“Good Epidemiology Practice” Guidelines for Pesticide Exposure Assessment

Julie E. Goodman 1,*, Robyn L. Prueitt 2, Paolo Boffetta 3,4, Crispin Halsall 5 and Andrew Sweetman 5

1 Gradient, One Beacon Street, 17th Floor, Boston, MA 02108, USA
2 Gradient, 600 Stewart Street, Suite 1900, Seattle, WA 98101, USA; rprueitt@gradientcorp.com
3 Stony Brook Cancer Center, Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY 11794, USA; paolo.boffetta@gmail.com
4 Department of Medical and Surgical Sciences, University of Bologna, 40126 Bologna, Italy
5 Lancaster Environment Center, Lancaster University, Lancaster LA1 4YQ, UK; c.halsall@lancaster.ac.uk (C.H.); a.sweetman@lancaster.ac.uk (A.S.)

* Correspondence: jgoodman@gradientcorp.com; Tel.: +1-617-395-5525

Received: 21 May 2020; Accepted: 9 July 2020; Published: 15 July 2020

Abstract: Both toxicology and epidemiology are used to inform hazard and risk assessment in regulatory settings, particularly for pesticides. While toxicology studies involve controlled, quantifiable exposures that are often administered according to standardized protocols, estimating exposure in observational epidemiology studies is challenging, and there is no established guidance for doing so. However, there are several frameworks for evaluating the quality of published epidemiology studies. We previously developed a preliminary list of methodology and reporting standards for epidemiology studies, called Good Epidemiology Practice (GEP) guidelines, based on a critical review of standardized toxicology protocols and available frameworks for evaluating epidemiology study quality. We determined that exposure characterization is one of the most critical areas for which standards are needed. Here, we propose GEP guidelines for pesticide exposure assessment based on the source of exposure data (i.e., biomonitoring and environmental samples, questionnaire/interview/expert record review, and dietary exposures based on measurements of residues in food and food consumption). It is expected that these GEP guidelines will facilitate the conduct of higher-quality epidemiology studies that can be used as a basis for more scientifically sound regulatory risk assessment and policy making.

Keywords: epidemiology; methodology; exposure assessment; pesticides

1. Introduction

Good Laboratory Practice (GLP) guidelines are a set of principles for the planning, performance, monitoring, recording, reporting, and archiving of non-clinical laboratory studies. The intention of GLP guidelines is to ensure the quality, reliability, and integrity of scientific research. The United States Environmental Protection Agency (US EPA) monitors compliance with GLP guidelines for all test data submitted to the Agency in support of pesticide product registration, as required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) [1].

While there are several frameworks for assessing epidemiology studies (e.g., LaKind et al. [2], NTP [3], von Elm et al. [4]), unlike toxicology studies, there are no universal standards like GLP for developing epidemiology study protocols. This is disconcerting because epidemiology evidence has recently factored more prominently in regulatory hazard and risk assessments of pesticides and other chemicals [5,6].
Epidemiology studies are generally observational in nature, and there are several epidemiology study designs. For example, in case-control studies, individuals with (cases) and without (controls), a specific disease are identified, and then exposure is measured or estimated in each person [7]. In cohort studies, a cohort, or group of individuals who share a common characteristic (e.g., place of residence or occupation), is followed over time, and individual exposures and diseases are documented [8,9]. In cross-sectional studies, individual exposure and disease status are ascertained together at one point in time or over a short, defined period [8,9].

Observational epidemiology studies of pesticide exposures can be useful for generating new hypotheses, but many studies are not informative for inferring causation between pesticide exposures and potential diseases or other health effects due to various critical methodological limitations. For example, the lack of temporality (i.e., exposures are not measured or estimated prior to the outcome) in cross-sectional studies means that these studies cannot inform causation. Another example is that in case-control studies, recall bias can have a substantial impact on exposure assessment and can sometimes lead to spurious associations. To assess causation, any epidemiology study investigating health effects or diseases associated with a particular exposure should test one or more biologically plausible hypothesis and should define a priori outcomes that are consistent with the evaluated hypothesis. In addition, epidemiology studies must be of sufficient quality to inform causal determination and quantitative risk assessment, two key elements in pesticide regulations [10]. For causal determinations, studies need to establish the presence of an effect following an exposure. For quantitative risk assessment (dose-response analysis), studies need to not only establish the presence of an effect, but also the magnitude of an effect in relation to the level of the exposure.

There have been various efforts in recent years to develop “Good Epidemiology Practice” (GEP) guidelines for improving the quality of epidemiology research [11–13] and protocols to aid in specific aspects of pesticide exposure and risk assessment [14–16], but GEP guidance for pesticide research is not available. We developed a preliminary list of considerations for GEP for environmental epidemiology studies; these are based on various study quality guidelines and frameworks (Table 1). Some of these considerations are applicable to all study designs, while others are tailored to certain designs. Of the considerations in this list, we determined that exposure characterization is one of the most critical areas for which standards are needed in epidemiology studies of pesticide exposure. As such, while the goal is to eventually develop a larger, complete set of GEP guidelines for all phases of the design, conduct, and reporting of epidemiology studies of pesticides, this paper is specific to detailed guidance for exposure characterization.

Table 1. Requirements for Conducting High-Quality Epidemiology Studies.

| Category                        | # | Requirement                                      |
|---------------------------------|---|--------------------------------------------------|
| Objectives and Study Plans      | 1 | Clearly state study objectives                    |
|                                 | 2 | Review ethical guidelines for human research      |
|                                 | 3 | Create and follow an a priori study protocol      |
|                                 | 4 | Write and follow a Standard Operating Procedure (SOP) |
|                                 | 5 | Write and follow a quality assurance plan         |
|                                 | 6 | Describe all deviations from study protocol       |
|                                 | 7 | Provide dates of study initiation and completion  |
|                                 | 8 | Document roles and responsibilities of all staff  |
| Study Design                    | 1 | Report study design and setting (e.g., date, location) |
|                                 | 2a| Document participant selection process and participant inclusion/exclusion criteria |
|                                 | 2b| Use consistent participant recruitment methods to ensure that baseline differences between groups are minimized |
|                                 | 3 | Report participant characteristics (e.g., age, sex) |
|                                 | 4a| Report study size                                |
Table 1. Cont.

| Category                   | #  | Requirement                                                                 |
|----------------------------|----|-----------------------------------------------------------------------------|
| Exposure Characterization  |    |                                                                             |
| 4b                         | Use a sufficient study size so that estimates are not subject to a large     |
|                            |    | degree of imprecision                                                       |
| 4c                         | Conduct and report study power analysis                                     |
| 5                          | Blind outcome assessors to exposure status                                   |
| 6a                         | Report participation rate/attrition                                          |
| 6b                         | Maintain similar attrition rate across groups                                |
| 6c                         | Minimize loss to follow-up/ensure a high response rate                       |
| 6d                         | Discuss the potential for selection bias                                     |
| 7a                         | Provide detailed discussion of comparison groups                             |
| 7b                         | Ensure that comparison groups are similar to cases/exposed subjects         |
| 1                          | Choose exposure metric in outcome-relevant time window                       |
| 2                          | Report exposure levels and units of measurement                              |
| 3                          | Use a measurement that is sensitive, valid, and applied consistently a       |
| 4                          | Assess exposure independent of outcome                                       |
| 5                          | Assess and report the potential for exposure measurement error/misclassification |
| 6                          | Report the stability and storage of biological samples, as applicable        |
| 7                          | Describe QA/QC procedures, limits of detection or quantification, standards |
|                            | recovery, measures of repeatability, and investigation and prevention of     |
|                            | contamination through appropriate use of blanks                            |
| 8                          | Ensure that there are a sufficient number of samples (to be statistically    |
|                            | meaningful for the investigation) or, in the instance of a single sample,    |
|                            | evidence that errors are negligible                                          |
| 1a                         | Provide detailed statistical methods                                         |
| 1b                         | Use appropriate statistical techniques                                       |
| 1c                         | Document all calculations and analyses                                       |
| 2                          | Report all data sources (including raw data upon request of regulator)       |
| 3                          | Report data measurement methods                                              |
| 4                          | Perform and report QA/QC methods for outcome measurement                     |
| 5                          | Provide collection date and signature of person entering data                |
| 6a                         | Use validated outcome assessment methods                                     |
| 6b                         | Discuss potential for outcome misclassification                             |
| 7a                         | Identify sources of bias and confounding a priori based on hypothesis        |
|                            | being tested                                                                 |
| 7b                         | Report how confounding and bias are addressed                                |
| 7c                         | Control for co-exposures                                                     |
| 7d                         | Reduce possibility for bias through design b                                 |
| Outcome Assessment Methods |    |                                                                             |
| 1a                         | Report the results of all measured outcomes and adjusted and unadjusted      |
|                            | analyses (i.e., complete outcome reporting)                                 |
| 1b                         | Report the results of sensitivity, subgroup, or other analyses               |
| Study Results              |    |                                                                             |
| 1                          | Report study limitations                                                     |
| 2                          | Provide an interpretation of results                                         |
| 3                          | Discuss issues of generalizability                                           |
| 4a                         | Report the funding source/provide a Conflict of Interest statement           |
| 4b                         | Discuss whether the funding source affected design or interpretation        |
| Discussion                 |    |                                                                             |
| 5                          | Discuss other sources of bias                                               |

# = Numbering for the list of requirements in each category; QA/QC = Quality Assurance/Quality Control; a That is, use well-established, validated, quantitative exposure assessment methods at the individual level, with as little measurement error as possible; b for example, through statistical methods or sensitivity analyses.
2. Materials and Methods

We developed this guidance based on a review of numerous existing guidance and regulatory documents that aim to improve the quality and reporting of a variety of different types of evidence, including from human, animal, and in vitro studies. This includes the exposure characterization the US EPA Office of Pesticide Programs (OPP) discusses in “Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides” [10], and GLP documents for toxicity studies (primarily WHO [17]) and pesticide residues [18]. We also considered existing post hoc study quality assessment systems—specifically, the US EPA Integrated Risk Information System (IRIS) Risk of Bias (RoB) framework and the National Toxicology Program (NTP) Office of Health Assessment and Translation RoB tool, as well as the LaKind et al. [2] BEES-C tool, peer-reviewed articles on exposure assessment methods for epidemiology, and our own research on exposure characterization and study-quality evaluation methods (see for example, Goodman et al. [19] and Lynch et al. [20,21]). Combining overarching principles and specific guidance from each of these documents, tailored where possible specifically to pesticides, we developed the GEP criteria for exposure assessment with requirements for the design, conduct, and reporting of studies that can inform causation and quantitative risk assessment.

3. Proposed GEP Guidelines for Pesticide Exposure Assessment

We organized guidelines for pesticide exposure assessment based on the type of data available. Biomonitoring and environmental sampling involve direct measurements of pesticides, their metabolites, or other biomarkers. In contrast, questionnaires and interviews provide different types of exposure data, such as information on the presence, duration, or frequency of exposure. Sampling and interview data may be used for all exposure routes (i.e., dermal, ingestion, and inhalation) and most types of exposures, including those in occupational (e.g., farmhands, sprayers, pest control professionals, greenhouse workers, and chemical manufacturers) or non-occupational (e.g., residential pesticide users and individuals who live or work near sprayers) settings. However, they are not sufficient for addressing dietary exposures to pesticides, as this involves measuring the concentrations of pesticide residues in foods and assessing the consumption of these foods.

Thus, the proposed GEP guidelines for pesticide exposure assessment, as presented in Tables 2–4, are based on the sources of exposure data that share common requirements (i.e., biomonitoring and environmental samples, questionnaire/interview/expert record review, and dietary exposures based on measurements of residues in food and food consumption). These guidelines primarily apply to exposure assessment in both cohort and case-control studies, for which, unlike cross-sectional studies, temporality between the exposure and the outcome can be established. Some specific criteria are noted to differ by study design, however. The criteria also apply to exposures to both single substances and complex mixtures. Most criteria apply to both causal inference and quantitative risk assessment, and we specify with underlined text in the tables where additional requirements are needed for quantitative risk assessment.
Table 2. Good Epidemiology Practice (GEP) Criteria for Pesticide Exposure Assessment Using Biomonitoring, Personal Monitoring, and Environmental Sampling Data.

| Category                      | Criteria for Causal Inference and Quantitative Risk Assessment                                                                                                                                  | Comments                                                                                     |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study Protocol                | 1. An a priori protocol/study plan with defined mechanistic hypotheses is required, including reference to a thorough Standard Operating Procedure (SOP) that details sampling protocols and internal quality control.  
2. Health outcomes being investigated in the study plan should consider biologically plausible mechanisms.  
3. The protocol should include all details regarding study design and implementation. Note any deviations.  
4. While all details of the protocol will not be included in a journal article, the documents should be available on request and submitted for any studies being considered for pesticide registration and policy-making.                                                                                                                                                                                                 | Formal quality programs may be followed, such as the International Organization for Standardization (ISO). See WHO [17] Good Laboratory Practice (GLP) guidance for further information. |
| Validity and Reliability of Sampling | 1. Exposure assessed via the same methods and within the same timeframe across all groups.  
2. Samples collected under controlled conditions; contamination assessed (e.g., via blanks analysis).  
3. Contamination from storage materials, the matrix (e.g., external contamination on toenail samples), and other sources fully considered and controlled via equipment selection, cleaning, etc.  
4. All glassware, reagents, organic solvents, and water should be checked for possible interfering contaminants.  
5. For some environmental samples, the available methods may not be well standardized, such as wipe sampling for dust exposure. In these cases, the researcher must conduct research to fill any knowledge gaps (e.g., best wipe material), and conduct method validation to optimize the methods [22]. | With regard to time frame, while not all samples will necessarily be taken at the same time (e.g., studies with rolling enrollment), the researcher must evaluate whether pesticide concentrations may have changed over time (e.g., due to environmental degradation, changing pesticide use) and assess how any changes may impact results.  
For biological samples that are time-varying (within a person) due to chemical metabolism or other factors, particularly within a single day or across weeks, the researchers must assess and either standardize sample collection across participants or adjust/stratify results to account for differences.  
In instances where timing affects results, stratification or other methods for evaluating inconsistencies across measures may be utilized [3].  
For wipe sampling, consult relevant guidance (e.g., Battelle 2007 [22]). |
| Exposure Window               | 1. The exposure window of the chosen biomarker/metric reflects the time period during which the exposure could have effects relevant to the outcome of interest. It considers induction and latency and is based on biological and clinical pathways. | Not applicable to case-control studies. For a developmental endpoint, the metric should capture the exposure that occurred during the period of fetal development associated with that effect (e.g., for congenital heart defects, exposure occurs during cardiac development). Similarly, for cancer, the exposure must precede the diagnosis by a sufficient latency period (typically, at least 5 years for hematologic neoplasms and 10 years for epithelial neoplasms). |
| Time Integration              | 1. The biomarker or personal/environmental sampling data correspond(s) to the most relevant exposure metric (e.g., average, cumulative, peak), based on the studied outcome and known biological variability. |                                                                                              |
| Specificity                   | 1. Metric is specific to the exposure of interest.  
2. For biological samples, the biomarker must be the parent compound of interest or a toxicologically relevant metabolite that represents an internal dose that is well correlated with external exposure.  
3. The toxicokinetics of the parent compound in the body are understood and have been considered in choosing the metric and designing the sampling protocol. | For example, dialkylphosphates, the urinary metabolites of organophosphates (OPs), are not specific to individual OPs, so they are not informative regarding specific OPs [23].  
For personal monitoring and environmental exposures, several exposure metrics may be needed to provide sufficient information. Confirmatory tests can be conducted to ensure positive identification of the exposure of interest [18]. |
| Sensitivity                   | 1. Metric is sensitive (i.e., measurable down to a low limit of detection that is low enough to detect chemicals in a sufficient percentage of the samples to inform the causal or research question)  
2. There must also be high confidence in the ability of the instruments used to provide the needed level of sensitivity. |                                                                                              |
Table 2. Cont.

| Category                                      | Criteria for Causal Inference and Quantitative Risk Assessment                                                                                     | Comments                                                                                                                                 |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Validity and Reliability of Analytical       | 1. The analytical test methods have been validated (e.g., by assessment of repeatability within a laboratory and reproducibility of the method at multiple laboratory sites). In the case of a novel test, sufficient information must be provided regarding the within-laboratory validation, and any uncertainties should be discussed.  | As noted in US EPA guidance for regulatory risk assessment, if, for example, a frequency of detection limit of five percent is used, “then at least 20 samples of a medium would be needed (i.e., one detect in 20 samples equals a five percent frequency of detection)” [24]. |
| Methods                                       | 2. Reliability should be assessed via intraclass correlation coefficient (ICC) or similar assessment.                                                    | If using ProUCL for environmental assessment, a minimum of 4-5 samples are required.                                                                 |
| Number of Samples and Replicates             | 1. A sufficient number of replicates per sample is required to ensure data validation and assessment of data variability.                            | For example, adjust urine measurements for creatinine (for dilution) or blood measurements for lipid content (for associations between chemicals stored in fat and where lipids may be confounders or covariates). |
|                                              | 2. For personal monitoring and environmental samples, ensure there are a sufficient number of total samples for the specific detection limit and/or to achieve sufficient power for the necessary statistical analysis (see example under comments). |                                                                                                                                                                                                   |
| Consideration of Matrix Effects              | 1. Adjust exposure estimate, as needed, based on the matrix and any matrix effects during sample processing. Both adjusted and unadjusted concentrations and results should be reported. | For example, adjust urine measurements for creatinine (for dilution) or blood measurements for lipid content (for associations between chemicals stored in fat and where lipids may be confounders or covariates). |
|                                              | 2. Matrix effects must be investigated in the early phase of studies and used to inform the methods chosen and/or to put sample treatment remedies in place. Investigations can include comparing the response of an analyte in a standard solution and in a post-extraction spiked sample (matrix-matched standard). Preventative measures such as correcting for analyte losses during pre-treatment, may also be performed [25]. |                                                                                                                                                                                                   |
| Sample Storage and Stability                 | 1. Verify the stability of the substance of concern in the samples, given the matrix, storage conditions, and duration of storage. Samples may have some known losses, but differences between low and high exposures can be assessed. | For many biological samples, storage at a range of −80 to −130 degrees Celsius is preferred [26], deviation of this general standard must be justified. Samples that have undergone thawing and refreezing must be evaluated against spiked samples subjected to the same conditions [2]. Fluctuations in storage conditions should be avoided. |
| Reporting Requirements                        | 1. The study protocol should be made publicly available.                                                                                           | To determine concentrations most representative of potential exposures, results above and below the limit of quantification should be considered together. Use one-half the limit of quantification as a proxy concentration if there is reason to believe the chemical is present below the limit of quantification, or use the limit of quantification value itself if there is reason to believe the concentration is closer to this value. Only use a value of zero if there is specific information indicating that the chemical is not likely to be present in a sample [24]. |
|                                              | 2. Details regarding the consideration and fulfillment of the above criteria (e.g., all sample collection, handling, processing, and storage; evidence of sample stability; analytical methods; method sensitivity, specificity, validity, and reliability; and Quality Assurance/Quality Control [QA/QC] procedures) should be reported. |                                                                                                                                                                                                   |
|                                              | 3. Limits of detection and limits of quantification should be stated for the target analyte, and the proportion of samples at or below these values should be recorded. |                                                                                                                                                                                                   |
|                                              | 4. Any deviations from the SOP/protocol and justifications for such deviations should be reported.                                                   |                                                                                                                                                                                                   |
|                                              | 5. While some of these details may need to be omitted for peer-reviewed publication, the information should be provided in supplemental material or made available upon request. |                                                                                                                                                                                                   |

GEP = Good Epidemiology Practice; WHO = World Health Organization.
Table 3. GEP Criteria for Pesticide Exposure Assessment Using Questionnaires, Interviews, and Expert Record Review.

| Category                      | Criteria for Causal Inference and Quantitative Risk Assessment                                                                                                                                                                                                 | Comments                                                                                                                                                                                                 |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study Protocol                | 1. An a priori study protocol must include standard and detailed specifications for developing questionnaires and conducting interviews, training personnel, extracting, coding, and processing data, keeping records and storing data, and quality assurance (QA) and quality control (QC) procedures that minimize the potential for bias and human error. | Not applicable to case-control studies. For a developmental endpoint (e.g., congenital heart defects), the exposure metric should capture the exposure that occurred during the period of fetal development associated with that effect (e.g., fetal cardiac development). For cancer, the exposure must precede the diagnosis by a sufficient period of time (typically, at least 10 years). |
| Exposure Window              | 1. The exposure metric should be assessed in the time period during which the exposure could have effects relevant to the outcome of interest. The selection of the exposure window should consider induction and latency and should be based on biological and clinical pathways.                                                                 |                                                                                                                                                                                                           |
| Study Population              | 1. The study population should be representative of the target population with regard to the exposure distribution (i.e., it should capture the entire exposure range).                                                                                                                                         |                                                                                                                                                                                                           |
| Design of Self-administered and Interview Questionnaires | 1. The questions should be clear and simple so as to avoid ambiguity and enhance recall.  
2. Ideally, questionnaires should be designed with multiple ways of obtaining a specific piece of information, to allow for an internal cross-check of the validity of the provided answers. | For example, when assessing occupational exposures, workers should be asked about factors that are easily recalled, such as tasks, raw materials, equipment, and processes [27]. Avoid loading questions, such as, “Did you ever feel ill after using the pesticide product?” |
| Blinding                      | 1. Blinding of study participants and researchers should be implemented, if possible, to reduce the potential for information bias. Particularly for retrospective studies, exposure must be assessed independent of outcome.                                                                 | The study participants should be blinded to the specific research question (i.e., the exposure of interest).  
For retrospective studies, the person(s) conducting the interviews or reviewing records/questionnaires should be blinded to the outcome status of the study participants, if possible. |
| Validation of Exposure Assessment Methods | 1. Self-reported exposures from questionnaires and interviews should be validated by objective records or measurements. For quantitative risk assessment, self-reported exposure information needs to be validated against biomonitoring or environmental sampling data, ideally in a subset of the study population.  
2. For record review, the expert needs to be sufficiently qualified and rely on environmental measurements to determine the relative rankings of the study participants with regard to the exposure. For quantitative risk assessment of occupational exposures, a valid job-exposure matrix, based on environmental sampling data, should be constructed. The environmental sampling should capture the temporal changes and variations in the exposures by task. | For example, self-reported use of pesticides can be validated with purchasing/inventory records, biomonitoring data, or personal/environmental exposure monitoring.  
Self-reported use of pesticides can be combined with Geographic Information Systems (GIS) methods to develop surrogate exposure estimates, but due to inability to assess fine spatial variations, GIS can introduce uncertainty or error into exposure estimates, and approaches should be validated on multiple datasets [23–25].  
For assessing occupational exposures by record review and/or job-exposure matrix, the expert should have relevant experience and credentials (i.e., certified industrial hygienist). |
| Reporting Requirements        | 1. The study protocol should be made publicly available.  
2. Details regarding personnel training and credentials, questionnaire development, computer software employed, data extraction and processing, and methods used to estimate exposure should be reported.  
3. Any deviations from the study protocol and justifications for such deviations should be reported. |                                                                                                                                                                                                           |

GEP = Good Epidemiology Practice; Underlining indicates criteria that are needed for quantitative risk assessment.
Table 4. GEP Criteria for Assessing Dietary Exposures to Pesticides Using Environmental Sampling and Questionnaires/Interviews/Record Review.

| Category                        | Criteria for Causal Inference and Quantitative Risk Assessment                                                                 | Comments                                                                                                                                                                                                 |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Residue in Food (Environmental Sampling) | 1. An a priori protocol/study plan is required, including reference to a thorough Standard Operating Procedure (SOP) that details sampling protocols and addresses internal quality control. | Formal quality programs may be followed, such as the International Organization for Standardization (ISO). See WHO [17] guidance for further information.  |
|                                 | 2. The protocol should include all the details regarding the design and implementation of the study. Any deviations should be noted.            | In total diet studies (TDSs), the necessary processing and preparation of foods creates a risk of contamination or chemical losses; as such, QA methods are particularly important for these types of studies [32]. |
|                                 | 3. While all details of the protocol will not be included in a journal article, the documents should be available on request and submitted for any studies being considered for pesticide registration and policy-making. |                                                                                                                                                                                                          |
| Study Protocol and QA/QC Procedures | 1. The selection of foods for sampling must include all types of foods that are generally consumed to assess total dietary exposure.   | See WHO et al. [33] for further information.                                                                                                                                                                |
|                                 | 2. Several batches or lots of each food must be sampled to determine the ranges of residue levels. Alternatively, bulk samples from multiple batches/lots can be used to assess average pesticide residue levels. |                                                                                                                                                                                                          |
|                                 | 3. If relying on existing samples (e.g., a market basket food survey, FDA pesticide residue monitoring program), the researchers must verify that the food sampling meets the criteria outlined here. When using a market basket (MB, also known as a TDS approach), the researcher must follow general guidance outlined by WHO et al. [33], which includes specifications for sampling and processing methodology. |                                                                                                                                                                                                          |
| Representative Food Sampling     | 1. Exposure assessed via the same methods and within the same timeframe across all groups.                                       | With regard to timeframe, while not all samples will necessarily be taken at the same time (e.g., studies with rolling enrollment), the researcher must evaluate whether pesticide concentrations may have changed over time (e.g., due to environmental degradation, changing pesticide use) and assess how any changes may impact results. For biological samples that are time-varying (within a person) due to chemical metabolism or other factors, particularly within a single day or across weeks, the researchers must assess and either standardize sample collection across participants or adjust/stratify results to account for differences. |
|                                 | 2. Samples collected under controlled conditions; contamination assessed (e.g., via blanks analysis).                           | In instances where timing affects results, stratification or other methods for evaluating inconsistencies across measures may be utilized [7].                                                                 |
|                                 | 3. Contamination from storage materials, the matrix (e.g., external contamination on toenail samples), and other sources fully considered and controlled via equipment selection, cleaning, etc. | For MB and TDS methods, consult guidance by WHO et al. [33] and FDA [34,35].                                                                                                                                 |
|                                 | 4. All glassware, reagents, organic solvents, and water should be checked for possible interfering contaminants.                  |                                                                                                                                                                                                          |
|                                 | 5. For MB or TDS methods, preparation and analysis of food as consumed is critical because preparation techniques, including pooling, washing, and heating, affect pesticide levels. |                                                                                                                                                                                                          |
| Validity and Reliability of Sampling | 1. Metric is specific to the exposure of interest.                                                                                     |                                                                                                                                                                                                          |
|                                 | 2. The residue measured must be the parent compound of interest or a toxicologically relevant metabolite/derogation product that represents an internal dose that is well correlated with external exposure. |                                                                                                                                                                                                          |
| Specificity                      | 1. Metric is sensitive (i.e., measurable down to a limit of detection that is low enough to estimate the chemical in a sufficient percentage of the samples to inform the causal or research question). | For TDS/MB surveys, pooled samples are usually used. Chemical concentrations may be altered in a pooled sample (concentrated or diluted). Therefore, the analytical methods used must be of a higher sensitivity compared with those used for food compliance monitoring. |
|                                 | 2. There must also be high confidence in the ability of the instruments used to provide the needed level of sensitivity.                                                                 |                                                                                                                                                                                                          |
| Category                        | Criteria for Causal Inference and Quantitative Risk Assessment                                                                                                                                                                                                                                                                                                                                 | Comments                                                                                                                                                                                                 | Table 4. Cont.                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Validity and Reliability of Analytical Methods | 1. The analytical test methods must be suitable for the food type (e.g., raw food versus processed food; consideration of lipid/water content of the food) and the substance of interest.  
2. The analytical test methods have been validated (e.g., by assessment of repeatability within a laboratory and reproducibility of the method at multiple laboratory sites). In the case of a novel test, sufficient information must be provided regarding the within-laboratory validation, and any uncertainties should be discussed.  
3. Validity should be assessed via intraclass correlation coefficient (ICC) or similar assessment. |                                                                                                                                                                                                                                                                      | See WHO et al. [33] for further information.                                                                                           |
| Number of Samples and Replicates | 1. Ensure there are a sufficient number of total samples for the specific detection limit and/or to achieve sufficient power for the necessary statistical analysis. For screening TDS surveys, 20–30 samples may be sufficient. For refined analyses, as many as 200–300 samples may be needed [33].  
2. A sufficient number of replicates per sample is required to ensure data validation and assessment of data variability. |                                                                                                                                                                                                                                                                      | For example, measurement in food using Liquid Chromatography-Mass Spectrometry (LC-MS) is complicated by compound and matrix-dependent response suppression or enhancement, otherwise known as matrix effect (see Niessen et al. [25]). |
| Consideration of Matrix Effects | 1. Adjust exposure estimate, as needed, based on the matrix. Both adjusted and un-adjusted concentrations and results should be reported. |                                                                                                                                                                                                                                                                      | Stability of the substance of concern (e.g., the pesticide residue) in fresh or stored food must be verified. For example, recovery analysis using spiked samples should be employed or established prior to analysis. Storage conditions and duration should be reported. |
| Sample Storage and Stability | 1. Verify the stability of the pesticide residues in the samples, given the matrix, storage conditions, and duration of storage. Samples may have some known losses, but differences between low and high exposures can be assessed. |                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                           |
| Reporting Requirements | 1. SOPs and the study protocol should be made publicly available.  
2. Details regarding the consideration and fulfillment of the above criteria (e.g., all sample collection, handling, processing, and storage; evidence of sample stability; analytical methods; method sensitivity, specificity, validity, and reliability; and QA/QC procedures) should be reported.  
3. Any deviations from the SOP/protocol and justifications for such deviations should be reported.  
4. While some of these details may need to be omitted for peer-reviewed publication, the information should be provided in supplemental material or made available upon request. |                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                           |
| Food Consumption (Questionnaires, Interviews, Record Review) |                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                           |                                                                                                                                                                                                           |
| Study Protocol | 1. An a priori study protocol must include standard and detailed specifications for developing questionnaires (or using validated questionnaires) and conducting interviews; training personnel; extracting, coding, and processing data; keeping records and storing data; and quality assurance (QA) and quality control (QC) procedures that minimize the potential for bias and human error. |                                                                                                                                                                                                                                                                      | Not applicable to case-control studies. For a developmental endpoint (e.g., congenital heart defects), the exposure metric should capture the exposure that occurred during the period of fetal development associated with that effect (e.g., fetal cardiac development). For cancer, the exposure must precede the diagnosis by a sufficient period of time (typically, at least 10 years). |
| Exposure Window | 1. The exposure metric should be assessed in the time period during which the exposure could have effects relevant to the outcome of interest. The selection of the exposure window should consider induction and latency and should be based on biological and clinical pathways. |                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                           |
Table 4. Cont.

| Category | Criteria for Causal Inference and Quantitative Risk Assessment | Comments |
|----------|---------------------------------------------------------------|----------|
| **Time Integration** | 1. The assessment of dietary intake should aim for habitual or long-term consumption of foods. 2. For 24-hour dietary recall and food diaries, a sufficient and representative number of days should be used to estimate habitual consumption. | - Because pesticide residues are typically present in foods at very low concentrations, long-term cumulative or cumulative average exposures are generally the most relevant metrics for any potential health effects. - For 24-hour recall and food diaries, multiple days are needed to sufficiently capture temporal variations in diet (e.g., week days vs. weekends, seasons). |
| **Study Population** | 1. The study population should be representative of the target population with regard to the consumption distribution (i.e., include the range of consumption). | - |
| **Design of Self-administered and Interview Questionnaires** | 1. The questions should clear and simple so as to avoid ambiguity and enhance recall. 2. The questions should be sufficiently comprehensive and detailed to address specific research questions. For quantitative risk assessment, the questions should capture ordinal or semi-quantitative exposure information. | - For 24-hour dietary recall, the interviewer should probe for information on food types, preparation methods, portion sizes, etc. - Self-administered questionnaires should include foods generally consumed and culturally specific to the target population. The questionnaires should also include questions regarding consumption behaviors (e.g., frequency, preparation methods, and portion size). |
| **Blinding** | 1. Blinding of study participants and researchers should be implemented, if possible, to reduce the potential for information bias. Particularly for retrospective studies, exposure must be assessed independently of outcome. | - The study participants should be blinded to the specific research question (i.e., the foods/pesticides of interest). - For retrospective studies, the person(s) conducting the interviews or reviewing questionnaires/records should be blinded to the outcome status of the study participants, if possible. |
| **Validation of Dietary Assessment Methods** | 1. Dietary records/food diaries are the gold standard for dietary assessment. 2. Food frequency questionnaires and 24-hour dietary recalls should be validated against dietary records. | - Study participants should undergo training to ensure their dietary records are properly conducted and can provide robust information on food consumption. |
| **Reporting Requirements** | 1. The study protocol should be made publicly available. 2. Details regarding personnel training and credentials, questionnaire development, computer software employed, data extraction and processing, and methods used to estimate exposure should be reported. 3. Any deviations from the study protocol and justifications for such deviations should be reported. | - |

FDA = Food and Drug Administration; GEP = Good Epidemiology Practice; QA/QC = Quality Assessment/Quality Control; WHO = World Health Organization; Underlining indicates criteria that are needed for quantitative risk assessment.
3.1. Biomonitoring and Environmental Sampling

Table 2 presents the criteria for estimating pesticide exposures with biomonitoring (e.g., urine, blood), personal exposure monitoring (e.g., dermal wipes or washes, breathing zone air sampling) or environmental sampling data (e.g., surface wipes, ambient air monitoring). Biomonitoring integrates exposures from different routes to quantify the amount of a substance absorbed by the body, whereas personal exposure monitoring characterizes exposure at the point of entry into the body [10]. Biomonitoring and personal exposure monitoring are generally considered the best sources of data for estimating actual exposure concentrations, though they are often conducted over a limited time period that may not be sufficient to accurately reflect longitudinal patterns of exposure [10]. Environmental sampling characterizes substance concentrations in environmental media and is useful for estimating exposures defined by geographical boundaries (such as in ambient air and drinking water), but can be less reliable for assigning individual-level exposures [10].

Some criteria in Table 2 are general, while others are specific to biomonitoring, personal monitoring, or environmental sampling data. The categories of criteria include study protocol; the validity and reliability of sampling; exposure window; time integration, specificity, and sensitivity of the exposure metric; the validity and reliability of the analytical methods; sample replicates; consideration and adjustment of matrix effects; sample storage and stability; and reporting requirements.

3.2. Participant Questionnaires and Interviews

Table 3 presents the criteria for estimating pesticide exposures with questionnaires, interviews, and/or expert record review. Such methods are typically used to assign categorical levels of exposure that are surrogates for actual exposure levels [10]. The categories of criteria for these methods include study protocol, exposure window, study population, the design of self-administered and interview questionnaires, the blinding of study participants and investigators, validation of exposure assessment methods, and reporting requirements.

3.3. Dietary Exposures

Table 4 presents the GEP criteria for assessing dietary exposures to pesticide contamination or residues in food. The assessment of dietary pesticide exposures requires two components: measuring the concentrations of pesticide residues in foods and assessing the consumption of these foods. Separate criteria are presented for these two components. The former component warrants similar criteria to those for environmental sampling, with a few specific categories modified to be applicable to foods. The latter component generally requires the use of questionnaires, interviews, or food diaries. On the basis of the criteria presented in Table 3, the criteria for this component are tailored towards assessing food consumption.

4. Discussion

The goals of epidemiology studies vary, and while many are useful for hypothesis generation, they are not all informative for inferring causation. Unlike toxicity studies in laboratory animals, for which the exposures are well characterized and a set of GLP guidelines are available, there are no such guidelines (to the authors’ knowledge) available to ensure the quality and reliability of exposure assessment in epidemiology studies. Regardless, epidemiology studies are being used more often in risk assessment, and while many organizations have proposed criteria on which to judge the quality and reliability of epidemiology studies (e.g., see Lynch et al. [21]), there are no standard guidelines, such as GLP, that can be used to ensure the reliability and appropriateness of epidemiology study results for risk assessment.

We proposed GEP criteria for pesticide exposure assessment, for each of the three general types of data available (biomonitoring and environmental sampling; questionnaires and interviews; and dietary exposures). Although the proposed criteria could be subdivided further by data type or study design,
they are intended to represent a balance between widely-applicable guidelines that are flexible enough to be applied to many different chemicals and research questions and more specific guidance that details expectations for different study designs and exposure data. Our criteria have a greater level of detail than existing guidance (e.g., the OPP epidemiology framework; [10]) and existing study quality evaluation systems (e.g., see Lynch et al. [21]), but are intended to be concise enough to maintain clarity and ease of compliance.

We note that, similar to GLP guidelines, we did not include scores that align with the importance of each category of GEP criteria. While all categories are important, study results may still be reliable if all categories are not met. For example, even if sample storage and stability are not verified, it is possible that both are sufficient. However, we do believe several categories are critical and must be met for a study to be used in risk assessments. In studies where exposures are measured, the validity and reliability of sampling and analytical methods must be confirmed, and sensitivity and specificity must be considered. When exposure information is ascertained by records or interviews, these methods must also be validated. If this is not carried out, then it is difficult to determine the reliability of exposure estimates. If exposure is not reliable, then the results are uncertain and open to question. Unreliable exposure estimates can lead to exposure misclassification, which generally refers to the incorrect assignment of participants to categories of exposure (e.g., low and high), or exposure measurement error, which generally refers to errors with measures of exposure on a continuous scale.

Exposure misclassification can be either differential (i.e., misclassification differs between exposed and unexposed groups) or non-differential (i.e., all groups have an equal likelihood of being misclassified) [36]. Although it is often stated that non-differential misclassification always biases effect estimates toward the null, both types of misclassification can bias effect estimates in either direction [37].

In its recent draft position paper on the use of epidemiology studies in pesticide risk assessment and management, the European Food Safety Authority (EFSA) Panel on Plant Protection Products and their Residues (PPR) noted:

While it is commonly assumed by some that non-differential misclassification bias produces predictable biases toward the null (and thus systematically under-predicts the effect size), this is not necessarily the case. Also, the sometimes-common assumption in epidemiology studies that misclassification is non-differential (which is sometimes also paired with the assumption that non-differential misclassification bias is always toward the null) is not always justified (e.g., see Jurek et al. 2005. [38]).

In fact, several quantitative analyses have demonstrated realistic scenarios under which approximately non-differential exposure measurement errors can bias results away from the null [36,39,40]. For example, Jurek et al. [36] showed that associations measured in datasets with low exposure prevalence are especially vulnerable to exposure misclassification that is nearly, but not completely, non-differential. For quantitative risk assessment, the direction and magnitude of exposure measurement error/misclassification and the impact on results should be evaluated quantitatively through simulations and sensitivity analyses. While exposure measurement error/misclassification may not ever be entirely eliminated, conducting exposure assessments using GEP will help minimize the impact of this bias.

As the proposed guidelines in this paper are specific for exposure assessment, we plan to develop similar detailed guidelines for other aspects of epidemiology studies. However, the aspect of confounding bears mentioning here, as many potential confounders will be measured in the same way as the exposures of interest and should be subject to the same criteria for assessment. For example, certain potential confounders (e.g., body mass index [BMI], smoking, and alcohol consumption) can be measured by questionnaire and/or interviews, whereas others (e.g., co-exposures to other pesticides or chemicals) can be measured through biomonitoring or environmental sampling. Thus, some GEP guidelines specific to the aspect of confounding would also be relevant to those for exposure assessment.
These guidelines should be used to design epidemiology studies moving forward and also to evaluate studies conducted in the past so that it can be determined how the results of these studies should be considered in a regulatory setting (e.g., how they contribute to the weight of evidence regarding causation, and whether and how they should be used in quantitative risk assessment or for comparing human exposures to doses in animal toxicity studies). The more criteria a study satisfies, the more robust the study quality and results will be. Although studies that do not fulfill these criteria should not be used for causal inference or quantitative risk assessment, they may still be important for generating new hypotheses and can contribute considerably to advancing the science.

5. Conclusions

It is expected that the GEP guidelines proposed in this paper will facilitate the conduct of higher-quality epidemiology studies that can be used as a basis for more scientifically sound regulatory risk assessment and policy making.

Author Contributions: Conceptualization, J.E.G. and R.L.P.; methodology, J.E.G., R.L.P., P.B., C.H., A.S.; writing—original draft preparation, J.E.G. and R.L.P.; writing—review and editing, P.B., C.H., A.S.; project administration, J.E.G.; funding acquisition, J.E.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by CropLife America.

Acknowledgments: The authors thank Heather Lynch for her contributions to the development of Good Epidemiology Practice and Jasmine Lai and Lynn Kodama for their editorial review.

Conflicts of Interest: J.E.G. and R.L.P. are employed by Gradient, a private environmental consulting firm. The work reported in this paper was conducted during the normal course of employment, with financial support provided by CropLife America. Gradient has conducted work on pesticide epidemiology methodology in regulatory comments to US EPA and EFSA. That work informed this manuscript; however, it did not influence the work presented here. P.B. declares no conflict of interest. C.H. and A.S. are university-employed scientists who receive funding for research on chemicals in the environment from a variety of sources, including UK public sector research funders such as the Natural Environment Research Council. CropLife America received a draft of this manuscript before it was submitted for publication, but was not involved with the conception or drafting of the manuscript. The authors have the sole responsibility for the writing, content, and conclusions in this article.

References

1. US EPA. Good Laboratory Practices Standards Compliance Monitoring Program, 2017. United States Environmental Protection Agency. Available online: https://www.epa.gov/compliance/good-laboratory-practices-standards-compliance-monitoring-program (accessed on 7 April 2020).
2. LaKind, J.S.; Sobus, J.R.; Goodman, M.; Barr, D.B.; Fürst, P.; Albertini, R.J.; Arbuckle, T.E.; Schoeters, G.; Tan, Y.-M.; Teeguarden, J.; et al. A proposal for assessing study quality: Biomonitoring, environmental epidemiology, and short-lived chemicals (BEES-C). *Instrument. Environ. Int.* 2014, 73, 195–207. [CrossRef] [PubMed]
3. National Toxicology Program (NTP). OHAT Risk of Bas Rating Tool for Human and Animal Studies, 2015. National Toxicology Program U.S. Department of Health and Human Services. Available online: https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf (accessed on 7 April 2020).
4. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gotzsche, P.C.; Vandebroucke, J.P. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Int. J. Surg.* 2014, 12, 1495–1499. [CrossRef] [PubMed]
5. US EPA. Memorandum to D. Friedman (US EPA, Pesticide Re-evaluation Division): Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review; Office of Chemical Safety and Pollution Prevention: Washington, DC, USA, 2016; p. 41.
6. US EPA. Atrazine Human Health Risk Assessment (Draft); Office of Chemical Safety and Pollution Prevention: Washington, DC, USA, 2018; p. 212.
7. Paneth, N.; Susser, E.; Susser, M. Origins and early development of the case-control study: Part 1, early evolution. *Soz. Praventivmed.* 2002, 47, 282–288. [CrossRef] [PubMed]
8. Rothman, K.J.; Greenland, S. Cohort studies. In Modern Epidemiology, 3rd ed.; Rothman, K.J., Greenland, S., Lash, T.L., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2008; pp. 100–110.

9. Khoury, M.J.; Millikan, R.; Gwinn, M. Genetic and molecular epidemiology. In Modern Epidemiology, 3rd ed.; Rothman, K.J., Greenland, S., Lash, T.L., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2008; pp. 564–579.

10. US EPA. Framework for incorporating human epidemiologic & incident data in risk assessments for pesticides (Draft); Office of Pesticide Programs: Washington, DC, USA, 2016; p. 51.

11. de Kraker, M.E.A.; Abbas, M.; Huttner, B; Harbarth, S. Good epidemiological practice: A narrative review of appropriate scientific methods to evaluate the impact of antimicrobial stewardship interventions. Clin. Microbiol. Infection 2018, 23, 819–825. [CrossRef]

12. Alba, S.; Mergenthaler, C. Lies, damned lies and epidemiology: Why global health needs good epidemiological practice guidelines? BMJ Global Health 2018, 3, e001019. [CrossRef]

13. Hoffmann, W.; Latza, U.; Baumeister, S.E.; Brungger, M.; Buttman-Schweiger, N.; Hardt, J.; Hoffmann, V.; Karch, A.; Richter, A.; Schmidt, C.O.; et al. Guidelines and recommendations for ensuring good epidemiological practice (GEP): A guideline developed by the German Society for Epidemiology. Eur. J. Epidemiol. 2019, 34, 301–317. [CrossRef]

14. Jones, K.; Basinas, I.; Kromhout, H.; van Tongeren, M.; Harding, A.; Cherrie, J.; Povey, A.; Sidel Ahmad, Z.; Fuhrimann, S.; Ohlander, J.; et al. Improving exposure assessment methodologies for epidemiological studies on pesticides: Study protocol. JMIR Res. Protoc. 2020, 9, e16448. [CrossRef]

15. Ohlander, J.; Fuhrimann, S.; Basinas, I.; Cherrie, J.; Galea, K.; Povey, A.; van Tongerer, M.; Harding, A.; Jones, K.; Vermeulen, R.; et al. Systematic review of methods used to assess exposure to pesticides in occupational epidemiology studies, 1993–2017. Occup. Environ. Med. 2020, 77, 357–367. [CrossRef]

16. Villaverde, J.; Sevilla-Moran, B.; Lopez-Goti, C.; Alonso-Prados, J.; Sandin-Espana, P. QSAR/QSPR models based on quantum chemistry for risk assessment of pesticides according to current European legislation. SAR QSAR Environ. Res. 2020, 31, 49–72. [CrossRef] [PubMed]

17. World Health Organization (WHO). Handbook: Good Laboratory Practice (GLP): Quality Practices for Regulated Non-Clinical Research and Development, 2nd ed.; WHO Library on behalf of the Special Programme for Research and Training in Tropical Diseases: Geneva, Switzerland, 2009; p. 328.

18. Joint FAO/WHO Food Standards Program. Guidelines on Good Laboratory Practice in Residue Analysis (Revised). 2010. Available online: http://www.codexalimentarius.net/download/standards/378/cxg_040e.pdf (accessed on 7 April 2020).

19. Goodman, J.E.; Prueitt, R.L.; Sax, S.N.; Pizzurro, D.M.; Lynch, H.N.; Zu, K.; Venditti, F.J. Ozone exposure and systemic biomarkers: Evaluation of evidence for adverse cardiovascular health impacts. Crit. Rev. Toxicol. 2015, 45, 412–452. [CrossRef]

20. Lynch, H.N.; Loftus, C.T.; Cohen, J.M.; Kerper, L.E.; Kennedy, E.M.; Goodman, J.E. Weight-of-evidence evaluation of associations between particulate matter exposure and biomarkers of lung cancer. Regul. Toxicol. Pharmacol. 2016, 82, 53–93. [CrossRef][PubMed]

21. Lynch, H.N.; Goodman, J.E.; Tabony, J.A.; Rhomberg, L.R. Systematic comparison of study quality criteria. Regul. Toxicol. Pharmacol. 2016, 76, 187–198. [CrossRef]

22. Battelle, S. A Literature Review of Wipe Sampling Methods for Chemical Warfare Agents and Toxic Industrial Chemicals; EPA/600/R-07/004; Report to US EPA, Office of Research and Development.US EPA: Washington, DC, USA, January 2007; p. 56.

23. Spaan, S.; Pronk, A.; Koch, H.M.; Jusko, T.A.; Jaddoe, V.W.; Shaw, P.A.; Tiemeier, H.M.; Hofman, A.; Pierik, F.H.; Longnecker, M.P. Reliability of concentrations of organophosphate pesticide metabolites in serial urine specimens from pregnancy in the Generation R Study. J. Expo. Sci. Environ. Epidemiol. 2015, 25, 286–294. [CrossRef]

24. US EPA. Risk Assessment Guidance for Superfund. Volume I: Human Health Evaluation Manual (Part A) (Interim Final); NTIS PB90-155581, EPA-540/1-89-002; Office of Emergency and Remedial Response: Washington, DC, USA, 1989.

25. Niessen, W.M.; Manini, P.; Andreoli, R. Matrix effects in quantitative pesticide analysis using liquid chromatography-mass spectrometry. Mass Spectrom. Rev. 2006, 25, 881–899. [CrossRef]
26. Vaught, J.B.; Henderson, M.K. Biological sample collection, processing, storage and information management. In Molecular Epidemiology: Principles and Practices; Rothman, N., Hainaut, P., Schulte, P., Smith, M., Boffetta, P., Perera, F., Eds.; International Agency for Research on Cancer (IARC): Lyon, France, 2011; pp. 23–42. Available online: https://publications.iarc.fr/Publications/media/download/139868b153f74693289ae66d767a8cb1ca667df4f1b.pdf (accessed on 7 April 2020).

27. Teschke, K.; Smith, J.C.; Olshan, A.F. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. Am. J. Ind. Med. 2000, 38, 385–388. [CrossRef]

28. Teysseire, R.; Manangama, G.; Baldi, I.; Carles, C.; Brochard, P.; Bedos, C.; Delva, F. Assessment of residential exposures to agricultural pesticides: A scoping review. Eur. J. Epidemiol. 2020, 15, e0232258. [CrossRef]

29. Brody, J.G.; Vorhees, D.J.; Melly, S.J.; Swedis, S.R.; Drivas, P.J.; Rudel, R.A. Using GIS and historical records to reconstruct residential exposure to large-scale pesticide application. J. Expo. Anal. Environ. Epidemiol. 2002, 12, 64–80. [CrossRef]

30. VoPham, T.; Wilson, J.P.; Ruddell, D.; Rashed, T.; Brooks, M.M.; Yuan, J.M.; Talbott, E.O.; Chang, C.H.; Weissfeld, J.L. Linking pesticides and human health: A geographic information system (GIS) and landsat remote sensing method to estimate agricultural pesticide exposure. Appl. Geogr. 2015, 62, 171–181. [CrossRef]

31. Avanasi, R.; Shin, H.M.; Vieira, V.M.; Bartell, S.M. Impacts of geocoding uncertainty on reconstructed PFOA exposures and their epidemiological association with preeclampsia. Environ. Res. 2016, 151, 505–512. [CrossRef]

32. Nasreddine, L.; Rehaiime, M.; Kassaify, Z.; Rechmany, R.; Jaber, F. Dietary exposure to pesticide residues from foods of plant origin and drinks in Lebanon. Environ. Monit. Assess. 2016, 188, 485. [CrossRef] [PubMed]

33. Towards a Harmonised Total Diet Study Approach: A Guidance Document; World Health Organization (WHO): Geneva, Switzerland; Food and Agricultural Organization of the United Nations (FAO): Rome, Italy; European Food Safety Authority (EFSA): Parma, Italy, 2011; p. 72. Available online: https://www.who.int/foodsafety/publications/tds_guidance/en/ (accessed on 7 April 2020).

34. US Food and Drug Administration (US FDA). Pesticides and chemical contaminants: Total Diet Study. Program No. 7304.839. In Compliance Program Guidance Manual; U.S. Food and Drug Administration: Washington, DC, USA, July 2018; p. 31.

35. US Food and Drug Administration (US FDA). Total Diet Study Design. Center for Food Safety and Nutrition (CFSAN); Office of Analytics and Outreach: Washington, DC, USA, March 2018. Available online: https://www.fda.gov/food/FoodScienceResearch/TotalDietStudy/ucm184232.htm (accessed on 7 April 2020).

36. Jurek, A.M.; Greenland, S.; Maldonado, G. How far from nondifferential does exposure or disease misclassification have to be to bias measures of association away from the null? Int. J. Epidemiol. 2008, 37, 382–385. [CrossRef] [PubMed]

37. Armstrong, B.G. Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup. Environ. Med. 1998, 55, 651–656. [CrossRef] [PubMed]

38. European Food Safety Authority (EFSA) Panel on plant protection products and their residues (PPR). Scientific opinion of the PPR panel on the follow-up of the findings of the External Scientific Report “Literature review of epidemiological studies linking exposure to pesticides and health effects” (Final). EFSA J. 2017, 15, 500. [CrossRef]

39. Dosemeci, M.; Wacholder, S.; Lubin, J.H. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am. J. Epidemiol. 1990, 132, 746–748. [CrossRef]

40. Flegal, K.M.; Keyl, P.M.; Nieto, F.J. Differential misclassification arising from nondifferential errors in exposure measurement. Am. J. Epidemiol. 1991, 134, 1233–1244. [CrossRef]