# Protocol: Evaluation of Human Cancer Studies on Exposure to Pentachlorophenol and By-products of its Synthesis for the Report on Carcinogens

## Background Information

Pentachlorophenol (CASRN 87-86-5) is a wide spectrum biocide that has been used extensively, primarily as a fungicidal wood preservative, in the United States and elsewhere since the mid-1930s. In 1987 the U.S. EPA restricted the use of pentachlorophenol to non-residential use, primarily to the treatment and preservation of utility poles and cross arms, railroad ties, wharf pilings, and laminated beams and fence posts.

The NTP convened a public webinar (information available at http://ntp.niehs.nih.gov/go/pcpwebinar) and an information group to receive public or scientific input related to differentiating potential cancer effects of pentachlorophenol exposure from effects due to occupational co-exposures or to chemical by-products of pentachlorophenol synthesis in human (webinar) and animal (informational group) studies. One of the major issues discussed in these forums was the nature of pentachlorophenol by-products, and the recognition that virtually all exposure to pentachlorophenol includes exposure to by-products formed during its synthesis, predominantly the higher chlorinated dibenzodioxins (hexachlorodibenzo-*p*-dioxins, heptachlorodibenzo-*p*-dioxins, octachlorodibenzo-*p*-dioxins), higher chlorinated furans hexachlorobenzene and other higher chlorinated phenols (tetrachlorophenol, trichlorophenol). 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD has rarely been detected in commercial preparations of pentachlorophenol (WHO 1987), thus the presence of this molecule in a pentachlorophenol preparation is considered to be a contaminant rather than a by-product of its synthesis. Based on the input from the public webinar and an information group, the NTP has defined the candidate substance to be pentachlorophenol and by-products of its synthesis (hereafter called "pentachlorophenol).

Pentachlorophenol has been selected as a candidate substance for possible listing in the RoC based on an adequate database of cancer studies and significant U.S. exposure. This protocol is limited to the procedures used to prepare the human cancer studies section of the draft RoC monograph and describes (1) the RoC listing criteria used in the evaluation, (2) the key scientific issues, and (3) the procedures and guidelines for each step in the cancer evaluation process.

## RoC Listing Criteria for Evaluating Carcinogenicity from Studies in Humans

*Sufficient evidence of carcinogenicity from studies in humans*: indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

*Limited evidence of carcinogenicity from studies in humans*: causal interpretation is credible, but alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded.

## Key Scientific Questions for the Cancer Evaluation of Pentachlorophenol

The available studies on exposure to pentachlorophenol and human cancer consist primarily of (1) retrospective cohort studies or nested case-control studies of pentachlorophenol users and producers and cancer mortality or incidence, (2) case-control studies primarily of non-Hodgkin lymphoma (NHL) and soft-tissue sarcoma, providing risk estimates for exposure to

pentachlorophenol or information specific for exposure to pentachlorophenol, and (3) studies (primarily population-based case-control studies) of exposure to chlorophenols or occupations (such as sawmills or wood treatment) associated with chlorophenols, which vary in the extent and quality of information related specifically to exposure to pentachlorophenol. Based on cohort or case-control studies identified among workers with potential exposure to pentachlorophenol, the principal cancers of concern are NHL, multiple myeloma, soft-tissue sarcoma, and to a lesser extent kidney cancer. Liver cancer is also considered a site of *a priori* concern based on findings of increased liver tumors in animal studies. Other cancer sites may be considered in the evaluation if there is an adequate database to evaluate those sites. When considering potential contaminants or co-exposures, the strongest evidence for the carcinogenicity of TCDD from studies in humans is from all cancers combined.

### *The key question for the evaluation is:*

- What is the level of evidence (sufficient, limited, or inadequate) for the carcinogenicity of pentachlorophenol from studies in humans?

### *Secondary questions are as follows:*

- Which epidemiologic studies should be included in the review?
- What are the methodological strengths and limitations of these studies?
- What are the potential confounders for cancer risk for the cancer endpoints in these studies?
- Is there a credible association between exposure to pentachlorophenol and any cancer endpoint?
- If so, can the relationship between cancer endpoints and exposure to pentachlorophenol be explained by chance, bias, or confounding?

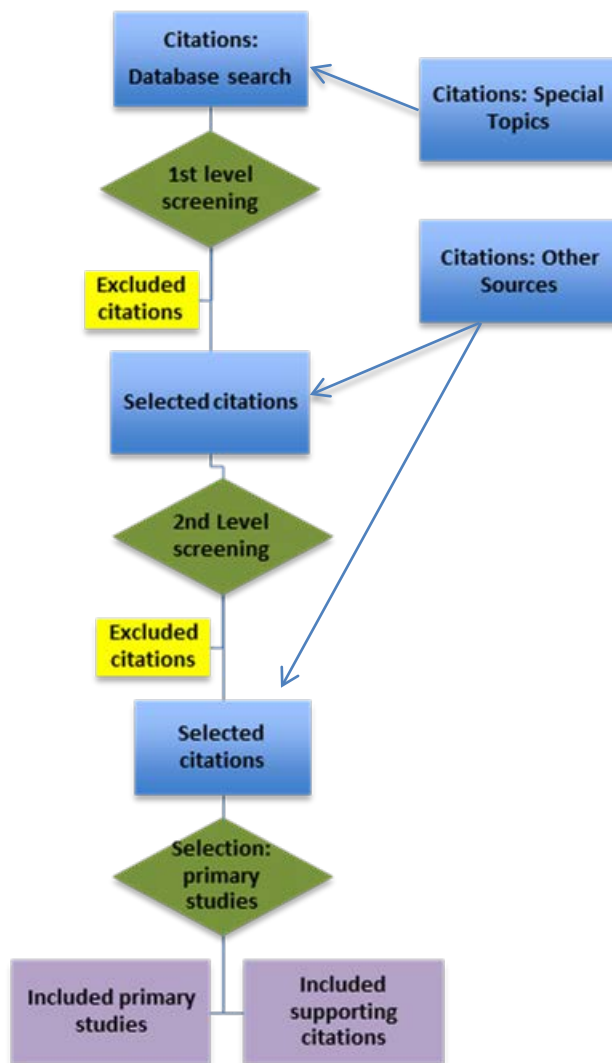### *Steps in the Cancer Evaluation Process:*

The steps for conducting the human cancer evaluation are outlined below. The procedures and guidelines for conducting each step are described in Appendices A through D.

1. Selection of the literature included in the cancer evaluation (Appendix A)
2. Systematic extraction of data from the epidemiologic studies (Appendix B)
3. Assessment of the quality of the individual epidemiologic studies (Appendix C)
4. Assessment of the level of evidence of carcinogenicity (sufficient, limited, or inadequate) of pentachlorophenol from studies in humans (Appendix D)

## Appendix A: Selection of the literature included in the human cancer evaluation

This section discusses procedures to identify and select literature relevant for the human cancer evaluation, including the literature search strategy and inclusion and exclusion criteria. This literature includes the primary epidemiologic studies, which form the basis for cancer evaluation, and supporting literature (e.g., included supporting citations) that may be relevant for the interpretation of the studies. The first step in the process is to develop a literature search strategy and associated inclusion/exclusion criteria to identify the relevant literature, and the second step is to select the primary epidemiologic studies from this database. Figure 1 is a schematic of the process, which is described in detail below.

**Figure 1. Literature identification and selection process**

# 1 Identification of relevant citations for cancer evaluation

The identification of the relevant literature for the cancer evaluation includes strategies for searching for citations and inclusion/exclusion questions for selecting the relevant citations from the searches.

## 1.1 Literature search strategy

Potential exposure to pentachlorophenol has occurred historically primarily in the following occupational settings: (1) production of pentachlorophenol and pentachlorophenol-containing pesticides; and (2) application of pentachlorophenol pesticides in wood preserving, plywood manufacturing, heavy lumber and sawmill working, and utility and fence post manufacture and use. These exposure scenarios are used to develop search terms in the literature search strategy. The following approaches for identifying literature will be employed.

1. Literature searches of three scientific databases – PubMed, Scopus, and Web of Science – using a pre-determined range of search terms. Search terms for potential pentachlorophenol exposure, e.g., terms related to exposure scenarios and terms specific for pentachlorophenol are combined (using "and") with search terms for epidemiologic studies and combined (using "and") with search terms for the outcome, cancer. The specific search terms are listed in the table below. (See Figure 1, Citations: Database.)

| Substance-specific search terms | Cancer search terms | Epidemiologic search terms |
|---|---|---|
| (Pentachlorophenol OR hydroxypentachlorobenzene OR pentachlorobenzene OR pentachlorophenate OR Dowicide EC-7 OR Dowicide 7 OR chlorophenols OR chlorinated phenols OR polychlorinated phenols OR (wood and preserv*) OR lumber OR sawmill OR fenc*) | cancer OR tumors or lymphoma or leukemia or multiple myeloma or soft tissue sarcoma | epidemiolog* OR case-control OR cohort OR case-report OR case-series OR workers OR meta-analysis [publication type] |

2. Full-text searches of a Quosa-based database of case-control studies on occupational exposure (general) using the term pentachlorophenol or its synonyms.[1] (See Figure 1, Citations: Database.)
3. Searches of a pre-determined standard list of general sources including U.S. and international government agency reports, authoritative reviews and related reports (e.g., International Agency for Research on Cancer, U. S. Environmental Protection Agency, Agency for Toxic Substances and Disease Registry, European Union, National Academy of Sciences, National Institute for Occupational Safety and Health) to identify any additional primary epidemiologic studies together with supporting reviews and material that may be relevant for the interpretation of the primary studies. (See Figure 1, Citations: Other Sources.)

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[1] pentachlorophenol , 87-86-5 (CASRN), hydroxypentachlorobenzene, pentachlorobenzene, pentachlorophenate, Dowicide EC-7, Dowicide 7

4. Citation searches from articles, reports, and reviews identified above to identify any additional primary studies or other relevant literature. (See Figure 1, Citations: Other Sources.)
5. Additional literature searches may be conducted on special topics or issues. Examples include searches for information on co-exposures found in the different occupational settings, or information on exposure measures, each of which would require different search terms.

The scientific database search strategies will be saved in Scopus, Web of Science, and PubMed, respectively, which automatically send out weekly notifications concerning newly identified citations using the saved search strategy.

## 1.2 Selection of relevant literature

Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using pre-defined inclusion and exclusion criteria (see below). Multi-level screening of the literature identified from the searches is conducted (see Figure 1); the initial screening is based on titles and abstracts only (Level 1), and subsequent screening is based on full-text PDFs (Level 2 and 3).

Literature is screened at each level by two reviewers using inclusion/exclusion criteria for each level as listed below. The objective of Levels 1 and 2 is to identify literature that is useful for the cancer evaluation section, including primary research studies, reviews, and studies on relevant issues (such as confounders) related to cancer evaluation of pentachlorophenol. In general, the inclusion and exclusion criteria are similar at each level, but because screening of the literature at Level 1 is done using titles and abstracts, the "bar" for excluding literature is very high; a more detailed review of the studies for inclusion/exclusion is conducted at Level 2 using the full text article. The objective of the Level 3 review is to select the primary epidemiologic studies that will be discussed in the cancer review, as described in Section 3, below.

***Inclusion/exclusion questions: Level 1 (titles and abstracts)***

*(1) Does this publication appear to contain information on potential exposure to pentachlorophenol (including exposure inferred from knowledge of an exposure scenario) and human cancer? Relevant information includes, but is not limited to, epidemiologic studies, descriptive studies, pooled analyses, meta-analyses, reviews, letters to editors, exposure-assessment studies (for use in epidemiologic studies), exposure-validation or relevant epidemiologic studies of biomarkers, and information on co-exposures or potential confounders and other special topics of relevance to the evaluation.*

❑ Yes
❑ No

*(2) If the response to Question 1 is "No," identify all reasons that apply from the list below for excluding this publication from the Human Cancer section.*

❑ (a) No information is provided on potential exposure to pentachlorophenol in this study.
❑ (b) The study is not a study in humans or related to an issue or information relevant to interpreting the epidemiologic data.

*Inclusion/exclusion questions: Level 2 (full text)*

*(1)    Does this publication contain relevant information (as defined above) on potential exposure to pentachlorophenol (including exposure inferred from knowledge of an exposure scenario) and human cancer?*

❑ Yes
❑ No

*(2) If the response to Question 1 is "No," identify all reasons that apply from the list below for excluding this publication from the Human Cancer section.*

❑ (a) No information is provided on potential exposure to pentachlorophenol in this study.

❑ (b) Potential exposure to pentachlorophenol is likely in the study or is mentioned in the review or publication, but the publication is not one of the following:

(i) an epidemiologic study (such as cohort, case-control, cross-sectional, ecological, pooled, meta-analysis) or descriptive study (such as case report or case-series) that provides information on human cancer.

(ii) a review, letter to the editor, or abstract, or other type of study providing relevant information related to pentachlorophenol and human cancer.

(iii) a study or other source of data that provides information, such as on exposure assessment or biomarkers, relevant to evaluating the epidemiologic studies.

❑ (c) The publication does not provide information on co-exposures or potential confounders or other special topic(s) relevant to the evaluation.

## 2      Selection of primary epidemiologic studies

Primary epidemiologic studies to be used in the human cancer evaluation will be selected from the Level 2-selected references and must meet the criteria listed below in Questions 1 to 3. Analytical studies (such as case-control studies, cross-sectional studies, cohort studies or pooled analyses) in which potential exposure to pentachlorophenol can be established by quantitative or qualitative exposure assessment, or by the authors' report, or if it is a study of mixed chlorophenols in which there is a high probability that exposure is predominantly to pentachlorophenol are included as primary studies. Studies of mixed chlorophenols in which no specific data are provided on the constituent chlorophenols, or in which pentachlorophenol is stated or known to be a minor constituent of the exposure mix, are excluded from the review.

Any primary epidemiologic studies (such as descriptive studies) on potential exposure to pentachlorophenol that were retrieved from the literature search strategy and not included in the cancer evaluation, and the reason for their exclusion, will be identified in the monograph. Information from multiple publications relating to the same study population may be included in the draft monograph, but the publications will be counted as one study.

"Included supporting citations" (see Figure 1) refers to other literature (such as studies on co-exposures, potential confounders or exposure assessments, reviews, or meta-analyses) that help inform the evaluation of the primary studies and that will be cited in the monograph.

*Exclusion/inclusion questions*

*(1)    Is the publication a peer-reviewed, primary research study on potential exposure to pentachlorophenol and human cancer?*

❑ Yes
❑ No

*(2)  If the answer to question 1 is yes, does the study report a risk estimate (or information to calculate a risk estimate) for cancer?*

❑ Yes
❑ No

## Appendix B: Systematic extraction of data from the epidemiologic studies

Two independent reviewers will extract data (such as methods and findings) from the individual studies into a database in a systematic manner using standardized instructions and questions. The database contains "fields" that are specific for the different types of extracted information (such as study population characteristics, exposure assessment, analytical methods and results). The instructions (questions or guidelines) describe the specific type of information that should be summarized or entered into each "field." The fields will be used to populate tables used in the monograph.

For the cohort and case-control studies, the reviewer will usually extract data from the latest published follow-up or update for each cancer endpoint included in the study. Other relevant information (such as exposure data or re-analyses) from earlier and related publications on the same or overlapping study population will also be included in the review.

Quality assurance and quality control of data extraction and database entry will be accomplished by (a) double-checking of each data entry by the two independent reviewers and (b) flagging any discrepant entries and resolving them by mutual discussion in reference to the original data source.

## Appendix C: Assessment of the quality of the individual studies

Each primary study will be systematically evaluated for its ability to inform hazard identification. Studies that will be given the most weight in the evaluation are those that provide the most valid (i.e., low risk of systematic error or biases) and precise (i.e., low risk from random error) risk estimates, and that have adequate ability (e.g., sufficient power and adequate range of exposure) to detect an effect. In addition, studies should accurately report their findings and apply appropriate analytical methods for calculating risk estimates. The procedures (questions and guidelines) for evaluating the different components of study quality are described in Sections 1.0 to 4.0, below. The guidelines state characteristics of ideal studies; however, most epidemiologic studies typically do not meet all of these ideals, and the evaluation of their ability to identify a cancer hazard is performed in the context of how close or far they approach these ideals.

### 1 Reporting quality questions

Is there adequate documentation and reporting of the (1) description of the selection and follow-up of the population, (2) methods to assess exposure and disease, (3) analytical methods, and (4) cancer findings?

### 2 Analyses of biases: *a priori questions and* guidelines

The application of the RoC listing criteria to the body of studies on pentachlorophenol includes an analysis of whether any association observed between exposure to pentachlorophenol and cancer can be explained by chance, bias, or confounding. The first step in the assessment is to evaluate the study methods to determine whether there is a potential bias. Biases in observational studies are often classified into three major categories: (1) selection bias, (2) information bias, and (3) confounding (Rothman *et al.* 2008).[2] Studies with a lower potential for bias are generally considered to be the most informative for the cancer evaluation. However, the presence of a potential bias in a study does not necessarily mean that the findings of the study should be disregarded. Therefore, an important step in the process of evaluating biases is to determine the probable impact of the described biases on study results—that is, the magnitude of distortion and the direction in which each bias is likely to affect the outcome of interest. This step is reflected in the second part of the questions questions and is analyzed in the assessment of the level of evidence (Appendix D).

Questions and guidelines for evaluating methods used to select the study population and obtain information on exposure and disease are provided in Sections 2.1. and 2.2. The approach for evaluating confounding, which is a key issue in the cancer evaluation of pentachlorophenol, is discussed in Section 3. 0.

### 2.1 Selection and attrition

Studies will be evaluated for the potential for selection or attrition bias. The questions are somewhat different depending on the study design.

***Questions***

- Are the unexposed subjects and exposed subjects from the same underlying population? If not, what information is available to estimate the potential direction and relative magnitude

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[2] Rothman K, Greenland S, Lash T. 2008. *Modern Epidemiology, 3rd Edition*. New York: Lippincott, Williams, and Wilkins, 851 pp.

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of distortion from the bias? Is there any evidence of a healthy worker hire effect?[3] If so, what is the direction and relative magnitude of the distortion from the bias on the risk estimate?

- In case-control studies, are controls selected from the same underlying population as the cases using similar inclusion/exclusion criteria? If not, what is the likely direction and relative magnitude of distortion from the bias?
- In case-control studies, is there any evidence that the methods used to identify and select the controls and/or cases are related to exposure to pentachlorophenol? If so, what information is available to estimate the direction and magnitude of distortion from any potential bias?
- Is there any evidence for self-selection or that refusal to participate in the study is related to both exposure and disease status? If so, what information is available to estimate the direction and magnitude of distortion from the bias?
- Is the ascertainment of vital status at the end of the follow-up period in cohort studies adequate? Does it differ between the exposed and unexposed subjects? Is there any evidence to suggest that completeness of follow-up is related to both exposure and disease status? If so, is it possible to predict the direction and magnitude of distortion from the bias?
- Is there any evidence of a healthy worker survivor effect or left truncation in cohort studies? If so, were appropriate analyses performed to control for the potential bias? Is it possible to predict the direction and relative magnitude of distortion from any uncontrolled (residual) bias?

### *Guidelines*

In cohort studies, the exposed and unexposed groups should ideally be similar in all respects except for exposure to pentachlorophenol. Occupational cohorts would consist of all potentially exposed employees within a given plant or exposure setting (employed over a specified period of use of pentachlorophenol) compared with similar unexposed employees from within the same plant or setting (i.e., internal controls) to minimize the healthy worker effect and other differences between exposed and unexposed groups. When external referents are used in e.g., SMR or SIR studies, local (or regional) mortality or incidence rates are generally, but not always, preferable to national rates.

Systematic biases may be introduced if the length and completeness of follow-up differ between exposed and unexposed groups and are related to the outcome of interest. Ideally, the total loss to follow-up should be less than approximately 5% over the duration of the study observation period. Overall, studies should have more than 80% to 90% total follow-up, although incidence studies may have greater loss to follow-up than mortality studies.

In nested and population-based case-control studies, controls and cases should be selected from the same underlying population (or cohort) and should be representative of the population (or cohort) from which they were selected. Controls should be free of any diseases related to pentachlorophenol exposure; the use of controls with diseases related to pentachlorophenol exposure would bias towards the null. Ideally, participation rates should be high and should be similar for cases and controls, although it is recognized that participation rates in population-based case-control studies are often lower than those in a hospital-based study.

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[3] The healthy worker effect can also be considered as a confounder.

## 2.2    Information (observation) bias

Studies will be evaluated for their adequacy in measuring exposure and disease endpoints, including missing data and the probability of misclassification of exposure and disease.

### *Questions*

- What is the method used to assign exposure to subjects according to their potential for pentachlorophenol exposure? Does the method permit exposure assessment for individual subjects or only for exposure groups? Is the exposure measure qualitative, semi-quantitative, or quantitative? Are errors (if any) in classifying exposure similar (i.e., non-differential misclassification) or different (i.e., differential misclassification) across study groups? If there is evidence for misclassification of exposure, what is the direction and relative magnitude of distortion from the bias?
- Are exposure data missing for the cases and controls or cohort members? Were missing data imputed, and if so, how was this done and are these methods adequate?
- What is the level of confidence that the study was able to identify and classify subjects accurately and completely with respect to cancer endpoints? Was disease assessed similarly across study groups? If disease was misclassified, is it possible to predict the direction and relative magnitude of distortion from the bias?

### *Guidelines: exposure assessment*

One of the most important aspects of a study is the ability to characterize exposure at the individual level. The ideal would be to have quantitative estimates of exposure to pentachlorophenol and relevant co-exposures for each individual that are based on a job-exposure matrix or expert assessment that link the subject's occupational history (e.g., job or department titles, task descriptions, duration of employment, calendar years worked) with data on relevant production methods or applications that are calendar-year specific. Exposure estimates using multiple metrics (such as cumulative, peak, average) improve the quality of the assessment, but are rarely applied to available studies of pentachlorophenol exposure. Studies inferring exposure to pentachlorophenol in studies where only mixed chlorophenols are identified or where job titles or occupations alone are available have a higher probability of non-differential misclassification of exposure. In general, exposure is better characterized in occupational cohort studies of production workers or users than in population-based case-control studies, but in both types of studies misclassification is typically non-differential, usually biasing towards the null. Recall bias in case-control studies in which occupational exposure is assigned based on job titles is less likely to be a concern than in studies using self-assessment of chemical-specific exposures (e.g., use of questionnaires with exposure check-lists).

In the case of pentachlorophenol exposure, the route and intensity of exposure may vary widely depending on whether the exposure occurs among pentachlorophenol production workers, users, or residential populations. Pentachlorophenol is rapidly absorbed through the skin, and, among certain users, e.g. sawmill workers, dermal exposure has been estimated to be up to 95% of the exposure relative to other routes.[4] Thus, methods to estimate exposure (such as JEM or biomonitoring) should consider the most relevant route of exposure for the study population. The use of levels of polychlorinated dibenzodioxins and furans, which have longer half-lives in the body than pentachlorophenol itself,  as "fingerprint" indicators for commercial and technical grade pentachlorophenol has been proposed to model past exposures to pentachlorophenol. A few

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[4] Demers, PA, *et al*. (2006). Cancer and occupational exposure to pentachlorophenol and tetrachlorophenol (Canada). Cancer Causes Control; 17(6): 749-758.

studies have measured serum level of these products in subsets of workers who were exposed to pentachlorophenol in the past.[5,6] While measuring the profile of by-products may not be an ideal surrogate for estimating cumulative exposure and still result in some misclassification of exposure, it may be useful to distinguish pentachlorophenol-exposed from unexposed individuals.

*Guidelines: endpoint assessment*

Incidence data from population-based cancer registry sources generally provide more detailed and accurate diagnostic data and more accurate population (comparison) cancer rates than death certificate-based mortality data, while being less easy to access. The quality and completeness of the cancer registry incidence data, which can vary by e.g., collection methods, region and calendar period, will be evaluated. In the case of pentachlorophenol, the principal cancers investigated to date are NHL, multiple myeloma, soft tissue sarcoma, all cancers combined, and cancer of the liver, and kidney.

The classification of subtypes of lymphohematopoietic cancers has changed over the course of several editions of the International Classifications of Diseases (ICD) and may present challenges if histological data are unavailable to confirm subtypes.[7] Similarly, soft tissue sarcoma is accurately diagnosable only on the basis of both site (connective tissue) and histology.[8]  For these reasons, the accuracy of death certificate data may be limited for these cancer endpoints. In addition, cancer incidence data may be considerably more informative than mortality data (depending on ascertainment, reporting, and diagnostic accuracy) for cancers with relatively longer survival times and good treatment prognoses, such as low-grade non-Hodgkin lymphoma, chronic lymphocytic leukemia (CLL; now considered a form of lymphoma), or certain low-grade soft tissue sarcomas of e.g., the extremities. Length of follow-up is also critical in identifying cases or deaths from long latency cancer endpoints. For longer latency but lower survival cancers such as liver cancer, both incidence and mortality data may be of similar utility, assuming an adequate length of follow-up.

## 3      Approach for evaluating confounding

A key question in the evaluation of the level of evidence from human studies is whether an association (if any) between exposure to pentachlorophenol and cancer can be explained by confounding. The candidate substance is defined as pentachlorophenol and by-products of its synthesis and thus the higher chlorinated dibenzodioxins formed during the production of pentachlorophenol are not considered to be potential confounders. Potential confounders include any exposures or risk factors that could be associated with both exposure to pentachlorophenol and the disease outcomes of interest and that are not part of the disease pathway.

The evaluation of potential confounding will take into account the following:

- Identification of potential confounders. In the occupational cohorts and case-control studies included in the present review, pentachlorophenol-exposed workers or populations are

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[5] Collins J *et al.* (2008). Chlorinated dibenzo-*p*-dioxins, dibenzofurans and biphenyl profiles of workers with trichlorophenol and  pentachlorophenol exposures. Chemosphere; 27: S284-S289 and Collins JJ *et al.* (2007). Serum concentrations of chlorinated dibenzo-*p*-dioxins and dibenzofurans among former Michigan trichlorophenol and pentachlorophenol workers. J Exp Sci Env Epidemiol; 17: 541-548.
[6] McLean *et al.* (2009) Serum dioxin levels in former New Zealand sawmill workers twenty years after exposure to pentachlorophenol (PCP) ceased. Chemosphere; 74: 962–967.
[7] Weisenberger D. (1992). Pathological classification of non-Hodgkin's lymphoma for epidemiological studies. Cancer Res; 52: 5456s–5461s.
[8] Hoppin JA *et al.* (1998). Occupational chlorophenol exposure and soft tissue sarcoma risk among men aged 30-60 years. Am J Epidemiol; 148: 693-703

typically exposed to a number of co-exposures. These may have been quantified or noted by the study authors or may be inferred from expert knowledge of the occupational scenarios described by the authors. Whether or not a given co-exposure should be considered as a potential confounder depends on whether there is *a priori* evidence that the co-exposure is potentially associated with specific cancer(s) of concern.

- Assessment of analytical or statistical methods to control for variables with evidence of confounding (see Section 3.1) or other methods or information on the potential confounders.

- The magnitude of the risk estimate for exposure to pentachlorophenol or strength of exposure-response relationships and specific cancer endpoints (see Section 3.2).

## 3.1    Assessment of analytical methods to evaluate confounding

Studies will be evaluated for their adequacy in measuring potential confounders, such as occupational co-exposures, age, and lifestyle factors, and the appropriateness of the analytical methods and models used to control for confounding.

### *Questions*

- How well were co-exposures, age, or non-occupational risk factors measured in the study? If there are no actual data on confounders, are surrogate data on potential confounders available?
- Does the design or analysis control or account for important confounding through matching, stratification, multivariable analysis, or other approaches?
- Are the models used to control for confounding appropriate? What strategy was used to determine whether the variable belongs in the models? Is there evidence for under- or over-controlling for confounding, residual confounding, or negative confounding?

### *Guidelines*

Ideally, all potential confounders should be quantified and considered for inclusion in the statistical analysis for confounding, using appropriate statistical models. Final statistical models should only include "actual" confounders and not variables that have minimal effect on the risk estimate. Guidelines for evaluating methods to assess exposure to confounding are as follows:

*Occupational co-exposures*: Ideally, studies would provide quantitative exposure data for each potential confounder as part of a job-exposure matrix or expert assessment for each worker, but this is rare. However, some studies provide quantitative or qualitative data on co-exposures for subsets of workers, which can be used to evaluate potential confounding. In addition, knowledge of e.g., pentachlorophenol manufacturing processes or patterns of use in different occupations or populations under study (e.g., wood preservation or biomonitoring data, may also be helpful in providing relative estimates of the ratio of exposure to pentachlorophenol and exposure to the potential confounder.

*Non-occupational risk factors*: Ideally, quantitative information on other non-occupational exposures or lifestyle factors should be assessed, and preferably by in-person interview by interviewers blinded to the status of the respondent in cancer incidence studies, rather than via proxy respondents, work records, or other indirect methods. Residual confounding is more likely when only limited qualitative information (such as yes or no) is available. Few or no data are available on non-occupational risk factors in the available historical cohort studies of pentachlorophenol, other than, in some studies, data on non-cancer endpoints e.g., cirrhosis of the

liver, or smoking-related or alcohol-related diseases, which may provide indirect information on risk factors for specific cancer endpoints of concern.

## 3.2     Impact of potential confounders on study findings

Ideally, all potential confounders should be both quantified and subject to consideration for analysis for confounding, using appropriate statistical models, or confounding should be controlled for using other methods such as in the selection of the study participants. In many cohort studies, there is a paucity of quantitative co-exposure data at the individual level; however, an indirect evaluation of the impact of confounding from co-exposures may be conducted by considering (1) the relative levels of exposure to pentachlorophenol compared with exposure to the confounder, (2) the strength of the association of the potential confounder with the endpoint of interest, and (3) the magnitude of the risk estimate or strength of exposure-response relationship for pentachlorophenol and specific cancer endpoints. As noted above, indirect information on the relationship between the estimated levels of exposure (albeit based on crude approximations) to the confounder compared with the estimated level of exposure to pentachlorophenol may be available from exposure monitoring or biomonitoring studies of subsets of workers.

Typically, few or no data are available on non-occupational risk factors in historical cohort studies. Internal comparison groups and analyses can help reduce confounding from non-occupational risk factors. In the case of liver cancer, depending on the type of tumor, a number of non-occupational risk factors have been identified, including aflatoxins, estrogen-progestogen contraceptives, heavy alcohol consumption, tobacco smoking, betel quid, cirrhosis of the liver, viral infections (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus type 1 [HIV]), parasites (liver flukes and schistosoma), diabetes and obesity, long-term use of anabolic steroids, and certain inherited diseases.[9] Tobacco smoking is also a risk factor for kidney cancer. Non-occupational risk factors for NHL include viral infections (Epstein-Barr virus, HBV, HCV, HIV), immunosuppressive disorders, and exposure to immunosuppressive or chemotherapy drugs[10]. The etiology and risk factors for soft tissue sarcoma are poorly understood, and few non-occupational risk factors have been established, with the possible exception of certain inherited diseases and ionizing radiation exposure;[11] race (African Americans have approximately twice the rate of whites), obesity, and certain autoimmune disorders such as monoclonal gammopathy have been associated with some increase in the risk of multiple myeloma.[12] However, for most of these factors, unless there is an *a priori* reason to suspect that they are related to exposure to pentachlorophenol they would not be considered as confounders or effect modifiers.

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[9] http://monographs.iarc.fr/ENG/Classification/Table4.pdf.

[10] Hardell L and Axelson O. (1998). Environmental and occupational aspects on the etiology of non-Hodgkin's lymphoma. Oncol Res; 10: 1-5.

[11] http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb5/bb5-classifsofttissue.pdf.

[12] http://www.cancerresearchuk.org/cancer-info/cancerstats/types/myeloma/riskfactors/riskfactors.

## 4        Ability of the studies to detect an effect

Factors that influence the ability of a study to detect an effect (if present) include the statistical power of the study, the level, duration, or route of exposure to pentachlorophenol, the exposure range studied, and the length of follow-up in cohort studies (or follow-back in case-control studies). In general, study characteristics that increase the potential for random error (such as high loss to follow-up in cohort studies or low participation rates in case-control studies that are not related to exposure or disease status) will bias the study findings towards the null (see Section 2.1.1 for questions and guidelines).

### Questions

- Is there adequate statistical power to detect an effect in the exposed population or subgroups of the exposed population?
- What were the levels of exposure and the duration of exposure of the populations at risk in the cohort and case-control studies?
- Were risk estimates calculated for subgroups of workers with higher levels or longer durations of exposure?
- Was the follow-up or follow-back period adequate to allow for a cancer induction period of 20 years or greater?
- Was the relevant window of exposure taken into account in the exposure assessment in the case-control study of exposure to pentachlorophenol and childhood cancer?
- Were any analyses of exposure lagging adequate for detecting cancers with longer latency?

### Guidelines

The overall number of study participants and numbers in each exposure or case group will be evaluated in terms of power to detect given elevations of risk for specific cancer endpoints while controlling, if necessary, for potential confounding. For example, the incidences of NHL, liver cancer, and kidney cancer are relatively uncommon and soft tissue sarcoma is rare. In general, five year survival rates (with the exception of liver cancer) are relatively high and thus detection of these endpoints requires large sample sizes for adequate statistical power, particularly for mortality studies.[13] Ideally, studies should have at least 80% power to detect a 2-fold increased relative risk, although similar power to detect a smaller increase in risk would be preferred, given the evidence from studies of 2,3,7,8-TCDD, which have reported relatively low increases in the magnitude of all-cancer risk (i.e., < 1.5). Studies of workers in industries or occupations with higher levels of exposure, or workers with longer duration of exposure and sufficient variability in exposure, are generally the most informative for evaluating cancer risk. Studies evaluating exposure groups in which the majority of workers classified as "exposed" have in fact very low exposure, very short duration of employment, or limited evidence of actual exposure may be inadequate to detect an effect due to a dilution effect.

Inadequate follow-up (or follow-back in case-control studies) may bias findings toward the null for cancer endpoints with longer latencies. In the case of e.g., NHL and other lymphohematopoietic

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[13] Age-adjusted annual incidence or mortality rates (per 100,000 males or females) in the United States from 2006-2010 (US SEER Statistics) for the cancer sites of interest are as follows: (1) NHL – 23.9 (male) and 16.4 (female) for incidence and 8.2 (male) and 5.1 (female) for mortality,  (2) myeloma – 7.5 (male) and 4.8 (female) for incidence and 4.3 (male) and 2.7 (female) for mortality, (3) soft tissue cancers (which include soft tissue sarcoma and other cancers) – 4.0 (male) and 2.8 (female) for incidence and 1.5 (male) and 1.1 (female) for mortality, (4) liver – 11.9 (male) and 4.0 (female) for incidence and 8.3 (male) and 3.4 (female) for mortality, (5) kidney and renal pelvis – 21 (male) and 10.6 (female) for incidence and 5.8 (male) and 2.6 (female) for mortality. Annual incidence rates for soft tissue sarcoma for earlier periods have been reported at approximately 1 per 100, 000.

cancers, latencies appear to vary considerably in some studies of occupational exposures, ranging from 2 to 60 years in some cases.[14] In the case of soft tissue sarcoma, latencies following occupational exposure to multiple dioxins appear to range widely but can exceed 20 years.[15] Multiple myeloma has also been reported to have a long latency, exceeding 20 years, in association with radiation exposure, but is less clear with respect to other possible risk factors. Liver cancer has been associated with a minimum latency of 20 years in association with e.g. vinyl chloride exposure[16] but may be considerably longer for e.g. infectious disease risk factors. Ideally, follow-up or follow-back periods should exceed 15 – 20 years to permit adequate determination of these and other solid tumors with longer latencies, particularly in mortality studies; however, shorter follow up periods may be more relevant for e.g. lymphohematopoietic cancers.

## 5      Analytical methods

The use of appropriate analytical methods will be evaluated. Analysis of exposure-response relationships (using either linear models or exposure categories, or other methods to evaluate the shape of the exposure-response curve) and calculation of trends using quantitative exposure assessments adds more information than analysis by simple binary exposure categories, as does analysis of tumor site by average, cumulative, peak, or duration of exposure, time since first exposure, calendar periods of exposure, and exposure lags. Evaluating the shape of the exposure-response curve is considered to be a positive attribute of a study. Without *a priori* knowledge, it is difficult to know which exposure metric is most appropriate for evaluating causality, so a positive relationship observed with any exposure metric is a concern. In addition, all analyses should examine and, if necessary, adjust for demographic variables and other potential confounders of *a priori* interest, if not done so in the study's design. Evidence of under- or over-controlling for confounding, multicollinearity, and residual confounding will also be evaluated. In the absence of information on confounders, analyses using internal referents who are similar to the exposed subjects can help reduce potential confounding (see Appendix D for further discussion on the evaluation of methods to assess potential confounding). Ideally, analytical methods should also identify and consider potential modifying variables; however, many studies do not have adequate statistical power to adequately evaluate effect modification.

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[14] Olssen H, Brandt L. (1988). Risk of Non-Hodgkin's lymphoma among men occupationally exposed to organic solvents. Scand J Work Environ Health 14: 246-251

[15] Fingerhut M. *et al.* (1991). Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzodioxin. N Engl J Med; 324: 212-218.

[16] Lelbach WK. (1996). A 25-year follow-up study of heavily exposed vinyl chloride workers in Germany. Am J Ind Med; 29: 446-458

**Appendix D: Synthesis**

This section outlines the approaches for synthesizing the findings across the body of studies for each cancer endpoint and making a recommendation on the level of evidence (e.g., sufficient, limited, or inadequate) of the carcinogenicity of pentachlorophenol from studies in humans. Studies with the lowest risk of bias and greatest sensitivity to detect an effect will be identified by using the questions and guidelines described in Appendix C, and these studies are given the most weight in the assessment. The application of the RoC listing criteria to the body of studies on pentachlorophenol includes evaluating (1) whether there is credible evidence for an association between exposure to pentachlorophenol and cancer, and (2) whether such an observed association can be explained by chance, bias, or confounding. Several existing guidelines – strength of the association, consistency across studies, evidence of an exposure-response gradient, and temporality of exposure[17]– are used to help guide the evaluation of these questions. It should be noted that they are not criteria, and with the exception of temporality, each and every element is not required to demonstrate causality. Emphasis should be placed on evaluating the extent to which biases, or confounding by co-exposures that may also cause cancer could explain observed increases in cancer risk.

The cancer assessment will evaluate the following:

- *Temporality.*
- *The consistency of findings across studies with the most adequate methodologies*, as evaluated according to the guidelines described in Appendix C. Consistency needs to be evaluated in the context of variations in outcome definitions, exposure assessment methodologies, exposure levels or duration of exposure of the population, exposure windows, length and completeness of follow-up, or other differences in population characteristics or study methodologies. The evidence from methodologically more limited studies will also be evaluated including an evaluation of whether such limitations can help explain any inconsistent findings.
- *The strength of observed associations between pentachlorophenol exposure and cancer.* The strength of the association can be important in evaluating whether specific confounders or biases can explain the observed association; however, the fact that an association is weak does not necessarily rule out a causal relationship. There are many examples of weak associations between an exposure to a substance and an endpoint that are nevertheless considered to be causal (e.g., environmental tobacco smoking and lung cancer).
- *Evidence for an exposure-response gradient.* A positive exposure-response relationship (which does not necessary need to be monotonic) generally provides more convincing evidence of a causal association than a simple excess of disease. However, there may be biological or methodological reasons for not observing a gradient, and the absence of evidence for an exposure-response relationship is not strong evidence *per se* for the absence of a causal association.
- *Evidence for associations with appropriate latency.*
- *Alternative explanations of chance, bias, or confounding.* The process for identifying potential biases was discussed in Appendix C, Section 2, and that for evaluating potential confounding was outlined in Appendix C, Section 3. As noted in Appendix C, the presence of bias in a study does not mean that the study should be disregarded; the potential for the bias should be analyzed to determine its impact (including the direction and magnitude) on the study findings (e.g., risk estimates for pentachlorophenol and cancer). The finding of consistent,

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[17] Hill AB. (1965). The environment and disease: association or causation? Proc R Soc Med; 58 (5): 295-300.

elevated, positive associations across studies in different populations, with different study designs, and in different occupational settings reduces the likelihood that specific biases or potential confounders in individual studies can explain the associations observed across the body of studies.