CRITIQUE OF "WAITING TO DIE", A REPORT ISSUED BY THE UNIVERSITY NETWORK FOR HUMAN RIGHTS

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1. Summary

On July 24, 2019, the University Network for Human Rights (UNHR) released via its website a document entitled "*Waiting to Die:* Toxic Emissions and Disease Near the Louisiana Denka/DuPont Plant."[2] This document (the "UNHR Report" or the "Report") describes an analysis that compares prevalence of cancer and other health outcomes in a sample of residents living in a 2.5 km radius surrounding the Denka plant in St. John the Baptist Parish, Louisiana to estimated prevalence developed using a simulation based on US national cancer data from the SEER program[3]. The UNHR Report, however, does not include sufficient details to complete a comprehensive evaluation of the study design and its conduct. The details that are provided in the UNHR Report suggest that the simulation methods used in the Report were non-standard and applied incorrectly. Moreover, elements of the UNHR Report's study design suggest biases, especially selection and information bias, which may have influenced the results of the Report. Given the lack of critical details and apparent errors in research methods, it is unlikely the Report would be accepted for publication in a scientific journal in its current form. Accordingly, little scientific weight should be attached to the UNHR Report.

2. Introduction

Generally accepted "best practices" for conducting epidemiological research include use of a study protocol that documents all aspects of study design and execution. This protocol should be referenced and summarized in the "Methods" section of any report documenting the study. It should include the specific text of questionnaires and planned communications between the researchers and participants, the sampling plan and its rationale, power or sample size calculations to justify the number of people included and to support the planned statistical analyses, and a full description of the statistical analysis plan. The protocol should also document all methods used to validate the data collection methods used, along with results of the validation. The UNHR Report does not indicate that the researchers prepared and followed a protocol or enrolled participants according to a pre-defined sampling plan, nor does it specify how or why they chose to include 250 households per zone. The Report does not describe whether the sizes and boundaries of the zones included in the study area were selected to be representative of a specific population, were selected for convenience, or for some other reason. There is no information provided in the Report regarding the development, testing, and possible revisions to the questionnaires, and there is no information in the Report regarding validation of self-reported medical data, e.g., against physician reports or review of medical records.

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[2] https://www.humanrightsnetwork.org/.

[3] The Surveillance, Epidemiology, and End Results (SEER) program collects and publishes data on cancer incidence and survival from population registries in the United States. The program is supported by the Surveillance Research Program in the Division of Cancer Control and Population Sciences of the National Cancer Institute. More information is available at the program website: https://seer.cancer.gov/about/overview.html.

The missing and incomplete information about the study methods make it difficult to fully evaluate the validity of the results. The information that is provided suggests that errors in the design, execution, and analysis of the study may have influenced the results. Key features of the study design and analysis are discussed in further detail, below.

The limited information that is provided in the UNHR Report to describe the design and execution of the project suggests several sources of error.

Selection bias might have influenced the results of the UNHR Report. Selection bias occurs when factors that influence participation are also associated with either the exposure (in this case, residential area in one of the two study zones was implicitly defined as a surrogate for exposure) or the outcome under study, such that an artificial difference between study groups is introduced into the data. Indications of potential selection bias in the UNHR report are as follows:

- 50% of the targeted homes in zone 1 provided responders, compared with 20% in zone 2. This indicates different levels of interest by residents in the two zones, which might be due to the recruitment strategies or the ways in which the study was presented in the informational flyers or in verbal communications with potential respondents. Any of these factors could have resulted in a higher actual or reported proportion of people with illnesses, including cancers, participating from zone 1 compared with zone 2.
- Homes were visited between the hours of 9 am and 7 pm. In community-based studies, good research methods indicate contact should be attempted at a variety of times during the day and during both weekdays and weekends, in order to enroll both employed and unemployed persons. Those who are employed are more likely to be healthy and less likely to be at home during business hours than unemployed persons. The survey strategy described in the report is likely to have resulted in a group of respondents that is less healthy than the general population of the targeted areas.
- Gender, race, age, and their correlates, are all potentially associated with risks for various diseases and correlates of disease risks, including the diseases that were discussed in this report.
    - No information is provided about the distribution of respondents according to gender or age.
    - Respondents from the two zones differed with respect to race:
        - Zone 1 respondents were more likely to be Black than zone 2 respondents (93.2% vs. 68%), and less likely to be White (4.9% vs. 26.6%) or other/unknown race/ethnicity (1.9% vs. 5.4%).
        - This demonstrates that the respondents from the two zones differ in health-relevant ways that should be accounted for in the analysis. This will be discussed in greater detail later in this critique. No information about other potential causes or correlates of the diseases of interest were provided, however, so the extent to which this potential selection bias may have influenced the results cannot be determined.

Information bias might have influenced the results presented in the UNHR Report. Information bias occurs when the quantity or quality of the information collected differs systematically for participants in one group compared with another. Because the survey takers visited each home, they could not have been blinded as to the zone in which they were collecting data and might have interacted with respondents differently according to zone, based on their own conscious or unconscious expectations. For example, the survey takers might have probed more completely for health-related information when working with respondents in zone 1 than in zone 2. If this occurred, the respondents in zone 1 would seem to have

more health problems than the respondents in zone 2, purely because of the manner in which information was elicited.

Misclassification of the outcome might have influenced the results presented in the UNHR report. Misclassification might have occurred either as a result of the information bias, described above, or due to reporting errors. Reporting errors can occur if respondents did not understand the survey questions accurately. This is common in survey research and is more likely to occur if questionnaires are not pretested adequately. Good research practice indicates that survey questions should be pretested, that at least a sample of the data collected should be validated against some other source of information, and that the direction and likely magnitude of any bias should be evaluated. The UNHR report did not describe any data validation efforts and did not discuss the potential effects of bias on the reported results.

3. Cancers

The UNHR report described the use of “validated questionnaires” to collect information from survey respondents. The source of the questionnaire language and the steps taken to validate the questionnaires are not described. Respondents reported on their own health status, and the health status of their household members. There is no description of attempts to validate survey responses against, e.g., medical records or physician reports.

The UNHR Report attempts to compare expected cancer prevalence in the two zones with cancer prevalence derived from the respondents’ seemingly unverified self-reported diagnoses. The expected prevalence of cancer was estimated from a simulation.

There are several conceptual errors in their approach:

- “Cancer” is a term that encompasses many different diseases. The scientific and medical communities recognize that different types of cancers develop due to different biological mechanisms and have different risk factors.
- Using current residential area as a surrogate for exposure requires the assumption that all survey respondents and their household members have lived in the same zone for decades. This is because cancers have a long latency interval between exposure and disease onset. For solid tumors, the latency interval is generally 20-30 years. It also requires the assumptions that residential area is associated with some carcinogenic exposure, and that exposure is the same for all residents in the area.
- Certain chemical exposures have been demonstrated to cause some cancers, but no chemical causes all cancers. The UNHR report contends that the cancers reported by respondents are all due to chloroprene exposure.
- Very small sample sizes in the zones, especially within gender, age category and racial strata, result in unstable and unreliable cancer prevalence estimates.
- Using self-reports and surrogate reports for household members may introduce error into the identification of cases. If misclassification occurred and was different for zone 1 and zone 2 respondents, the results of the analysis would be biased (see above).
- No other risk factors, apart from age, sex, race, and residential zone, were discussed in the Report.

Errors in the quantitative analysis might have produced the results in the UNHR Report. Instead of comparing the cancer prevalence estimated by the respondents’ self-reports with published cancer

prevalence for the region or the state (which could be problematic due to issues with study design and execution as described above), the authors described simulations that they called “Monte Carlo simulations” to estimate the expected cancer prevalence in the two zones. They did this incorrectly. Monte Carlo methods are algorithms that use repeated random sampling to estimate results that cannot be obtained otherwise. Monte Carlo methods can be used to estimate probabilities of uncertain events by generating representative values from the appropriate probability distribution. The authors did not use Monte Carlo methods in that they did not estimate the probability of an event by sampling from an underlying probability distribution. In fact, the probability of the event (cancer) was known *a priori* from SEER data.

Instead, the authors created a hypothetical population using the gender-, age- and race-distribution of the survey respondents by creating, for each survey respondent, a hypothetical population member of the same gender, age and race. They then obtained published 23-year cancer prevalence data for the entire US, grouped by gender, age and race, from SEER. They applied these 23-year national prevalence values to the hypothetical local population such that each member of the hypothetical population was randomly assigned a value of 0 (no cancer) or a value of 1 (cancer) based on the published gender-, age- and race-specific national probability of having had cancer in the past 23 years; this was repeated 10,000 times. The authors provided the following example:

> “For example: According to SEER data, 23-year cancer prevalence among Black men between the ages of 60 and 69 is about 12.8%. In our simulated population, every Black male in his 60s was randomly assigned a value of 1 with probability p = 12.8% (otherwise, a value of 0 with probability 1-p = 87.2%). […] The process was then repeated 9,999 times to generate a total of 10,000 simulations.”

There are several problems with this approach:

- The national data from SEER might not be applicable to the small geographic areas defined by zone 1 and zone 2 included in the study. Cancer rates may differ between the study areas and the US as a whole for many reasons. The Report did not indicate that such differences were evaluated. If such differences exist, then comparisons between local cancer prevalence and prevalence reported at the national level are likely to be incorrect due to confounding.
- Applying the group prevalence to individuals and summing over individuals is not the same as applying group prevalence to a group. Based on the description of the simulation provided in the Report, individuals in the simulated population were randomly classified as cancer cases or non-cases repeatedly (10,000 iterations), based on the SEER cancer prevalence. This resulted in 10,000 versions of the simulated population with a different cancer prevalence (potentially ranging from 0% to 100%) possible in each version. For example, if the approach described in the Report were used for a published cancer prevalence of 10%, one of the 10,000 simulated populations may have a 0% cancer prevalence, a second simulated population may have a 20% cancer prevalence, a third simulated population may have a 60% cancer prevalence, a fourth simulated population may have a 10% cancer prevalence etc. Therefore, the approach described in the Report allows for an unrealistic range of prevalences in the simulated population and is invalid. It is important to notice that the cancer prevalence is approximately equal to the published prevalence (10% in the example above) only when averaged over all 10,000 simulated populations.
- Creating 10,000 versions of the simulated population with (i) an *average* cancer prevalence over all 10,000 versions equal to the published SEER prevalence, but (ii) different cancer prevalences possible in different versions of the simulated population, may result in an artificially low median prevalence. This can be explained as follows: If the prevalence in one simulated population is

higher than the published prevalence, then the prevalence in one or more other versions of the simulated population must be lower than the published prevalence (such that, when averaged over all 10,000 versions of the simulated population, the prevalence is equal to the published value). For example, say the published prevalence is 10%. If one of the 10,000 simulated populations has a prevalence of 60%, then *several* other simulated populations must have prevalences of less than 10% so that the average prevalence remains at 10%. As a result, high prevalences in a *few* of the 10,000 simulated populations force prevalences of less than 10% in *many* of the simulated populations. This results in the overall distribution of prevalence estimates being shifted lower. If prevalences less than the published value occur in 50% or more of the simulated populations, then the median prevalence over all versions is artificially low.

It can be shown that the entire difference between the prevalence among survey respondents and the median prevalence estimated for the hypothetical population shown in Figure 1.1 of the Report might be explained by the flawed simulation.

Furthermore, the reason for carrying out this simulation is not clear. The Louisiana Tumor Registry has published a report that summarizes actual cancer incidence and prevalence rates for St. John the Baptist parish and supplies data that allow direct comparisons between actual cancer risks for residents of the parish and risks for residents of the region and the state, as a whole. Using actual data means no estimation is required. Using the region and the state for comparison with the study regions is more appropriate than using data for the US as a whole, as discussed above. The comparisons supported by the Tumor Registry are more meaningful and reliable than comparisons between a simulated population and a group of volunteer respondents, as was provided in the UNHR report.

The authors repeated this type of simulation for subgroups of the respondents defined by reported smoking status and for households instead of individuals, and the same conceptual and methodological issues apply. Note that for the household analysis, the authors seem to have assigned the same value of age, sex, and race to all members of the household. If so, this would add further inaccuracy into the results.

In addition to cancers, the survey respondents were questioned about a collection of non-specific symptoms and signs, with the implicit assumption that residential area in zone 1 or zone 2 provides a valid surrogate measure of some exposure that is relevant to the risk of these symptoms and signs.

4. Child health

For child health, respondents were asked to report on the occurrence of headaches and nosebleeds among children in the household.

Headaches and nosebleeds are non-specific, i.e., each may have many causes and neither represents a definitive sign of disease or ill-effects due to any one exposure. The questions used to obtain information from the respondents about the children’s conditions, including any definitions or explanations, were not provided in the report. As noted above, the respondents’ reports do not appear to have been verified in any way, e.g., by contacting the children’s physicians.

There are three overarching issues with this analysis:

- Errors due to misclassification of the children (see Introduction, above) might influence the results but cannot be evaluated from the information provided in the report.
- Selection bias or information bias, as described in the Introduction, might explain the differences in reported numbers of children in the two zones with these conditions, completely or in part.
- The differences were not assessed statistically.

5. Symptoms in adults

Respondents were asked to report on a collection of non-specific signs and symptoms.

- All the symptoms are non-specific and can be the result of many individual causes or groups of causes.
- The questions used to obtain information from the respondents about themselves and members of their households, including any definitions or explanations provided to the respondents, were not provided in the report.
- There is no information in the Report to indicate respondents’ self-reports were verified in any way, e.g., by contacting physicians or reviewing medical records.

Tachycardia was defined in the UNHR Report based on number of pulse beats per minute. The UNHR Report does not describe methods used to count pulse beats among the respondents. If pulses were counted by the survey takers, an appropriately conducted study would include standardized procedures to obtain valid counts, including timed rests for the respondents prior to having their pulses counted. The UNHR Report does not indicate whether the presence or absence of tachycardia was verified, e.g., through information obtained from respondents’ physicians.

There are several overarching issues with the analysis of tachycardia:

- Misclassification errors could occur, if tachycardia was inaccurately self-reported.
- Misclassification could occur due to measurement error, if pulse rates were counted by the survey takers without due care.
- Misclassification could occur due to measurement error, if pulse rates were counted by the survey takers under inappropriate conditions (e.g., without timed rests).
- Selection bias or information bias, as described in the first section of this critique, might explain the differences in reported numbers of respondents in the two zones with tachycardia, completely or in part.
- The authors used the same simulation method described for cancer outcomes in their assessment of the prevalence of tachycardia in zone 1 and zone 2 respondents. The same errors apply to these analyses as to the analysis of cancers.

The UNHR Report reported on prevalence of a variety of symptoms in adult respondents, specifically: chest pain/palpitations; wheezing and difficulty breathing; headaches, dizziness, and lightheadedness; eye pain/irritation and watery eyes; cough, sneezing, and sore/hoarse throat; skin rash/irritation and itchy skin; and fatigue/lethargy.

All of these symptoms are non-specific and can be the result of many individual causes or groups of causes. The questions used to obtain information from the respondents, including any definitions or explanations provided to the respondents, were not provided in the UNHR Report. The respondents’ responses do not appear to have been verified, e.g., by contacting physicians.

The UNHR Report compared the proportions of respondents in zone 1 and zone 2 who reported these symptoms, as they did for headaches and nosebleeds reported in children.

There are three overarching issues with this analysis:

- Errors due to misclassification (see Introduction) might influence the results but cannot be evaluated from the information provided in the report.
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- Selection bias or information bias, as described in the Introduction, above, might explain the differences in reported numbers of respondents in the two zones with these conditions, completely or in part.
- The differences were not assessed statistically.

6. Perceptions and concerns

Respondents were also asked about perceptions of chemical odors and concern about pollution. The UNHR Report compared the proportions of respondents in zone 1 and zone 2 who reported perceiving chemical odors inside and outside of their homes, and the proportions who reported feeling concerned about air pollution using the same methods they employed for the analysis of symptoms, above.

There are three overarching issues with this analysis:

- Errors due to misclassification (see Introduction) might influence the results but cannot be evaluated from the information provided in the report.
- Selection bias or information bias, as described in the Introduction, above, might explain the differences in reported numbers of respondents in the two zones with these conditions, completely or in part.

  The differences were not assessed statistically.

7. Conclusions

The UNHR Report does not include sufficient details to complete a comprehensive evaluation of the study design and its conduct. The information that is included suggests biases, especially selection and information biases, may have influenced the results. The details that are provided in the UNHR Report suggest that the simulation methods used for some of the analyses were non-standard and applied incorrectly, and errors might explain the results presented in the Report.