Protocol for a Systematic Review of observational epidemiologic studies on the association between exposure to Phthalates and health outcomes

GMH Swaen and M Zeegers NUTRIM, Maastricht University NL January 2015

Scope

Phthalates are a group of synthetically produced compounds used in cosmetics, flooring adhesives, medical tubing, toys, food packaging materials etc. Metabolites and the parent compounds are detectable in urine and serum samples of the general population. From the multitude of phthalates that exist, eight (normally fewer and in varying combinations) are measured in human urine or plasma (diethyl phthalate or DEP, di-butyl phthalate or DBP, di-n-butyl phthalate or DiBP, butyl benzyl phthalate or BBzP, di-n-octyl phthalate or DOP, di-isodecyl phthalate or DIDP, di-isononylphthalate or DINP, and di-2-ethylhexyl phthalate or DEHP). In many instances the parent compound is not measured but its metabolite(s). Because of their relatively short half-life in the human body the time between exposure and sampling strongly affects the concentrations in the biomonitoring sample.

Toxicological studies in rodents with dose levels over a 1000 fold higher than in human exposure have demonstrated that certain phthalates can induce kidney, liver and lung toxicity and can have anti-androgenic effects on the male reproductive system in rats.

A wide range of health outcomes have been studied with respect to their correlation with varying sets of phthalates. These include, sperm motility, steroidogenesis, precocious puberty, birth weight, infant development, asthma, hypospadias, breast cancer, congenital heart defects, endometriosis etcetera.

The epidemiological studies vary in study design, including cross-sectional studies, cohort studies and case-control studies. The hypotheses mentioned in the papers generally do not specify which specific phthalate is thought to be associated with the health outcome. Many studies utilize already existing databases such as the United States National Health And Nutrition Examination Survey (NHANES) or existing birth cohort studies.

The combination of these factors has resulted in an extremely heterogenic and complex literature base with positive and negative findings that are difficult to interpret. A Systematic Review therefore is warranted, but it also requires a thorough understanding of the research. We believe that a reliable systematic review of the phthalate literature can only be made if the underlying research protocols are included in the analysis. We therefore will contact the corresponding author of every selected article and request a copy of the protocol and ask if he/she is willing to participate in a survey about how the research was conducted.

The project has the objective to conduct a Systematic Review of published articles and protocols of epidemiological studies on phthalates and health. The Systematic Review will:

1. assess the completeness of reporting of these articles
2. assess the quality of the underlying protocols
3. assess the concordance between the published articles and underlying protocols
4. assess the determinants of protocol provision

The research articles included in the Systematic Review will be evaluated with respect to the completeness of reporting by means of the STROBE items as listed in Appendix I and their
methodological characteristics by means of the checklist in Appendix II. The items in the STROBE checklist are seen as signalling items, indicating where the reporting is incomplete or lacking sufficient detail for a proper interpretation of the article findings. The quality of the protocol will be assessed by means of an adapted version of the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) checklist, given in Appendix III. Protocol concordance will be measured by comparing the protocol and the research article on a number of key items and by means of a subsequent telephone interview with the corresponding author (see Appendix IV for the introductory e-mail and V for the questionnaire and an example of how this questionnaire will be tailored (appendix VI). The determinants of protocol provision will be studied by means of the non-response questionnaire (appendix VII) and the methodological characteristics checklist (II).

First a list of publications on observational epidemiology studies on phthalates will be compiled by systematically searching the published literature. The selection process is as follows:

**Scientific paper eligibility**

A paper will be selected if it meets the following inclusion/exclusion criteria:

1. The paper reports the results of a primary cross-sectional, cohort, or case-control study in which the association between phthalate exposure and a health parameter is investigated in humans.

2. Studies reporting on phthalate exposure data only, such as temporal trends or exposure monitoring studies will be excluded. This criterion is added to specifically exclude the large number of biomonitoring studies that only report on the presence and level of human exposure to phthalates only.

3. Only papers in English will be included.

No limitations will be set on year of publication. The Medline and Embase databases, will be searched by means of the following combination of key words: “phthalate*” AND “epidemiol*” and “phthalate* AND “health”. An additional check for completeness will be made if the combinations of “phthalate* and “cross-sectional”, “phthalate*” AND “case-control” and “phthalate*” AND “cohort” will yield additional hits. The title and abstract of each hit in this list will be reviewed and if there is doubt about its eligibility the full paper will be reviewed. A list of all selected papers by date of publication will be generated. Next, all reference lists of the papers in this list will be reviewed to identify eligible papers that were not identified through the PubMed search. These will be added to the list of eligible papers. The reference lists of a number of literature reviews on phthalates will also be checked to assure completeness. Prospective citation scanning of 10 key papers will be used to further identify eligible publications. Finally the list will be shared with ECPI to check if there are any eligible papers ECPI is aware of that have not yet been included.

All selected papers meeting the criteria will be entered into a database, consisting of the information summarized in the appendix I. This section of the database is also used to keep track of e-mail and telephone communication in the course interviewing corresponding authors or other authors.
1. Assessing the completeness of reporting; STROBE conformity.

All selected publications will be assessed regarding STROBE conformity. The website on STROBE (www.strobe-statement.org) provides a checklist to score the reporting of papers on observational studies. Two independent scorers will score each publication on the 22 items of the STROBE checklist. For every item a score “reported” / “not reported” will be given. After a publication has been scored by the two assessors they will compare the scores with the aim of reaching consensus. In case of differing opinions this will be documented. The STROBE checklist is given in Appendix II.

This procedure will be pretested by applying the checklist to 10 observational epidemiology studies on bisphenol A, a compound for which publications similar to those on phthalates are available.

All selected papers will also be scored on a number of methodological characteristics. These will cover key items on methodology such as, level of detail in the hypothesis as stated in the paper, study design, primary collected data or secondary analysis of existing data, number of compounds (phthalates or metabolites) examined, type of exposure measurement, type of health outcome parameter, number of health outcome parameters reported, funding institution, affiliation of first author. The checklist is presented in Appendix II.

II. Protocol quality assessment

In the fourth part of the project the quality of the phthalate studies protocols will be assessed. Again, most checklists available for assessing protocol quality apply to either clinical trials or observational epidemiology studies in the area of pharmacoepidemiology. We have selected the checklist prepared by the European network of Centres for pharmacoepidemiology as the template for our checklist. We have deleted items specific to the pharmacoepidemiologic research field, and we have deleted items such as plans for communication, ethical issues, and amendments and protocol deviations. The checklist for assessing protocol quality is given in Appendix VII.

III Assessing the concordance between the protocol and the publication

The corresponding author of each selected paper will first be contacted via e-mail, with copies sent to as many co-authors as possible of whom an e-mail address can be found on the internet. For papers without a corresponding author, the first author will be contacted. In this e-mail the purpose of the project will be explained and the corresponding author will be asked if he/she is willing to participate. A reminder will be sent within 10 days after the initial e-mail. If no response is received the corresponding author will be contacted by telephone, provided a telephone number was given in the paper, or can be found on the internet. Three attempts will be made by phone to contact the corresponding author. If no response on the e-mails and phone calls is received, the publication will be coded as: no contact with the authors could be made. If the corresponding author can be reached and if he/she refuses to participate, the case will be coded as a refusal. A convenient time and date for the telephone interview will be set. The contents of the introductory e-mail message is described in Appendix I.

If the corresponding author, or a designated substitute, agrees to participate in the project, he/she will be asked to provide a copy of the protocol of the study. A protocol is loosely defined as a written document prepared prior to the study start, describing the procedures to be followed. This can be a
short two-page document for a student’s project, a request for data collected within an already conducted project such as NHANES, an elaborate grant proposal, or a submission to a medical ethical committee or human studies review board, preferably in English. If the protocol is not in English, the document will be translated by means of Google Translate. Resulting uncertainties will be resolved with the aid of the corresponding author. The telephone interview will only be conducted if a copy of the protocol has been shared.

It will be explained that the survey pertains to a specific publication. The participating corresponding author will be asked to have a copy of the protocol and the publication in front of him/her during the telephone interview. The telephone interview will consist of two parts: 1. A general part about how the research was conducted and what disciplines were included in the research group. 2. A set of questions relating specifically to the comparison between the protocol and the publication to assess the occurrence of Reporting Bias. The template of the questionnaire is attached in Appendix V. For each selected publication a tailored questionnaire will be constructed. In Appendix VI an example of the specific questions is given for a paper on BPA, in order to explain what type of specific questions will be included.

Each telephone interview will be conducted by Gerard Swaen, and will be recorded on tape. The tape will be used to verify the responses written down by Gerard Swaen and will be archived for future reference. This procedure will ensure that the responses given by the authors are recorded accurately and in a procedure that will assure validity.

The questionnaire to be used in the telephone interview will have a set of standard items, but also a set of tailored items to be determined after a copy of the protocol is received from the corresponding author.

**The telephone interview**

The main objective of the project is to assess to what extent the protocol was followed and to what extent the paper is a complete representation of work carried out. It is therefore necessary that each interview focusses on comparing the specific publication to the original protocol as written prior to the start of the project. On the other hand, the contents of the interview should be as comparable and uniform as possible to allow general summaries and conclusions. Therefore the interview will cover a set of standard questions about how the project was conducted and second a tailored set of questions to be determined after the protocol is compared to the publication. The responses will be written down by the interviewer and will be checked by means of the tape recording and if necessary corrected. A transcription of the tape recording will be made.

This approach will be pre-tested on five non phthalate publications. Five observational epidemiology publications will be chosen from colleagues who are willing to participate in this pretesting exercise. The tailored questionnaire will be made based on one of their publications. The telephone interview will be administered to them as described above. Afterwards, the colleagues will be contacted to collect suggestions for improvement.
3. Data analysis

In the first analysis a frequency distribution will be given of the response rate. As stated earlier, a paper of which the corresponding author and a second author both refuse to participate in the study is scored as a refusal. A paper for which the corresponding author and a second author do not reply to the introductory e-mail and telephone calls are scored as a non-responder. This will be displayed in the final report in the form of table 1. The percentage of papers for which a protocol could be obtained is calculated by dividing the number of protocols received by the sum of the responders and the refusals.

Table 1. Participation rates in the telephone interview

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<tr>
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<th>Total number</th>
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<tr>
<td>Number of included papers</td>
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<tr>
<td>No contact could be made</td>
<td></td>
<td></td>
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<tr>
<td>Refusals</td>
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<tr>
<td>Participants</td>
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Next, an analysis will be made to describe protocol compliance. Discrepancies may have occurred in the following fields: 1. Hypothesis/objective, 2. exposure measurement, 3. health effect parameter ascertainment, 4. Statistical analysis and 5. incomplete reporting of results. The noted discrepancies between the paper and the protocol will be classified into two types: minor discrepancies that probably have not affected study outcome and major discrepancies that probably have affected study outcome, either by making them positive/negative or by making the association statistically significant. The distinction between minor and major discrepancies will be further described in our report based on what type of discrepancies were observed between the protocol and the publication. Frequency distributions of these discrepancies will be reported as follows:

Table 2. Minor and major discrepancies by area

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<thead>
<tr>
<th></th>
<th>Minor discrepancies</th>
<th>Major discrepancies</th>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
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<tr>
<td>1. Hypothesis/objective</td>
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<tr>
<td>2. Exposure measurement</td>
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<td>3. Health effect parameter measurement</td>
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<tr>
<td>4. Statistical analysis</td>
<td></td>
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<tr>
<td>5. Incomplete results reporting</td>
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Finally a set of explorative analyses will be made, linking study characteristics to the frequency of discrepancies. For example, are protocol discrepancies more likely in studies using already existing data? Are protocol discrepancies more likely if there is no biostatistician involved in the project? Are studies of principle investigators reporting institutional publication pressure more likely to suffer from Reporting Bias? Are positive studies more likely to display protocol discrepancies than negative studies?
IV. Assessing the determinants of protocol provision

It is expected that not all corresponding authors will provide a copy of the protocol. Reasons for not providing the protocol will be inventoried by a short questionnaire that will be sent to those corresponding authors that do not provide a copy of the protocol. This short questionnaire will contain questions about whether the protocol has not been stored, whether the protocol has been lost, or other reasons why a copy of the protocol cannot be shared. General experience indicates that response rates to these type of non-response questionnaires is low. We therefore will use the checklist on study characteristics to assess if any of these are associated with non-provision. For example, positive/negative outcome or the use of an already existing database (e.g. NHANES) may be associated with the probability of protocol provision. This analysis will clarify the expected non-response.
Data archiving

Digital versions of all paper recording forms and copies of the communications with respondents will be stored for 10 years. The database and code book will also be stored for ten years. A depersonalized copy of the database, not traceable to individual responders will be prepared for external sharing. A copy of the syntax of the statistical analysis will also be archived and if requested will be made available.

Privacy protection

The privacy of the individual study participants will be safeguarded. No data traceable to individual respondents will be shared with persons other than M. Zeegers and GMH. Swaen or collaborators under their direct supervision.

Transparency

The final protocol will be placed on the website of the Maastricht University and the link will be provided to ECPI. The protocol will also be placed on the PROSPERO website, a website where these types of protocols are made publicly available. The results will be published in the form of one or several scientific papers to be submitted to scientific journals.
**Appendix I Completeness reporting checklist (STROBE checklist)**

**Publication identification** nr …. First 2 authors …………………

| Title and abstract | 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
(b) Provide in the abstract an informative and balanced summary of what was done and what was found  
( ) Reported. ( ) Not reported. Missing is |  |
|-------------------|---|-------------------------------------------------------------------------------------------------|

| Introduction | 2 | Explain the scientific background and rationale for the investigation being reported  
( ) Reported. ( ) Not reported. Missing is |  |
|---------------|---|-------------------------------------------------------------------------------------------------|

| Introduction | 3 | State specific objectives, including any prespecified hypotheses  
( ) Reported. ( ) Not reported. Missing is |  |
|---------------|---|-------------------------------------------------------------------------------------------------|

| Methods | 4 | Present key elements of study design early in the paper  
( ) Reported. ( ) Not reported. Missing is |  |
|----------|---|-------------------------------------------------------------------------------------------------|

| Methods | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  
( ) Reported. ( ) Not reported. Missing is |  |
|----------|---|-------------------------------------------------------------------------------------------------|

| Methods | 6 | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants  
(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed  
Case-control study—For matched studies, give matching criteria and the number of controls per case  
( ) Reported. ( ) Not reported. Missing is |  |

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<tr>
<th>Methods</th>
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8
Variables
Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.
Give diagnostic criteria, if applicable
( ) Reported. ( ) Not reported.  Missing is

Methods
Data sources/ For each variable of interest, give sources of data and details of methods of
table measurement assessment (measurement). Describe comparability of assessment methods if there is
more than one group
( ) Reported. ( ) Not reported.  Missing is

Methods
Bias Describe any efforts to address potential sources of bias
( ) Reported. ( ) Not reported.  Missing is

Methods
Study size Explain how the study size was arrived at
( ) Reported. ( ) Not reported.  Missing is

Methods
Quantitative Explain how quantitative variables were handled in the analyses. If applicable,
variables describe which groupings were chosen and why
( ) Reported. ( ) Not reported.  Missing is

Methods
Statistical Describe all statistical methods, including those used to control for confounding
methods
(b) Describe any methods used to examine subgroups and interactions
(c) Explain how missing data were addressed
(d) Cohort study—If applicable, explain how loss to follow-up was addressed
Case-control study—If applicable, explain how matching of cases and controls was
addressed
Cross-sectional study—If applicable, describe analytical methods taking account of
sampling strategy
(e) Describe any sensitivity analyses
( ) Reported. ( ) Not reported.  Missing is

Results
Participants (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible,
examined for eligibility, confirmed eligible, included in the study, completing follow-up,
and analysed
(b) Give reasons for non-participation at each stage
(c) Consider use of a flow diagram

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**Results**

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<tr>
<th>Data type</th>
<th>Number</th>
<th>Description</th>
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</table>
| Descriptive | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate number of participants with missing data for each variable of interest  
(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |

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<th>Data type</th>
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<th>Description</th>
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| Outcome | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time  
*Case-control study*—Report numbers in each exposure category, or summary measures of exposure  
*Cross-sectional study*—Report numbers of outcome events or summary measures |

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<th>Data type</th>
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<th>Description</th>
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| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
(b) Report category boundaries when continuous variables were categorized  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |

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<tr>
<th>Data type</th>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>Other analyses</td>
<td>17</td>
<td>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</td>
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**Discussion**

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<tr>
<th>Number</th>
<th>Description</th>
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<tr>
<td>18</td>
<td>Summarise key results with reference to study objectives</td>
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<th>Reported</th>
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<tr>
<th>Limitations</th>
<th>Number</th>
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<tbody>
<tr>
<td>19</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
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<th>Reported</th>
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</table>
**Discussion**

**Interpretation**  20  Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

( ) Reported. ( ) Not reported.  Missing is

……………………………………………………………………………………………………

**Discussion**

**Generalisability**  21  Discuss the generalisability (external validity) of the study results

( ) Reported. ( ) Not reported.  Missing is

……………………………………………………………………………………………………

**Other information**

**Funding**  22  Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

( ) Reported. ( ) Not reported.  Missing is

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Any further remarks, not covered above:

……………………………………………………………………………………………………

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Checklist II Characteristics of the study methodology and study characteristics

<table>
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<tr>
<th>Study nr</th>
<th>Authors:</th>
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<tbody>
<tr>
<td>1. Continent 1=North America 2=Europe 3=South America 4=Asia 5=other</td>
<td></td>
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<tr>
<td>2. Journal category (SJR) Journal name</td>
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<tr>
<td>3. Affiliation first author 1=academia 2=government 3=research inst. 4=industry 5=hospital 6=other</td>
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<tr>
<td>4. Health outcome investigated</td>
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<tr>
<td>5. Hypothesis includes other compounds than phthalates? 1=yes 2=no</td>
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<tr>
<td>6. Hypothesis for a specific phthalate? 1=yes 2=no 3=several specific phthalates</td>
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<tr>
<td>7. Type of data 1=primary data 2=secondary data (e.g. NHANES) 3=combination e.g. birth cohort with additional lab tests</td>
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<tr>
<td>8. Funding Institution: 1=government 2=university 3=research foundation 4=industry 5=none stated</td>
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<tr>
<td>9. Design: 1=cross-section 2=cohort 3=case-control 4=other</td>
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<td>10. Exposure data: 1=single BM sample 2=N BM samples 3=questionnaire 4=JEM 5=other</td>
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<tr>
<td>11. Exposure data collected while measured health outcome present 1=yes 2=no 3=after</td>
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<tr>
<td>12. Number of specific phthalates including categories tested with health outcome</td>
<td></td>
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<td>13. Health outcome data: 1=medical examination 2=lab test 3=self-report 4=other</td>
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<td>14. Power calculation or sample size requirement given? 1=yes 2=no</td>
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<tr>
<td>15. number of p values or 95% CIs 1=&lt;10 2=11-50 3=50+ 4=other</td>
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<tr>
<td>16. Adjustment for confounders 1=Yes 2=No</td>
<td></td>
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<tr>
<td>17. Study approved by ethical committee? 1=Yes 2=No 3=not required(?)</td>
<td></td>
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<tr>
<td>18. Study finding 1=positive 2=negative 3=indecisive 4=indecisive but interpreted as positive 5=indecisive but reported as negative (inconclusive = p≥0.05)</td>
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<tr>
<td>19. Positive findings for 1 or few phthalates or metabolites out of a list of more 1=Yes 2=No 3=not applicable</td>
<td></td>
</tr>
<tr>
<td>20. Positive association in agreement with phthalate specific hypothesis 1=Yes 2=No 3=Not applicable (either general hypothesis or negative results)</td>
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<tr>
<td>21. Authors conclude more research is needed 1=yes 2=no 3=other……..</td>
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<tr>
<td>22. Number of health outcome parameters tested in association with phthalate exposure.</td>
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Appendix III. Checklist for assessing the quality of phthalate study protocols (ENCePP adapted)

Study number: ………… First two authors……………………

Does the formulation of the research question and objectives clearly explain:
1. Why the research is conducted? Yes ☐ No ☐
2. The objectives of the study? Yes ☐ No ☐
3. Which formal hypotheses are to be tested? Yes ☐ No ☐
4. If applicable, that there is no a priori hypothesis Yes ☐ No ☐

Study design:
5. Is the study design clearly described? Yes ☐ No ☐
6. Does the protocol specify primary and secondary endpoints Yes ☐ No ☐ NA ☐
7. Does the protocol describe the measures of effect (e.g. RR, OR)? Yes ☐ No ☐

Source of study population:
8. Is the source population described? Yes ☐ No ☐
9. Is the sampling strategy described? Yes ☐ No ☐

Exposure measurement
10. Does the protocol describe how exposure is defined and measured? Yes ☐ No ☐
11. Does the protocol discuss the validity of the exposure measurement? Yes ☐ No ☐

Endpoint definition and measurement
12. Does the protocol describe how the endpoints are defined and measured? Yes ☐ No ☐
13. Does the protocol address known confounders? Yes ☐ No ☐
14. Does the protocol include a sample size requirement calculation? Yes ☐ No ☐

Statistical analysis
15. Is the choice of statistical technique described? Yes ☐ No ☐
16. Are the confounders described or how confounders will be determined? Yes ☐ No ☐
17. Are sub-group analyses defined? Yes ☐ No ☐

Data management and quality control
18. Does the protocol describe these procedures in sufficient detail? Yes ☐ No ☐
Appendix IV  

Template for the introductory e-mail for the telephone interview of the corresponding authors

Heading with the UM logo and the UM Research Institute Logo.

Dear Dr. ……

We currently are carrying out a Systematic Review of observational epidemiology studies on phthalates and health parameters. All included publications on this topic will be scored with respect to study quality and their reporting. In addition the project aims to describe how the studies have been conducted and what procedures have been followed. This project is funded by the European Council of Plasticisers and Intermediates (ECPI) a sector group of CEFIC. ECPI has no influence on how the study is conducted, analyzed or published.

The paper …… that was published in ….. meets the inclusion criteria for this Systematic Review. A short description of the project can be found on the Maastricht University website at:  Website link

We have constructed a short telephone questionnaire about how your study was conducted by your research team. The telephone interview will take not more than 20 minutes of your time.

We would be grateful if you and/or one of the co-authors of the paper would be willing to respond to these questions by phone. If you are willing to participate in this study, please let us know by replying to this invitation by e-mail and send us a suitable time for the telephone interview and a telephone number that we can call. If the proposed time is not suitable we will propose another date and time. If you and your co-authors are not willing to participate please let us know. We will also ask for a copy of the study protocol or the project proposal. The information provided will only be reported in an aggregated form. It will only be used for the purpose of this specific study and no information will be disclosed that can be traced back to a single paper or author. Corresponding authors who participate in our study will receive a copy of the final report. The telephone interview will be recorded on tape in order to assure accuracy of the responses as written down. The recording will be used for this purpose only.

Thank you in advance for your time and participation

Dr. Gerard Swaen

Prof. Maurice Zeegers

NUTRIM, Maastricht university, The Netherlands
Appendix V. The standard section of the questionnaire for the telephone interview

First of all the study team very much appreciates your willingness to participate in our project. The telephone interview will take approximately 20 minutes. Please keep in mind that the interview is about the following paper: ………………. that you co-authored in 20.. in the journal……… It is not about how you generally conduct epidemiology studies, but only about the paper mentioned. We will record your responses and send you a copy in order to provide you the opportunity to comment. The recorded data will be treated as confidential. The full dataset will not be shared with others. If it is requested to provide a copy of the dataset it will be provided only after identifiable parameters are deleted.

1. Study objective- In your paper it is stated that the objective of the study was to ……………………… Is this objective identical to the one stated in the study protocol

Yes .. No .. Other, namely ...........

2. Hypothesis- In your paper you mention ……. as the specific hypothesis or hypotheses. Are these identical to the hypotheses mentioned in the protocol

Yes … No … Other, namely…………

3. Hypothesis- Would you describe the study reported in the paper as a hypothesis testing or as a hypothesis generating project ? Hypothesis testing ……. Hypothesis generating……. Other namely………

4. Population- In your paper the study population was described as follows: ……………. Was the study population in accordance as the one described in the protocol?

Yes .. No .. Other, namely ………

5. Sample size- The paper mentions that the study population consisted of x subjects. Is this number similar to the population size given in the protocol?

Yes .. No .. Other, namely ………

6. Exposure- According to the paper exposure to phthalates was measured in the following way: ………… Was this according to the measurement strategy described in the protocol?

Yes .. No .. Other, namely ………

7. Exposure- Were there any other exposure parameters mentioned in the protocol that were not reported in the paper?

Yes .. No .. If yes, why? …………

8. Health outcome- In your paper …………… were presented as the health outcome parameter(s). Was this the primary outcome parameter(s) specified in the protocol?

Yes .. No .. Other, namely ………

9. Health outcome- Were any other outcome parameters added or omitted during the course of the project, that were not described in the protocol?
10. **Statistical analysis** - In order to investigate the association between phthalate exposure and the health parameter(s), you have conducted the following statistical analysis(ses), which are displayed in table(s) ……. Were these the techniques that were proposed in the protocol?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Other, namely ………</th>
</tr>
</thead>
</table>

11. **Statistical analysis** - Did you exclude data from the dataset, such as outliers?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>If yes, did this change the results? ………</th>
</tr>
</thead>
</table>

12. **Statistical analysis** - In your paper it is mentioned that the results were adjusted for the confounders ……. Were these confounders

| 1. specified in the protocol | Yes (=1) | No (=2) | Other, namely ……… |
| 2. determined following an a priori defined selection process? | Yes (=3) | No (=4) |
| 3. identified by means of explorative statistical analysis? | Yes (=5) | No (=6) |

13. **Statistical analysis** - Were any statistical analyses on the association between phthalate exposure and the health outcome parameters conducted that were not reported in the paper?

<table>
<thead>
<tr>
<th>Yes (=1)</th>
<th>No (=2)</th>
<th>If yes, why were they not reported? …………………..</th>
</tr>
</thead>
</table>

14. **Results** - In table(s) the results for … phthalates (or metabolites) are given. Which of these was the primary compound of interest? ……..

15. **Ethical review**. Was the protocol reviewed by an institutional review board or medical ethical committee? Yes (=1) No (=2)

   If yes, did the committee enquire whether the results were published? Yes (=1) No (=2)

   If yes, did they assess whether the study was conducted according to the protocol? Yes (=1)

| No (=2) |

16. **Disciplines**. Which of the following disciplines on PhD level were involved in the study?

| Epidemiology | Yes (=1) | No (=2) |
| Toxicology | Yes (=1) | No (=2) |
| Health Sciences | Yes (=1) | No (=2) |
| (Bio)Statistics | Yes (=1) | No (=2) |

17. **Publication Pressure**. Does the institution where the project was conducted encourage scientists to publish as many scientific papers as possible?

| Yes (=1) | No (=2) |

18. **Career perspective**. Is the number of scientific publication a part of the annual performance review of the authors employed by the institution where the project was conducted?

| Yes (=1) | No (=2) |
19. **Setting.** Was the project part of the work for a BS, MS or PhD thesis of one of the authors?

Yes(=1)  No(=2)

20. **Funding agency.** Did the funding agency influence the contents of the publication? Yes(=1)  No(=2)

By what type of organization was the project funded?

Not applicable(=1), governmental(=2), non-profit(=3), internal from institute(=4), industry(=5)  other(=6)

21. **Funding agency.** Did the funding agency require that the results are published in a scientific journal?

Yes(=1)  No(=2)  Do not know(=3)  Not Applicable(=4)

22. Were any publications planned prior to data analysis, that were not published?

Yes(=1)  No(=2)

23. Did you decide to publish any journal articles after having found an interesting result during the statistical analysis?  Yes(=1)  No(=2)

24. Did the principle investigator of the project have a tenured position at the time of the project?

Yes(=1)  No(=2)

25. Are you aware of the **STROBE** guidelines?  Yes(=1)  No(=2)

26. Specific question about the comparison between the protocol and the publication to be phrased after comparing the two. (see Appendix VI)

27. Specific question about the comparison between the protocol and the publication to be phrased after comparing the two. (see Appendix VI)

28. Specific question about the comparison between the protocol and the publication to be phrased after comparing the two. (see Appendix VI)
Appendix VI. Example of the tailored section of the telephone interview questionnaire (C)

The paper taken as example is: Meeker et al 2010 Semen quality and sperm DNA damage in relation to urinary Bisphenol A among men from an infertility clinic.

First of all the study team very much appreciates your willingness to participate in our project. The telephone interview will take approximately 20 minutes. Please keep in mind that the interview is about the following paper: Semen quality and sperm DNA damage etc. that you co-authored in 2010 in the journal of Reproductive Toxicology. It is not about how you generally conduct epidemiology studies, but specifically about the paper mentioned. We will record your responses and send you a copy in order to provide you the opportunity to comment. The recorded data will be treated as confidential. The full dataset will not be shared with others. If it is requested to provide a copy of the dataset it will be provided only after identifiable parameters are deleted.

1. Study objective- In your paper it is stated that the objective of the study was to assess the relationship between urinary BPA concentrations and semen quality and sperm DNA damage in men recruited through a United States fertility clinic. Is this objective identical to the one stated in the study protocol?
Yes .. No .. Other, namely …………

2. Hypothesis- In your paper you mention no specific association between a specific compound and specific health parameter as the specific hypothesis or hypotheses. Are these identical to the hypotheses mentioned in the protocol?
Was the no specific hypothesis mentioned in the protocol?
Yes … No … Other, namely………..

3. Hypothesis- Would you describe the study reported in the paper as a hypothesis testing or as a hypothesis generating project? Hypothesis testing …… Hypothesis generating…….. Other namely………

4. Population- In your paper the study population was described as follows: subjects were recruited during 2000-2004 from an ongoing study on the relationship between environmental agents and reproductive health. Was the study population in accordance as the one described in the protocol?
Yes .. No .. Other, namely …………..

5. Sample size- The paper mentions that the study population consisted of 190 subjects. Is this number similar to the population size given in the protocol?
Yes .. No .. Other, namely …………..

6. Exposure- According to the paper exposure to phthalates was measures in the following way: A single spot urinary sample was collected from each subject on the day of their clinic visit. Was this according to the measurement strategy described in the protocol?
Yes .. No .. Other, namely …………..
7. **Exposure**- Were there any other exposure parameters mentioned in the protocol that were not reported in the paper?

Yes .. No .. If yes, why? ............

8. **Health outcome**- In your paper .......... were presented as the health outcome parameter(s). Was this the primary outcome parameter(s) specified in the protocol?

Yes .. No .. Other, namely ..........

9. **Health outcome**- Were any other outcome parameters added or omitted during the course of the project, that were not described in the protocol?

Yes .. No .. Other, namely ..........

10. **Statistical analysis**- In order to investigate the association between BPA exposure and the health parameter(s), you have conducted the following statistical analysis(ses), which are displayed in table 4 and 5. Were these the techniques that were proposed in the protocol?

Yes .. No .. Other, namely ..........

11. **Statistical analysis**- Did you exclude data from the dataset, such as unlikely outliers?

Yes .. No .. If yes, did this change the results? ............

12. **Statistical analysis**- In your paper it is mentioned that the results were adjusted for the confounders specific gravity, age, BMI, abstinence period, current smoking and time of urine sample. Were these confounders 1. specified in the protocol Yes .. No .. Other, namely ............

2. determined following an a priori selection process? Yes …. No……..

3. identified by means of explorative statistical analysis? Yes…. No……

13. **Statistical analysis**- Were any statistical analyses on the association between BPA exposure and the health outcome parameters conducted that were not reported in the paper? For example: Comparison subjects were those that were above the reference level for all three (semen) parameters (N=76, table 1). Was this approach conform the protocol or was it chosen during the analytical process?

Yes .. No .. If yes, why were they not reported? ......................

14. **Results**- In table(s) the results for Not applicable for this study: only one exposure parameter studied… phthalates (or metabolites) are given. Which of these was the primary compound of interest? ............

15. **Ethical review**. Was the protocol reviewed by an institutional review board or medical ethical committee? Yes (=1) No (=2)

If yes, did the committee enquire whether the results were published? Yes(=1) No(=2)

If yes, did they assess whether the study was conducted according to the protocol? Yes(=1)
16. **Disciplines.** Which of the following disciplines on PhD level were involved in the study?

- Epidemiology  
  - Yes(=1)  
  - No(=2)
- Toxicology  
  - Yes(=1)  
  - No(=2)
- Health Sciences  
  - Yes(=1)  
  - No(=2)
- (Bio)Statistics  
  - Yes(=1)  
  - No(=2)

17. **Publication Pressure.** Does the institution where the project was conducted encourage scientists to publish as many scientific papers as possible?

- Yes(=1)  
- No(=2)

18. **Career perspective.** Is the number of scientific publication a part of the annual performance review of the authors employed by the institution where the project was conducted?

- Yes(=1)  
- No(=2)

19. **Setting.** Was the project part of the work for a PhD thesis of one of the authors?

- Yes(=1)  
- No(=2)

20. **Funding agency.** By what type of organization was the project funded?

- Not applicable(=1), governmental(=2), non-profit(=3), internal from institute(=4), industry(=5), other(=6)

21. **Funding agency.** Does the funding agency require that the results are published in a scientific journal?

- Yes(=1)  
- No(=2)  
- Do not know(=3)  
- Not Applicable(=4)

22. Do you remember any discussions about how more publications can be produced by the project?

- Yes(=1)  
- No(=2)

23. Did the principle investigator of the project have a tenured position at the time of the project?

- Yes(=1)  
- No(=2)

24. Are you aware of the **STROBE** guidelines?  

- Yes(=1)  
- No(=2)

25. Has the project been registered at a **clinical trials register**?  

- Yes(=1)  
- No(=2)  
- if yes which one?

26. **Statistical analysis** Room for a targeted question about the statistical analysis: In table 5 the adjusted linear regression coefficients for change on outcome parameters is given. In the third and fourth column these are given for the subgroup of subjects with 2 or more BPA samples. Was this analysis proposed in the protocol?

- Yes…..  
- No ….
27. **Statistical analysis.** On page 533 it is stated that four sets of models were constructed. Was this approach described in the study protocol?

Yes ..... No ..... How were these models developed and selected?

28. Room for specific question on discrepancies between protocol and publication
Appendix VIII. Protocol provision questionnaire.

Dear Dr. ……

We have contacted you via mail and have also tried to call you several times, but we have had no response to our request for your participation in a Systematic Review of published articles on phthalates and health. We would be grateful if you could answer a short set of questions why you have not responded. Your answers will help us to better understand the reasons why authors have not participated in our study.

Reasons for not participating in the survey (check more if applicable):

1. I am too busy to participate in the survey. Yes(1)   No(2)
2. I don’t have the time to search our files for the protocol Yes(1)   No(2)
3. I am no longer doing research in the area of phthalate exposure. Yes(1)   No(2)
4. The study on phthalates that I co-authored is too long ago and I do not recollect the details well enough Yes(1)   No(2)
5. Your project is sponsored by industry and I do not participate in such studies Yes(1)   No(2)
6. Other reason for non-participation in the Systematic Review:…………………………

Protocol provision

7. The protocol is not available any longer because the files have been destroyed Yes(1)   No(2)
8. Our study was simple and we never developed a full protocol Yes(1)   No(2)
9. The principle investigator has left the institute and has not left a copy of the protocol Yes(1)   No(2)
10. The protocol is confidential and cannot be shared Yes(1)   No(2)
11. Other reason for not providing a copy of the protocol:   ………………………………………
Appendix VIII: list of items to be included in the database of the selected phthalate papers

- Year of publication
- Name of first author
- Full reference of the paper
- Name, email address and telephone number of the corresponding author
- Name and email address and telephone number of the first author, other than the corresponding author
- Name and email address and telephone number of the next author
- Name and email address of the third author
- Name and email address of the fourth author
- Name and email address of the last author
- Date that the introductory email was sent and to which email addresses
- Dates that reminders were sent
- Dates that other authors were contacted
- Date and telephone number for the planned telephone interview
- Date that the telephone interview was conducted
- Date that a refusal to participate was received
- Overall status of the data collection process (blank-no action yet, introductory e-mail sent on ….. to ….. date refusal received, date telephone interview planned, date telephone interview conducted, data collection for this paper completed on …….)
- Funding agency mentioned in paper: none given, governmental, non-profit, internal from institute, industry other.
- Health outcome parameter reported in paper
- Study results as reported in paper: 1= positive 2=negative
- Type of phthalate associated with which outcome
- Type of phthalate analyzed
- Confounders corrected for in the analysis
- Primary data used of secondary analysis 1=primary 2=secondary
- Continent corresponding author 1= North America, 2=Europe 3=Asia 4=Australia 5=other
- Authors conclude more research is needed? 1=yes 2=no
- Was the study approved by an ethical committee?
  Yes=1  No=2