualitative results suggest that the data obtained in June (considered the low spraying season) are due to environmental rather than occupational exposure. GLY gets eliminated from the body within 48-72 hours; this means that if the sampling were repeated on the same population a few days later, and the exposure conditions remained the same, a person who tested positive in the first sampling might test negative in a new one, and vice versa; the percentage of positives could range between 6.5% and 23%. We consider it necessary to conduct a new investigation during the high season (October or November), as environmental and occupational conditions could differ.

It is important to note that in the current scientific debate, focusing the analysis on the levels found in urine is questioned, as there may not be an "acceptable normal level" given the evidence of delayed epigenetic effects and endocrine disruption in the offspring of laboratory animals. This evidence is not ethically documented in humans because it would require a long-term longitudinal study with a similar non-exposed comparison group. Since it is an environmental factor, the entire population is at risk of exposure at some point, making it impossible to have a control group.

Although the reductionist conception of risk based on dose-response curves has been the subject of debate, we share that in 8 studies, urine sample values in occupationally exposed individuals ranged between 1.54 and 434.73 nmol/L, and in 14 studies of different matrices of the general population, between 1.54 and 44.95 nmol/L. Our results are shown in mmol/mol of creatinine (relative to a renal variable); however, for comparative purposes, when expressed in nmol/L and without normalization by the creatinine value, the mean is 5.7 (SD 5.3), within the range mentioned in other studies.

The georeferencing indicated that the positive cases are near the school; since children are more vulnerable to potential epigenetic and endocrine-disrupting effects, we suggest measuring a sample of students. Twenty-two percent of households reported a cohabitant with

Figure 4. Georeferencing of sampled blocks and blocks with individuals who tested positive for glyphosate. Streets with mosquito truck traffic and the location of silos and grain storage facilities in the town of French, Municipality of 9 de Julio, Buenos Aires Province, Argentina.

cancer in a population with an average age of 60 years, indicating high demands for care and attention (diagnosis, treatment, care networks, etc.).

Although there are highly complex laboratories that perform pesticide measurements, the referral circuits for acute poisoning or monitoring of exposure, whether environmental or occupational, are not standardized by the health system. To initiate the circuit, we propose digitizing community surveillance systems (such as reporting through apps) for both suspected exposure and possible agrochemical-related diseases. Both improvements would require state funding.

The community's appropriation of the research results, their dissemination, the contribution to the legislative treatment of a municipal ordinance, and the design of a page for the visibility of the participatory construction of future actions (www.saludfrench. com. ar) are considered results for the approach to complexity, as network strategies deployed, from the point of view of the inhabitants, thanks to IAP (*Investigación Acción Participativa*[23]) devices with PBPM methodologies.

From a systems theory perspective, the presence of a substance in urine, which was used only in the agricultural activities of the town, indicates that a higher level of organization within the system (economic interactions) influences an earlier evolutionary level of the system (biological interactions). For the system to evolve without detriment to its parts or levels, the forces must be balanced [20,21]. In the systemic model shown in Figure 2, we observe that the interrelation of variables at different levels allows us to consider that the dissipative forces of the system—those that eventually lead to its disappearance—would be influenced by the production model and not counterbalanced by care forces "through regulations, whether cultural-community-based or state normative[20]". According to Teeple[29], the evolution of "capital forces that generate capital" led to an uneven and dystopian development of the system because certain parts (corporations) grew, generating entropy at that level, which uses the energy of the other parts of the system. The reproduction of these forces in daily human interactions is the very thing that would lead to greater global social inequality and environmental harm[29].

By combining the perspectives of different actors, on the one hand, the transformative potential of joint actions was observed in obtaining cross-cutting responses to complex health problems (bottom-up associative force), and on the other hand, the attempt to avoid reproducing that force that seems to be gradually hindering, isolating, and extinguishing the vital organization of the city, influenced by global levels that pursue only productive interests (top-down dissipative forces). However, it is also evident that collaboration between scientific institutions, government agencies, civil society organizations, and the community (middle-out forces of institutionalized democratic processes) presents a challenge for promoting significant and sustainable changes in the town's health. System care actions, which if strengthened, could balance it.

In conclusion, in the systemic approach, the butterfly effect has a mathematical demonstration of how small changes in one part of the system can generate global modifications in the whole[30]. We consider that this research contributes to the salutogenic direction through reflection on the generative power of biocentric forces. In the words of a citizen of French: *We are surprised that we can achieve something like this in our town, surprised that someone cares about us. At the same time, it moves me that this small thing could be the beginning of something more.*

CONCLUSION

During periods of low fumigation, in rural populations with similar characteristics to the town of French there are people with GLY in their urine. This finding is a marker of the effect of French agricultural activity on the human body and responds to forces within the system that lead to the passive, involuntary, and chronic absorption of environmental chemicals, with little counteraction from cultural-community or state care forces. Since exposure to the environment has a global impact, individual care is insufficient unless the person relocates from that city.

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