TOXICOLOGICAL REVIEW

OF

Tetrachloroethylene (Perchloroethylene)

Appendices

(CAS No. 127-18-4)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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A. RESPONSE TO EXTERNAL PEER REVIEW COMMENTS AND DISPOSITION

The 2008 external review draft (ERD) of EPA's *Toxicological Review of Tetrachloroethylene (Perchloroethylene)* underwent a formal external peer review in accordance with U.S. Environmental Protection Agency (EPA) guidance on peer review (U.S. EPA, 2006c). The external peer review was performed by the National Research Council (NRC). NRC was tasked with evaluating the adequacy of the EPA assessment, the data and methods used for deriving the noncancer values for inhalation and oral exposures and the oral and inhalation cancer unit risks posed by tetrachloroethylene; whether the key studies underlying the draft IRIS assessment are of requisite quality, reliability, and relevance to support the derivation of the reference values and cancer risks; and whether the uncertainties in EPA's risk assessment were adequately described and, where possible, quantified. The major peer review comments below are those that potentially have a major impact on the revision of the ERD, and are quoted verbatim from NRC (2010). These quotations are from the Summary section unless otherwise noted.

A.1. Major NRC Introductory Comments and EPA Response

NRC Comment: The committee appreciates the extensive work that EPA has invested in the development of its draft assessment of tetrachloroethylene. However, the committee has identified concerns about some of the approaches that EPA used to evaluate the data on tetrachloroethylene and subjects about which inadequate information or rationales are used to support its risk assessment—factors that call into question the soundness and reliability of EPA's proposed reference values and cancer risk estimates for tetrachloroethylene. One of the overarching weaknesses of the draft assessment was a lack of critical analysis of the data on which EPA relied in evaluating methodologic strengths and weaknesses. That lack was particularly evident in the assessment of the epidemiologic data: study selection and conclusions appeared to be based heavily on results that showed positive associations, and other data and the strengths and weaknesses of the selected studies were not adequately taken into consideration. The committee observed similar problems in its review of EPA's evaluation of the genotoxicity evidence, in which preference appeared to be given to studies that reported positive results. Specifically, EPA did not analyze studies critically with respect to their methodologic strengths and weaknesses, nor did it organize its discussion clearly to provide an integrated consideration of the weight of evidence on the genotoxicity of tetrachloroethylene. Other mode of action evaluations were also hampered in this way.

EPA Response: EPA agrees that a balanced critical analysis of the data is necessary, and has significantly revised its assessment to make its evaluation of study methodological strengths and weaknesses more organized and transparent, and to address the appearance of study selection and conclusions being based heavily on results that showed positive associations, without adequate consideration of other data and the strengths and weaknesses of the selected studies. Specific changes with respect to evaluation of epidemiologic data, genotoxicity, and modes of action are described in the more detailed responses below.

A.2. Noncancer Assessment

A.2.1. Major NRC Comments on "Critical Noncancer End Point and Studies" and EPA Responses

NRC Comment: The committee found that EPA adequately supported its selection of neurotoxicity as the critical effect on which to base the RfC and RfD. The draft IRIS document illustrates that neurotoxic effects are the most sensitive effects of tetrachloroethylene and that reference values based on neurotoxic effects would be protective against other noncancer effects that occur at higher concentrations.

EPA Response: EPA accepts these NRC recommendations, and continues to rely on neurotoxicity as the critical effect (Section 5.1.1.1).

NRC Comment: EPA provides descriptions of the relevant neurotoxicity studies, but its evaluation of the epidemiologic literature could be improved by providing a critical evaluation of the validity of study designs and evaluation of the methods used for data collection and analysis, which the committee judges to be most important in selecting key studies.

EPA Response: EPA accepts these NRC recommendations. In agreement with NRC recommendations, the rationale for selecting principal studies of neurotoxicity has been more fully and transparently articulated (Section 5.1.1). Study strengths and weaknesses are judged according to the recommended criteria (e.g., study populations, exposure durations, quality of neurotoxicological tests and exposure measurements). EPA has also strengthened the presentation of human and animal studies and reorganized them by the domain, particularly (1) neurobehavior, (2) neurophysiology, (3) brain pathology, and (4) developmental neurotoxicity. As also suggested by the committee, the developmental neurotoxicity studies are grouped together in one section, and a more robust discussion of these studies is provided. EPA focuses on the neurotoxic effects (including developmental neurotoxicity) observed in studies of tetrachloroethylene, and does not comprehensively

review the neurotoxicity of structurally related solvents. The MOA discussion for neurotoxic effects (see Section 4.6.4) addresses mechanistic commonalities with other volatile organic solvents and alcohols but likewise focuses on tetrachloroethylene. Hypothesized mechanisms for the different neurological domains affected by tetrachloroethylene are addressed, as are potential molecular targets. EPA addresses recent animal studies identified by NRC (Boyes et al., 2009; Oshiro et al., 2008) and also includes three new epidemiological studies published or available since the release of the 2008 ERD of EPA's *Toxicological Review of Tetrachloroethylene (Perchloroethylene)*, including the final peer-reviewed report of New York State Department of Health study (NYSDOH, 2010; published by Storm et al., In Press) that was presented to NRC during the committee deliberations.

NRC Comment: EPA chose the 1995 study by Altmann et al. as the critical one for determining the RfC and RfD because it involved an environmental exposure and used a standardized computer-assisted testing battery. Those are reasonable bases for the choice, but they do not outweigh methodologic deficiencies that seriously compromised the results of the study. Most important, the referent group was not appropriate. The group had more education than the exposed group and appeared to have pre-existing differences in cognitive abilities, which could account for its better test results. Evidence of residual confounding by education can be seen in the variability in reported results. For example, there was no association between tetrachloroethylene and visual evoked potentials; this is important because changes in the visual system and abnormalities in visual evoked potentials have been associated with tetrachloroethylene and other related solvents, and they are essentially unrelated to education. Other limitations of the study included the lack of a rationale for initial selection of study subjects, inadequacy of exposure characterization, and lack of a dose-response relationship. Finally, even though the test battery was performed properly, some of the tests have not been well validated with regard to what they reveal about brain damage.

Thus, the committee disagrees with EPA's selection of the 1995 Altmann et al. study as the basis of its risk calculations.

EPA Response: EPA agrees with these NRC recommendations. In particular, based on application of the criteria described above for conducting its critical review, EPA accepts the limitations of Altmann et al. (1995) identified by NRC, and as indicated in Section 5.1.1, relies on other studies as the basis for determining the RfC and RfD (see next response).

NRC Comment: In reviewing the database, the committee gave greater weight to studies that had the strongest methods; it neither chose nor excluded studies on the basis of their results. The set of studies that the committee judged to be more appropriate for supporting the RfC and RfD

include those of Altmann et al. (1990), Cavalleri et al. (1994), Gobba et al. (1998), Echeverria et al. (1995), and Boyes et al. (2009).

EPA Response: EPA modified its approach based on these recommendations. In particular, based on application of the criteria described above for conducting its critical review, EPA judged that three epidemiologic studies of chronic exposure were stronger for deriving an RfC and RfD (Section 5.1.1). These include two chronic neurotoxicity studies considered by NRC to be the strongest methodologically (Cavalleri et al., 1994; Echeverria et al., 1995), with follow-up reported in Gobba et al. (1998). EPA also included Seeber (1989) because of its strong exposure characterization, large number of subjects, and inclusion of an unexposed control group. EPA's preference for these studies relies on suitable methods for controlling confounding variables. Finally, because EPA prefers chronic studies for developing chronic reference values, the acute studies considered by NRC to be the strongest methodologically [the chamber study of Altmann et al. (1990) and the rodent study of Boyes et al. (2009)] are judged to support the neurotoxicity hazard of tetrachloroethylene, but are not as strong a basis as the chronic studies for POD derivation.

A.2.2. **Major NRC Comments on "Derivation of Reference Values" and EPA Responses**

NRC Comment: EPA derived sample inhalation reference values by using results from several supporting neurotoxicity studies for comparison with its principal study by Altmann et al. The committee found that some uncertainty factors were applied inconsistently; specifically, the application of the uncertainty factor to account for subchronic exposures in epidemiologic studies should be justified better. In some cases, EPA did not use such a factor; in other cases, it applied a value of 10 with weak justification.

EPA Response: EPA accepts these NRC recommendations, and has provided more thorough justification for the selection of all uncertainty factors (UFs) (Sections 5.1.3 and 5.2.3). With respect to the UF to account for subchronic exposures, because each of the selected principal studies was of chronic exposure, EPA did not apply this UF to any of the PODs. Comments regarding other UFs are discussed in the response to comments that follow.

NRC Comment: A factor of 10 was used consistently by EPA when a lowest observed-adverse-effect level (LOAEL) from a study was used instead of a no-observed-adverse-effect level (NOAEL). That is consistent with EPA policy. A benchmark dose (BMD) can be treated as a NOAEL, but no studies of neurotoxicity that could support a BMD calculation had been published when the draft was written. More recent studies of neurotoxicity would support such a

calculation (Oshiro et al. 2008; Benignus et al. 2009; Boyes et al. 2009). [NRC, 2010, Chapter 10]

EPA Response: EPA accepts these NRC comments, and has retained the value of 10 for the UF_L (LOAEL-to-NOAEL extrapolation) (Sections 5.1.3 and 5.2.3).

NRC Comment: The uncertainty factor for extrapolating animal data to humans is considered to have toxicokinetic and toxicodynamic aspects. EPA judged that an uncertainty factor of 3 was adequate to address these uncertainties. EPA applied that approach consistently, but the rationale for doing so was not adequately described. Specifically, the draft cites an EPA (1994) document, but it would have enhanced transparency if it summarized briefly why an uncertainty factor of 3, rather than the default factor of 10, was used. [NRC, 2010, Chapter 10]

EPA Response: EPA accepts this NRC recommendation. With respect to the UF for interspecies extrapolation from animals (UF_A), because each of the selected principal studies was in humans, EPA did not apply this UF to any of the PODs. For the "sample" RfCs and RfDs, where some animal studies were used, it is explained that the PODs are expressed as human equivalent concentrations, so the UF of 3 is applied to account for potential pharmacodynamic differences (Sections 5.1.3 and 5.2.3).

NRC Comment: The application of a default factor of 10 to account for interindividual variation is justified because of the paucity of data on sensitive populations, including developing and aging organisms. Its use is appropriate and in accor-dance with EPA guidance. [NRC, 2010, Chapter 10]

EPA Response: EPA accepts these NRC comments, and has retained the value of10 for the UF_H (human variability) (Sections 5.1.3 and 5.2.3).

NRC Comment: In the derivation of RfCs on the basis of neurotoxicity, EPA used a factor of 3 for database deficiencies because of the inadequacy of the experimental literature designed to characterize hazard and dose-response. Key deficiencies identified were inadequate data to address childhood or other life-stage susceptibility, a paucity of animal studies (especially studies of developing animals and of chronic, low-level exposures) designed to investigate neurotoxicity or to define and characterize dose-response relationships, and inadequate database on cognitive testing. It was unclear whether a factor of 3 was adequate to address these uncertainties because there was some overlap with the factor of 10 applied for human variation, which also addressed developmental concerns.

The committee recommends that EPA revisit and defend more clearly its decision to apply a factor of 3 for database deficiencies in light of new data and the committee's findings in

Chapter 3. New studies include, for example, recent papers from researchers in EPA's National Health and Environmental Effects Research Laboratory provide excellent data from well-designed studies using controlled, acute exposures that link deficits in visual function and signal detection with atmospheric tetrachlorethylene concentrations and instantaneous con-centrations in the brain. This includes papers by Oshiro et al. (2008) and Boyes et al. (2009) investigating function and by Shafer et al. (2005) on mechanisms, which is described in the IRIS document but not fully integrated. These studies link neural or behavioral effects to actual brain concentrations of tetrachloroethylene or to their estimated concentration using PBPK modeling. Thus, the animal literature on controlled acute exposure is now stronger. Notable gaps in the animal literature still include the paucity of studies of developmental or chronic exposures. Another consideration is that the committee found the human study of exposed children (Schreiber et al. 2002) to be methodologically flawed. The committee judges these to be serious gaps in the database, which suggests that a factor of 3 may be inadequate to account for database deficiencies. [NRC, 2010, Chapter 10]

EPA Response: EPA accepts these NRC recommendations. Based on concerns raised by the NRC, EPA re-examined the adequacy of the database and increased the UF_D from 3 to 10 (Sections 5.1.3 and 5.2.3).

NRC Comment: The committee derived candidate values by using the same studies as EPA and additional studies. The committee found that the reference values from the strongest studies were in the range of 6-50 ppb (or 0.04-0.34 mg/m3). That range is higher than the RfC of 0.016 mg/m^3 derived by EPA and is further supported when considered in the context of the full database (see further discussion below).

EPA Response: EPA revisited the above calculation based on NRC's annotation that their exercise was illustrative, and that some candidate values were subject to change based on implementation of their advice regarding the UFs. As discussed above, due to concerns raised by the NRC, EPA increased the UF_D from 3 to 10. With this change, the NRC-suggested range would be lowered to $0.01-0.10$ mg/m^3, which fully encompasses EPA's revised range of RfCs (0.02 to 0.06 mg/m^3) (see Section 5.1.3).

NRC Comment: EPA extrapolated the results of inhalation studies to derive the oral RfD for tetrachloroethylene. Physiologically based pharmacokinetic (PBPK) modeling was used to support the route-to-route extrapolation. The rationale behind that approach is sound and adequately explained by EPA, and the choice of dose metric (blood area-under-the-curve) was appropriate and adequately supported by the available evidence. However, the three models used by EPA were formulated and validated with data from inhalation exposures; none was validated

against blood concentrations that result from oral exposure. EPA empirically assumed a value for the rate of oral absorption of tetrachloroethylene; this assumption is inferior to direct estimation. Other PBPK models that use direct estimation are available, and their use may help to reduce the uncertainty in the assumed values; or additional PBPK models could be developed (see recommendation below for a harmonized PBPK model).

EPA Response: EPA accepts these NRC recommendations. EPA followed the NRC recommendations and developed a new harmonized PBPK model that incorporated available oral data from which the oral absorption rate could be estimated (Section 3.5) (Chiu and Ginsberg), which was used in the route-to-route extrapolations for the RfD calculations (Section 5.2.2). The response to recommendations with respect to PBPK modeling is discussed in more detail below (Section A.3.7)

A.2.3. **Major NRC Comments on "Graphical Presentation" and EPA Responses**

NRC Comment: EPA provides graphical comparisons of reference values, values that could be derived from supporting studies. Reference values derived from neurotoxicity data are presented, as are values based on other noncancer effects to illustrate dose dependence of multiple forms of observed toxicity. Overall, the committee supports the approach of presenting the evidence in this visual format. However, the committee recommends some revisions to improve illustration of the uncertainties being represented and to expand the presentation to include the larger body of literature on a particular end point to show how the RfC compares with sample reference values derived from studies that are methodologically sound but not judged to be critical for the RfC. Consistency between the RfC and such studies would provide additional support.

Figure S-1 provides an example illustration developed by the committee. It shows that the majority of sample values is centrally clustered, but there is a wide spread at the lower and higher ends. The overall range of the 19 sample reference values is 0.03-333 ppb (0.0002-2.6 mg/m3), but the range is reduced to about 6-50 ppb (0.04-0.34 mg/m3) when consideration is restricted to the five strongest studies. The RfC of 0.016 mg/m3 calculated by EPA on the basis of the 1995 Altmann et al. study falls below the range. The figure shows that sample reference values that could be derived from the full database of neurotoxicity studies provide some support for the range.

EPA Response: EPA accepts these NRC recommendations. In particular, EPA agrees that the graphical presentation of studies and resulting risk values is useful. EPA graphically portrayed the PODs for all the tetrachloroethylene neurotoxicity studies considered for dose-response analysis, with the principal studies highlighted (see Section 5.1, Figure 5-1). Separately, for the principal studies, EPA graphically presented the PODs and uncertainty

factors that used in the derivation of the noncancer RfC (see Section 5.1, Figure 5-2). Additionally, in agreement with NRC, EPA continues to provide "sample" reference values based on reproductive and developmental, kidney, liver, immunological, and hematological noncancer endpoints. Sample PODs and composite UFs for noncancer effects other than the critical effect of neurotoxicity are also graphically displayed (see Section 5.1, Figure 5-3), in accordance with the NRC recommendations.

A.2.4. Major NRC Comments on "Reproductive and Developmental Effects" and EPA Responses

NRC Comment: EPA's identification of the key animal and epidemiologic reproductive and developmental studies of tetrachloroethylene appears to be complete, but the committee recommends some reorganization and reconsideration of data to provide a more transparent and balanced characterization of the data. [NRC, 2010, Chapter 4]

EPA Response: EPA accepts this NRC recommendation, and has made revisions throughout Section 4.7. Consistent with NRC advice, the presentation of developmental and reproductive toxicity studies was reordered, and developmental studies were separated from reproduction studies, to emphasize the differences in exposure paradigm and types of endpoints assessed. Study strengths and deficiencies are presented in the individual study descriptions. Evidence from supportive in vitro and in vivo studies and the consistency of outcomes across species and protocols are described. Findings of parental (including maternal) toxicity and the treatment levels at which those effects were observed are also described for each study.

NRC Comment: The committee agrees with the selection of the Tinston (1994) two-generation reproductive-toxicity study and the Carney et al. (2006) developmental-toxicity study as supportive of a point of departure and an RfV. EPA's derivation of a comparative RfV based on the developmental toxicity of tetrachloroethylene is an important contribution to the tetrachloroethylene database. [NRC, 2010, Chapter 4]

EPA Response: EPA accepts this recommendation, and has included these studies in developing comparative "sample" RfCs and RfDs (Sections 5.1.4 and 5.2.4).

NRC Comment: However, the committee recommends that EPA revise the chapter to address the specific deficiencies discussed above regarding information presented on the animal reproductive and developmental studies. In particular, the revision should include: (1) a critical analysis of the described studies, including an assessment of the relationship of maternal toxicity

to developmental toxicity and the strengths, limitations, and consistency of the various study results; (2) characterization of maternal toxicity (e.g., mild or severe) associated with the studies listed in Table 4-10 and use of consistent nomenclature (ppm or mg/m3) for listing tetrachloroethylene concentrations; (3) the scientific basis for selecting the Tinston (1994) and Carney et al. (2006) studies as supportive of an RfV; (4) the scientific rationale for selecting the Tinston (1994) study instead of the Carney et al. (2006) study for derivation of the comparative RfV; (5) information on the mode of action for tetrachloroethylene-induced developmental toxicity which addresses the apparent contradictions raised in the committee's review that TCA may be the causative agent; and (6) characterization of the evidence for tetrachloroethylene-induced reproductive and developmental toxicity in animals based on EPA risk assessment guidelines. Stating explicitly whether the animal evidence is sufficient or insufficient for these important end points will help risk managers and others to more readily identify and protect against potential adverse health effects. It will also help to identify data gaps in the tetrachloroethylene database. [NRC, 2010, Chapter 4]

EPA Response: EPA generally accepts these NRC comments and has made revisions based on them throughout Section 4.7.

With respect to recommendation (1), EPA accepts this recommendation, and has as revised the individual study descriptions to include the critical analysis elements noted.

With respect to recommendation (2), it is difficult to determine the relationship between maternal and developmental toxicity in a developmental or reproductive toxicity study. Nevertheless, there is no evidence in the tetrachloroethylene mammalian developmental or reproductive toxicity study database that maternal toxicity compromised or confounded the evaluation of offspring toxicity. In the case of the Szakmary et al. (1997) developmental toxicity study in rats, the maternal toxicity observed at the mid- and high-dose levels did not affect the interpretation of the developmental toxicity observed at the lowest dose level, where only a 13% decrease in maternal body-weight gain (not a decrease in absolute body weight) was observed as compared to control.

With respect to recommendations (3) and (4), EPA accepts these recommendations and has discussed the basis and rationale for selecting studies in Section 5.1.

With respect to recommendation (5), EPA accepts this recommendation and has expanded the discussion of the MOA hypotheses for developmental outcomes to address the potential involvement of the metabolite TCA.

With respect to recommendation (6), EPA accepts this recommendation, and in accordance with EPA risk assessment guidelines for reproductive and developmental toxicity, an explicit statement that the database of animal and human studies was sufficient for the evaluation of developmental and reproductive toxicity was added to the document.

NRC Comment: In addition to revising the chapter, the committee also recommends that EPA consider conducting a bench-mark dose analysis and deriving an RfV based on the Carney et al. (2006) study in addition to, or instead of, the Tinston (1994) study. This will address the potential confounding effects of maternal toxicity at the 1,000 ppm exposure level observed in the Tinston (1994) study. [NRC, 2010, Chapter 4]

EPA Response: Endpoints from both Tinston (1994) and Carney et al. (2006), as well as from Beliles et al. (1980) and Nelson et al. (1980), were carried forward for potential RfC development (see Table 4-49). Sample RfCs were derived for reproductive and developmental effects (see Table 5-7) and were an order of magnitude greater than the candidate RfCs derived for neurological effects (see Table 5-3). The possible (but uncharacterized) influence of maternal toxicity on offspring outcomes at the highest dose tested (1,000 ppm) in the Tinston study would have no impact on the final noncancer reference value derivation.

A.3. Cancer Assessment

A.3.1. Major NRC Comments on "Epidemiologic Evidence Pertaining to Cancer" and EPA Responses

NRC Comment: One of the biggest difficulties in assessing the cogency of the EPA's assessment related to cancer is how the data are organized in the tables and some parts of the text. It would be much easier to evaluate the overall picture of results regarding tetrachloroethylene and a particular cancer if the tables were organized by cancer type as opposed to the current format, which organizes them by study design. The current format requires the reader to jump between sections for cohort mortality, incidence, and case-control studies. Studies are sometimes further categorized as to the type of worker included (for example, dry-cleaner vs degreaser); this makes it extremely difficulty to evaluate the overall consistency or lack of consistency in results related to specific cancers. [NRC, 2010, Chapter 9]

EPA Response: EPA accepts these NRC recommendations. EPA has significantly reorganized the data presentation by type of cancer as follows: neurotoxicity and brain cancers (see Section 4.1); kidney and bladder toxicity and cancer (see Section 4.2); liver toxicity and cancer (see Section 4.3); esophageal cancer (see Section 4.4); lung and respiratory cancer (see Section 4.5); immunotoxicity, hematologic toxicity, and cancers of the immune system (see Section 4.6); developmental and reproductive toxicity, and reproductive cancers (see Section 4.7). Epidemiologic observations on tetrachloroethylene and breast cancer are included in Section 4.7.

NRC Comment: Errors in reporting results also occur occasionally. For example, the draft reports (on page 4-150, lines 1-3), in relation to Hodgkin disease, "a statistically significantly elevated risk for male [sic] with a job title of dry cleaner or laundry worker (Costantini et al. 2001)." The result from Costantini et al. for that group in relation to Hodgkin disease was an OR of 2.5 (95% CI, 0.3-24.6), which is not significant and was based on a single case. [NRC, 2010, Chapter 9]

EPA Response: EPA accepts this recommendation and has corrected reporting errors.

NRC Comment: The overall impression is that data are presented to support a positive association between tetrachloroethylene and cancer and that studies that found no such association are criticized or minimized. EPA should provide a clearer discussion of criteria used to identify studies of merit and a more balanced critique to strengthen the draft IRIS assessment. [NRC, 2010, Chapter 9]

EPA Response: In agreement with NRC, EPA has also now included an updated and more balanced evaluation of the epidemiologic literature on tetrachloroethylene and cancer (throughout Section 4, as described above). Recent literature added to the epidemiologic evaluation comprised 27 epidemiologic studies on occupational tetrachloroethylene exposure and cancer, and one meta-analysis of bladder cancer and dry cleaning. These studies were published since 2004, the date of the comprehensive literature review in support of the 2008 ERD of EPA's *Toxicological Review of Tetrachloroethylene (Perchloroethylene).* As a supplement to the tabular summaries of epidemiologic observations organized by cancer site in Section 4, an appendix characterizes the design and methods more fully. The revised discussion of epidemiologic observations achieves a more balanced review by clarifying how EPA considered study methodological strengths and weaknesses, including evaluation of the exposure-assessment approach, study size, number of observed cancer events, choice of referent population, presence or absence of an exposure-response relationship, and the potential for alternative explanations such as chance, bias, or confounding. A synthesis of the epidemiologic cancer data is provided considering evidence across cancer sites. Major NRC Comments on "Classification" and EPA Responses

NRC Comment: EPA classified tetrachloroethylene as "likely to be carcinogenic to humans." The committee reviewed the classification guidance in EPA's 2005 Guidelines for Carcinogen Risk Assessment and the bioassay data available on tetrachloroethylene and concluded that EPA adequately documented that its classification has been based on the results of bioassays that

found increased incidences of hepatocelluar tumors, mononuclear-cell leukemia (MCL), renal tumors, and hemangiosarcomas in laboratory animals and to a lesser extent on epidemiologic evidence. EPA's decision to characterize tetrachloroethylene as likely to be a human carcinogen as opposed to "carcinogenic to humans" appropriately reflects the possibility that there are deficiencies or potential inaccuracies in interpretation of the data. Some of the possible deficiencies and inaccuracies are discussed below for each of the datasets.

EPA Response: EPA accepts these NRC recommendations, and continues to classify tetrachloroethylene as "likely to be carcinogenic to humans" (Section 4.10.3). EPA agrees with NRC that the epidemiologic literature on cancers provides limited evidence that tetrachloroethylene is carcinogenic in humans. The revised analysis affords a stronger foundation for EPA's conclusion that the epidemiologic evidence provides a pattern associating tetrachloroethylene exposure and several types of cancer, including bladder cancer, non-Hodgkin lymphoma, and multiple myeloma. Associations and exposure-response relationships were reported by studies using more precise exposure assessments for tetrachloroethylene. For other sites, including esophageal, kidney, lung, cervical, and breast cancer, more limited data provide a pattern of evidence associating tetrachloroethylene exposure and these cancers. One difference between these sets of data and the data for bladder cancer, non-Hodgkin lymphoma, and multiple myeloma is a more mixed pattern of observed risk estimates and an absence of exposure-response data from the studies using a quantitative tetrachloroethylene-specific cumulative exposure measure.. Studies published since 2004 provide additional support for site-specific conclusions.

NRC comments and responses regarding individual animal bioassay datasets are discussed below.

NRC Comment: *Mononuclear-Cell Leukemia*

An increased incidence of MCL in F344 rats has been reported in two bioassays. The biologic significance of the increases was debated by the committee because increases were observed in only one strain of rat, which is known to have a high background incidence of MCL, and because MCL's relevance to humans and the mode of action of tetrachloroethylene causing it are not understood. In considering the high background of MCL, the committee found a published assessment by Thomas et al. (2007) that applied statistical approaches (life-table analyses) to bioassays of the National Toxicology Program (NTP) to interpret dose response relationships. Tetrachloroethylene was one of five chemicals of 500 tested by NTP that showed statistically significant increases in MCL in both male and female rats despite the high background rates. The publication advocated that such statistical evidence be supported with a weight-of-evidence analysis of biologic data before conclusions were drawn.

The committee found some support from epidemiologic studies that suggested an association between tetrachloroethylene and lymphoma, but the data were relatively weak and inconsistent. A difficulty in interpreting the findings is a difference of opinion about the human relevance of MCL. Some committee members judged that similarities between a form of human leukemia (natural killer-cell large granular lymphocyte leukemia) and rat MCL and results of mechanistic studies that the committee recommended be added to EPA's assessment were adequate to establish human relevance; others believed that more research was needed to establish the relevance. The committee agreed that there was little information on a mode of action of tetrachloroethylene in increasing MCL and that it therefore was not possible to determine whether exposure to tetrachloroethylene results in initiation of new tumors or enhances the expansion or promotion of existing tumors.

EPA Response: EPA considered the various viewpoints presented by NRC regarding the human relevance of MCL. EPA agrees that the additional analyses and data identified by NRC are informative. EPA has added discussion of the additional studies and analyses recommended by NRC (see Section 4.6). Studies of the bone marrow toxicity of the mutagenic cysteine conjugate of tetrachloroethylene are presented in more detail, as an aid to increasing the transparency of the conclusion that active moiety(ies) of tetrachloroethylene contributing to MCL development in the F344 rat remains to be elucidated. EPA synthesized the available information utilizing the mode of action (MOA) framework articulated in the *Cancer Guidelines* to inform human relevance and dose-response in the low-dose region (U.S. EPA 2005). Recognizing the difficulty in interpreting the MCL findings, and in the absence of information to indicate that the observed positive effects in these studies are not relevant to humans, the observation of MCLs in these studies were included in the weight of evidence for assessing carcinogenic hazard to humans.

NRC Comment: *Hepatic Cancer*

Statistically significant increases in hepatic tumors were observed in male and female mice after oral or inhalation exposure. As in the case of MCL, the biologic significance of the increases was debated by the committee because B6C3F1 mice have a high background incidence of hepatic cancer. However, the findings were reproduced in several studies conducted in different laboratories and showed a dose-response relationship. There is also fairly substantial information for characterizing potential modes of action of hepatic-tumor formation relative to the data available on MCL and renal cancer. Although the committee recommended that EPA revise its presentation of the mode-of-action evidence on tetrachloroethylene-related hepatic cancer to clarify its position, most of the members agreed with EPA that the mode of action is complex and remains to be established. The latter members also agreed that there was

insufficient evidence to rule out human relevance. One member objected to those conclusions and to the committee's support of using hepatic cancer to quantify risk. He argued that in the absence of evidence of other contributing modes of action, the evidence is sufficient to conclude that the mode of action in mice is predominantly through activation of the peroxisome proliferator-activated receptor-alpha, a mode of action that he considered to be of little relevance to humans. His arguments are presented in a dissenting statement in Appendix B of the report.

EPA Response: EPA agrees with the majority of the NRC panel that the mode of action for hepatic tumors observed in male and female mice is complex and remains to be established, and that therefore there was insufficient evidence to rule out human relevance (Sections 4.3.5 and 4.10.5.3).

NRC Comment: *Renal Cancer*

Tetrachloroethylene caused a low rate of induction of renal tumors in rats. Although the increases were not statistically significant when compared with concurrent controls, EPA has used historical controls to calculate the chances of two of these rare carcinomas to occur by chance to be less than 0.001. Further-more, a dose-response trend was shown against the low background and the tumors in the treated rats were malignant whereas the tumors in the controls were not. EPA provided a strong evaluation of the potential modes of action for tetrachloroethylene-induced kidney cancer. The committee agrees with EPA that the mode of action of tetrachloroethylene tumorigenesis is not understood but that a mutagenic mode of action cannot be ruled out. Thus, renal tumors observed in tetrachloroethylene-treated rats were considered relevant to humans although additional characterization of quantitative relevance is desirable.

EPA Response: EPA agrees with the NRC panel that renal tumors observed in tetrachloroethylene-treated rats are considered relevant to humans. EPA has performed additional characterization of quantitative relevance through development of a harmonized PBPK model for tetrachloroethylene that includes the glutathione conjugation pathway (Section 3.5, and discussed below, Section A.3.7).

A.3.2. Major NRC Comments on "Selection of Tumor Type for Quantitative Assessment" and EPA Responses

NRC Comment: The committee was unable to reach consensus on the selection of the critical cancer end point. The majority of the members judged that the uncertainties associated with MCL (particularly the high background incidence, uncertainty about the dose-response relationship, and poor understanding of mode of action) were too great to support using MCL

data rather than data on hepatic or renal cancer for determining quantitative estimates of risk. Those members judged that the use of the MCL data could be justified only if it is EPA's policy to choose the most conservative unit risk when considering options but that such justification should be distinguished as a policy decision, not a scientific one. They believed that a more scientifically defensible approach would be to use the dataset that has the least uncertainty rather than the dataset that yields the highest estimate of risk. In their judgment, the hepatic-cancer data would have the least uncertainty, followed by the data on renal cancer and MCL.

Other members judged that the MCL data should be used for cancer-risk estimation. Their opinions were based on the observation that reproducible, statistically significant increases in MCL in male and female rats above the background incidence of MCL were found and that MCL was the cancer end point with the highest magnitude of response. They believed that use of the most sensitive response to quantify cancer risk decreases the uncertainty associated with potential differences in metabolism and susceptibility to tetrachloroethylene among exposed populations. They concluded that additional statistical analyses of the dose-response data and the addition of supporting mechanistic information identified by the committee would strengthen the existing support of the use of MCL in the draft assessment.

EPA Response: EPA considered the various viewpoints presented by NRC. EPA has clarified that establishing an upper bound estimate of human carcinogenic potency[1] involves multiple factors and considerations, including (a) magnitude and robustness of the response, (b) role of metabolism, (c) carcinogenic MOAs, (d) dose-response model fit, and (e) resulting low-dose extrapolation predictions (see Section 5.4.4.2). EPA evaluated 6 datasets (rat MCL in males and females, rat kidney tumors in males, mouse liver tumors in males and females, mouse hemangiomas in males) that were considered suitable for dose-response analysis:

(a) In terms of magnitude and robustness of response (i.e., size of and statistical significance of effect), the mouse liver tumors and rat MCLs carry the greatest weight.

(b) In terms of the role of metabolism, data on the metabolic pathway involved was available for mouse liver tumors and rat kidney tumors, and only for the former could interspecies differences in metabolism be addressed quantitatively using the PBPK model.

(c) In terms of mechanistic MOA data, concrete MOA hypotheses are available for mouse liver tumors and rat kidney tumors, though even in these cases, data are inadequate to establish a carcinogenic MOA.

[1] As stated in the *Cancer Guidelines* (U.S. EPA, 2005): "Slope factors generally represent an upper bound on the average risk in a population or the risk for a randomly selected individual but not the risk for a highly susceptible individual or group. Some individuals face a higher risk and some face a lower risk. The use of upper bounds generally is considered to be a health-protective approach for covering the risk to susceptible individuals, although the calculation of upper bounds is not based on susceptibility data."

(d) In terms of the dose-response fit, both the mouse liver tumor and rat MCL data showed non-monotonic or supralinear dose-responses that led to poorer fits with the multistage model, with the other datasets adequately fit by the multistage model. As discussed below (comments and responses in Section A.3.5), alternative models/approaches were used to model the supralinear datasets.

(e) Finally, with respect to the low-dose extrapolation predictions, the dose-response analysis of the MCL data resulted in the highest potency estimate.

As discussed in Section 5.4.4.2, given the significant gaps in the scientific knowledge regarding the metabolites and mechanisms contributing to tetrachloroethylene-induced cancer, the factors relating the role of metabolism and MOA were not able to strongly discriminate among the datasets, and none of the datasets can be excluded on a metabolic or mechanistic basis. Based on the remaining factors, and recognizing the differences in opinion among the NRC panel members regarding the use of the MCL data for cancer quantification, the rat MCL data were selected for deriving the upper bound estimate of carcinogenic potency because of the magnitude of the observed response (similar to the other endpoints); the additional dose response modeling was able to fit the dataset's supralinearity, as well as estimate a BMDL (similar to the other endpoints); and it is the largest unit risk estimate, which is the preferred science policy choice of EPA. Therefore, EPA concluded that using the rat MCL data results in a reasonable upper bound estimate of human carcinogenic potency.

In addition, EPA agrees with the view of some members of the NRC panel that use of the most sensitive response to quantify cancer risk may decrease the uncertainty associated with potential differences in metabolism and susceptibility to tetrachloroethylene across exposed populations. However, in recognition of the opinion of some NRC panel members that the cancer risk estimates should be based on hepatic or renal tumors, a more robust discussion of the cancer risk that would be estimated from using these and other endpoints, along with a graphical comparison, has been added to Section 5.4.4.3 and 5.4.4.4.

A.3.3. **Major NRC Comments on "Mode-of-Action Considerations" and EPA Responses**

NRC Comment: The modes of action by which tetrachloroethylene produces increases in MCL, hepatic cancer, and renal cancer were an important consideration in EPA's and the committee's evaluations of the evidence. The analytic framework described in EPA's cancer guidelines for considering hypothesized modes of action was best applied in the draft IRIS assessment's

consideration of renal cancer. The evaluation focused on synthesizing the evidence to support the idea that multiple modes of action may play a role.

EPA Response: EPA accepts these NRC recommendations. In addition, EPA has included text and tabular summaries of the relevant data for the MOA hypotheses to better and more clearly support the conclusions. In agreement with the comments by the NRC, EPA concludes that neither the α2μ-globulin nor peroxisome proliferation MOAs is adequately supported as an operative or contributing MOA for renal cancers, but that a mutagenic MOA cannot be ruled out (Sections 4.2.4 and 4.10.5.3).

NRC Comment: However, for hepatic cancer, the committee found that the assessment lacked the organization to present and provide appropriate context for the evidence clearly. It therefore recommended that EPA revise its mode-of-action assessment for hepatic cancer to support better the conclusions that were drawn. Specifically, the committee suggested that the mode-of-action analyses would be improved by outlining the proposed sequence of hypothesized tetrachloroethylene-associated key events (possibly with a diagram). Transparency would be improved by presenting the details of experimental results in tabular form to allow the reader to understand more easily the relative potency of tetrachloroethylene, or its metabolites, in inducing both key events and tumors. In this context, species and strain differences could also be considered more easily. The goals of the presentation should be to lay out the timeline of key events explicitly in the context of dose, to evaluate concordance between early and late events, and to consider the relative contribution of chemical-specific data compared with information on categories of chemicals.

EPA Response: EPA accepts these NRC recommendations. EPA agrees with and has followed NRC's recommendations in revising the discussion of supporting evidence for the various hypothesized MOAs. In particular, EPA has reorganized its presentation of the pertinent MOA data and included additional analyses suggested by NRC (Sections 4.2.4, 4.3.5, 4.10.5.3, and Appendix C). Specifically, EPA addressed additional MOA hypotheses identified by the committee regarding epigenetic changes and cytotoxicity and secondary oxidative stress and significantly revised the presentation of the PPARα-activation MOA. As recommended by NRC, EPA presents the supporting evidence from studies of tetrachloroethylene, TCA, other compounds, and the rationale for species differences. Quantitative analyses of TCA, DCA, other known peroxisome proliferators, PPARα endpoints (including PPARα transactivation) and hepatic cancer are provided. Additional emphasis has been given to the deficiencies in the knowledgebase regarding the MOA for tetrachloroethylene.

NRC Comment: This approach should be applied to each hypothesized mode of action. Even if the data are ultimately judged to be insufficient to support a hypothesis, the exercise can be used to identify critical data gaps and to inform the direction of future research.

EPA Response: EPA accepts these NRC recommendations. In particular, EPA has undertaken significant revisions to more clearly specify the hypothesized MOAs for each tumor endpoint, and to present and analyze the evidence available to support conclusions about these hypothesized MOAs (Sections 4.2.4, 4.3.5, and 4.10.5.3). This includes clear presentation of experimental details in tabular form.

A.3.4. **Major NRC Comments on "Low-Dose Extrapolation" and EPA Responses**

NRC Comment: EPA's dose-response analyses of the various cancer datasets involved us-ing several models to extrapolate to doses below the experimental range. EPA considered six datasets: hepatocellular adenoma or carcinoma in male and fe-male mice, hemangiosarcoma in male mice, MCL in male and female rats, and renal tumors in male rats. It used the multistage model for each dataset because mode-of-action information was lacking or uncertain and the model was able to fit a broad array of dose-response patterns. However, because the studies used small numbers of dose groups and because the benchmark-dose software automatically fixed some parameters to zero to obtain convergence in model-fitting, the fitted models were nearly linear in the low-dose range. The imposed linearity explains the similarity among the slopes of the models and among the unit risks derived from the models.

EPA Response: EPA would like to clarify that the earlier modeling did not impose linearity on the subject data sets through the software implementation. EPA's software uses maximum likelihood estimation, a standard method; the software merely allowed for the possibility of linearity in the chosen model and did not select or fix parameters at zero, as suggested by the NRC comment. Although multistage model parameters are restricted to be non-negative, this only imposes monotonicity, not linearity. Also, the multistage model can take on more curvilinear forms, even with just first-order models. The methods used have been clarified further in the assessment (section 5.4.3.2.1).

NRC Comment: In the case of hepatocellular adenoma and carcinoma in male mice and MCL in female rats, EPA considered the fitted models acceptable solely on the grounds that statistical tests for goodness of fit had nonsignificant results ($p > 0.10$). The committee considers this to be a weak rationale in that the statistical significance of goodness-of-fit tests may not detect a poor fit when the number of animals per dose group is small.

EPA Response: EPA agrees that the reported model fits to the male mice hepatocellular tumors and female rat MCLs were not as descriptive of these data as the fits to other tumor data in the assessment. EPA disagrees, however, that the specific points made about judging goodness of fit are as generic as the NRC indicated. First, EPA notes that the use of $p = 0.1$ as a cut-off for goodness of fit was an error in the external review draft; it has been corrected to $p = 0.05$, which is relevant when there is a preferred model (section 5.4.3.2.1).

EPA agrees that adequate power of statistical testing is an important consideration when interpreting lack or presence of statistical significance. In the case of goodness-of-fit, however, four groups of 50 animals per dose group is the standard around which the risk assessment methods in use have been developed. Moreover, noting that arbitrarily manipulating sample size is contrary to goodness-of-fit notions, EPA could not replicate the reported result from NRC's simulated experiment using twice as many animals per dose group.

EPA also takes other factors into account in assessing goodness-of-fit. The absolute values of the standardized residuals for the reported fits for each of the highlighted data sets were within the recommended limit of ±2 units; this was part of the decision to accept the models reported previously. However, the visual fits for both data sets were not satisfying, as pointed out by the committee. Most importantly, in both cases, the *modeled* benchmark concentration for an extra risk of 10% (both the maximum likelihood estimate and the 95% lower bound) was *higher* than the concentrations at which 10% or more extra risk response was *observed*. Improved model fits to these data are discussed in the response to the next comment.

NRC Comment: The questionable fitting of the multistage model to some candidate datasets and insufficient consideration of alternative models contribute to underestimation of the overall uncertainties.

EPA Response: EPA agrees that the dose-response relationships for the highlighted data sets merited reanalysis, particularly in cases where the multistage model did not fit the data at lower doses. The additional analyses, discussed further below, resulted in better characterization of these data sets.

Several options to find better fitting models were considered, including: other model forms; substitution of historical controls for concurrent controls; exclusion of exposure groups from the analysis, starting with the highest exposure group; and consideration of dose-response analysis of combined males and females. These analyses (provided in detail in Section 5.4.4.1) resulted in use of a one-degree multistage model for the male hepatocellular tumors and in use of combined male and female rat MCL data and an alternate model

(Michaelis-Menten) for adequate characterizations of the low-dose data. Thus, these additional analyses address the concerns with respect to dose-response fitting of supralinear data sets. The resulting best supported benchmark concentration lower limits were lower than those EPA reported previously, which the NRC noted would lead to linear low-dose extrapolation that is not conservative.

NRC Comment: EPA adopted linear low-dose extrapolation, the default option, with several justifications. First, nonlinear, mechanistic models are unavailable for dose-response modeling because mode-of-action information on tetrachloroethylene is insufficient and support for dynamic models is unavailable. Second, because mathematical models are subject to uncertainties for low-dose extrapolation beyond the experimental dose range, linear extrapolation is more conservative than all sublinear (curvilinear) models. When individual thresholds in the human population are plausible, wide variation in threshold values typically implies a curvilinear shape of the dose-response relationship. Thus, linear extrapolation protects susceptible subpopulations. Third, a few of the candidate data, especially EPA's preferred male-rat MCL data, exhibit a linear dose-response relationship. Whereas those arguments are consistent with EPA's Guidelines for Carcinogen Risk Assessment, there is evidence in the candidate datasets that the underlying dose-response relationship can be supralinear (for example, in MCL in female rats). When that is the case, low-dose linear extrapolation is not conservative. EPA does not present the full ranges of variation and uncertainty in relation to model choice, in large part because it applied only linear or nearly linear dose-response models to all candidate datasets.

EPA Response: Responses to comments with respect to the range of uncertainty and variability are addressed below under "Uncertainty Analysis."

A.3.5. **Major NRC Comments on "Age-Adjustment Factor" and EPA Responses**

NRC Comment: EPA did not apply an age-adjustment factor to its cancer risk assessment, because there is little evidence that tetrachloroethylene or its oxidative metabo-lites directly damage DNA, because information about genotoxicity of gluta-thione (GSH) metabolites in cell assays other than Salmonella or in vitro experiments is lacking, and because the mode of action of tetrachloroethylene has not been established. In addition, there are no data on differential sensitivity to tetrachloroethylene carcinogenicity among life stages. The committee agrees that those are adequate reasons for not using an age-adjustment factor but suggests that the rationale can be strengthened if EPA follows the committee's suggestions for improving its analysis of the genotoxicity data and mode-of-action evidence.

EPA Response: EPA accepts these NRC recommendations. To better support its conclusions, EPA has substantially revised the genotoxicity section (see Section 4.8) in accord with NRC recommendations. Text and tabular study summaries of the available genotoxicity studies of tetrachloroethylene and its metabolites are presented, organized by test article (chemical entity) and further structured according to the assessed endpoint. Missing and more recently peer-reviewed and published studies as identified by the NRC committee are included. Additionally, the data for each test article are summarized, and an overall synthesis section is included.

A.3.6. Major NRC Comments on "Physiologically Based Pharmacokinetic Models" and EPA Responses

NRC Comment: Tetrachloroethylene can be viewed as being metabolized by three pathways. The predominant pathway is the cytochrome P-450 (CYP) pathway that produces metabolites that have been associated with hepatic cancer. Two other pathways involve the GSH conjugation pathway that produces metabolites that are further metabolized by the β-lyase pathway or the β-lyase-independent pathway, each of which produce metabolites that have been associated with renal cancer. To take those metabolic factors into account, EPA used three PBPK models to estimate human equivalent doses from animal studies and to perform route-to-route extrapolations. Each of the models used total metabolism of tetrachloroethylene as the dose metric. In some instances, EPA used a single model; in others, it used all three. The justification for using single or multiple models is not always clear. The committee observed that the models could yield different results because they were calibrated with different datasets, so comparisons among them were not straightforward. For consistency and to allow for better comparisons among end points, the committee recommends that EPA use a single PBPK model for its assessment. Ideally, the model would be a "harmonized" version of the three models used by EPA or of other relevant models (that is, a single model that integrates multiple exposure routes and tissue compartments).

The committee notes that the use of total metabolism as the dose metric for carcinogenicity reflects primarily the CYP metabolic pathway because of large differences in the flux of the metabolism between it and the GSH pathway. Using that dose metric does not reflect the contribution of the GSH conjugation pathway, which has been implicated in the development of renal cancer. EPA did not pursue the addition of the GSH pathway to any of the PBPK models, arguing that data on GSH-dependent metabolism are from in vitro studies or constitute measurements of urinary excretion products and do not represent toxic species in vivo. The committee agrees that the available data on the GSH pathway are more limited than the available

data on the CYP pathway but notes that in vitro and urinary metabolite data were used in the development of the CYP-based PBPK models chosen by EPA. Thus, better justification is necessary to rule out modeling the GSH pathway.

The committee recommends that EPA explore the possibility of adding the GSH pathway to a harmonized PBPK model. If such modeling is deter-mined to be infeasible, total metabolism can be used as a reasonably conservative dose metric. The modeling exercise would be useful in identifying data gaps that prevent successful modeling, which can be used to guide research that will allow more comprehensive PBPK models to be developed in support of the next IRIS reassessment of tetrachloroethylene.

EPA Response: EPA accepts these NRC recommendations, agrees that a "harmonized" PBPK model that includes data regarding the GSH pathway would be beneficial, and has developed such a model that integrates multiple exposure routes and tissue compartments (Section 3.5). Additionally, EPA followed the NRC advice of separating metabolism into three pathways (oxidation, GSH-conjugation with further β-lyase metabolism, and GSH-conjugation with further β-lyase-independent metabolism). The PBPK modeling analysis showed that the GSH conjugation pathway in humans remains highly uncertain and/or variable, and that additional data are needed to better quantify that pathway in humans (see Section 3.5). Therefore, the assessment does not rely on quantitative estimates of GSH pathway metabolism provided by the new PBPK model. Instead, the quantitative risk estimates presented in the revised assessment rely on estimates of blood tetrachloroethylene, oxidation of tetrachloroethylene, and route-to-route extrapolation from this new model. These dose metric estimates from the new model are robust and consistent with prior models and, thus, insensitive to model choice.

A.3.7. **Major NRC Comments on "Uncertainty Analysis" and EPA Responses**

NRC Comment: EPA has clearly identified key sources of uncertainty as part of its process of assessing the cancer risk posed by exposure to tetrachloroethylene, including human population variation, low-dose extrapolation, dose metrics, extrapolation from animals to humans, and the use of PBPK models for route-to-route extrapolation. The effect of uncertainties on risk estimates is assessed qualitatively in most parts of the IRIS draft except in dealing with such issues as the choice of dose-response models, the use of PBPK models, and, to a small degree, variation between studies. That approach reflects the current state of practice of uncertainty analysis.

EPA Response: EPA agrees with the NRC comments that its approach to uncertainty analysis reflects the current state of practice, and that emerging new methods for

quantification of overarching uncertainty, of variability, and of their cumulative effects could be considered when tetrachloroethylene is re-evaluated. In addition, as recommended by the NRC committee, EPA has retained tabular presentation highlighting EPA's choices and their effects on the determination of the upper bound of the risk estimate (section 5.4.5).

NRC Comment: In a few respects, the committee disagrees with EPA's presentation on uncertainties. For example, EPA notes narrow variation between cancer risks derived from four dose-response models. However, in its comparison, EPA used only data on male rats, and all four models were linear or nearly linear at lower doses. Failure to consider a wider array of feasible dose-response models, including multistage models of various orders, could lead to inadequate quantification of uncertainty associated with the choice of dose-response model.

The committee supports EPA's quantitative assessments of uncertainty with regard to choice of dose-response models, the use of PBPK models, and variation between studies. In particular, the committee found EPA's consideration of uncertainty due to different forms of dose-response models to be valuable, and it recommends that such quantitative evaluations be extended to all candidate datasets so that a fuller array of uncertainties can be assessed.

EPA Response: EPA accepts these NRC recommendations. In particular, EPA agrees that extending the quantitative evaluation of different models to all candidate data sets so that a fuller array of uncertainties at the point of departure (i.e., 10% extra risk level) is useful. EPA has conducted dose-response modeling on the basis of administered concentration for each of the JISA candidate data sets using the range of dichotomous dose-response models included in BMDS (Appendix D). The results of the suite of models were evaluated for goodness-of-fit. For datasets exhibiting supralinearity, models that led to both a better fit to the supralinear shape and a stable BMDL were considered for further application using PBPK model-based dose metrics. The results of this analysis showed that for datasets exhibiting supralinearity, the BMD estimated using the multistage model may lead to an underestimation of risk, consistent with the NRC comments. Moreover, in such cases, it can be challenging to obtain both a better fit than the multistage model and a stable lower bound estimate for the BMD.

A.4. Response to Public Comments – Noncancer Assessment

A.4.1. Critical Noncancer End Point and Studies

Public Comments: Several public commenters recommended specifying the criteria used to select studies of the best quality, to better support weight of evidence conclusions and principal study selection. Several commenters critiqued Altmann et al. (1995) based on factors such as small sample sizes, uncontrolled confounding, selection bias, the transient and subtle nature of the effects, the relevance of exposure scenario and the statistical analysis. Another public commenter submitted, and recommended consideration of (for RfC derivation and in choice of UF), the final peer-reviewed report of New York State Department of Health study (NYSDOH, 2010) (published by Storm et al. [2011, in press]). Other studies of neurological effects in residential populations were identified for use either in supporting an RfC based on Altmann et al. (1995) or in conduct of a meta-analysis together with Altmann et al. (1995). One commenter noted a lack of concordance from high to low exposures in human studies, and from human to animal studies.

> **EPA Response:** The EPA re-evaluation included the final peer-reviewed report of New York State Department of Health study (NYSDOH, 2010) (published by Storm et al. [2011, in press]) that was provided to EPA in public comments and presented to NRC during the committee deliberations. As discussed above in Section A.2.1, EPA followed NRC recommendations in more transparently presenting the rationale for evaluating and selecting principal studies of neurotoxicity.

A.4.2. Derivation of Reference Values

Public Comments: One commenter found that application of 3 for the UF_D (database) was unjustified, noting that the lack of data regarding childhood or other life stage susceptibility is adequately accounted for by the use of 10 for human variation. Another commenter noted that additional quantitative adjustment to account for sensitivity and susceptibility of children is needed in RfC derivation. One commenter remarked that median, rather than mean PERC concentration (the latter having been adopted by EPA), is more scientifically defensible as a POD. This commenter also questioned EPA's assumption of continuous exposure in the critical study supporting the RfC. The commenter recommended that EPA develop a time-weighted average exposure estimate, assuming 75% time in residence from Schreiber et al. (2002), the

population/percentile estimates from EPA's Exposure Factor Handbook, or using a biologically-motivated mathematical or PBPK-based approach.

EPA Response: Based on public comments and concerns raised by the NRC, EPA re-examined the adequacy of the database and increased the UF_D from 3 to 10 (See Sections 5.1.2, 5.1.3, and A.2.2). EPA continues to use mean exposure, based on the argument of Crump (1998) that arithmetic means are expected to represent total risk better than geometric means (see Section 5.1.1.3.2). The revised assessment uses mean exposures from occupational studies, which EPA time-weighted to represent continuous exposures.

A.4.3. Graphical Presentation

Public Comments: Several commenters endorsed graphical presentation of studies to illustrate the support of reference values by multiple studies, and one commented that a distributional quantitative uncertainty analysis should have been undertaken. An objection was raised to citing Fredriksson et al. (1993) as a supporting study, because no difference in responses was noted between doses which differed by 60-fold.

EPA Response: EPA has followed the NRC recommendations and agrees that the graphical presentation of studies and resulting risk values is useful (see Section A.2.3). In agreement with NRC advice, EPA does not conduct a quantitative uncertainty analysis. EPA agrees with concerns that the Fredriksson et al. (1993) is limited to support dose-response analyses, and does not include it among the tetrachloroethylene neurotoxicity studies considered for dose-response analysis.

A.4.4. Reproductive and Developmental Effects

Public Comments: Several commenters raised concern that the epidemiological studies for developmental and reproductive endpoints were not objectively reviewed. One commenter raised concern about presentation of the studies by and Fredricksson et al. (1993) and Szakmary et al. (1997) noting that in the latter study effects were only reported at doses causing maternal toxicity. They also raised concern about the presentation of potential MOA for developmental toxicity. They found incomplete and selective the presentation of studies examining cardiovascular malformations caused by tetrachloroethylene metabolites, noting that exposures at environmentally-relevant concentrations as an improbable cause for such effects. Other concerns raised by this commenter related to POD selection, citing a lack of transparency in LOAEL and NOAEL selection.

EPA Response: As presented in Section A.2.4, EPA has followed the NRC recommendations and revised the presentation of developmental and reproductive toxicity studies in accordance with NRC advice. Study strengths and deficiencies, and evidence from supportive in vitro and in vivo studies and the consistency of outcomes across species and protocols, are addressed. Findings of parental (including maternal) toxicity and the treatment levels at which those effects were observed are also described for each study. The developmental neurotoxicity evaluation by Fredricksson et al. (1993) is discussed at length in the neurotoxicity section of the assessment, with a brief summary included in the developmental toxicity section. Selection of PODs for endpoints selected for potential RfC development (see Table 4-49) has also been more transparently described.

A.5. Response to Public Comments – Cancer Assessment

A.5.1. Epidemiologic Evidence Pertaining to Cancer

Public Comments: Several commenters were critical of the presentation and interpretation of epidemiologic studies and the weight-of-evidence provided by these studies. A more clear, comprehensive and balanced review was recommended. Some commenters noted specific issues about particular studies, including Aschengrau et al., (1993), Lynge et al. (2006), Ruder et al. (2001), and Ma et al. (2010).

EPA Response: As discussed in Section A.3.1, EPA has followed the NRC recommendations and significantly reorganized the data presentation by type of cancer, included updated and more comprehensive evaluation of the epidemiologic literature, and clarified presentation of data from these studies, including those identified by public commenters. The revised analysis affords a stronger foundation for EPA's conclusion that the epidemiologic evidence provides a pattern associating tetrachloroethylene exposure and several types of cancer, including bladder cancer, non-Hodgkin lymphoma, and multiple myeloma.

A.5.2. Cancer Classification

Public Comments: Several commenters raised issues about the cancer classification. Some agreed with the classification of tetrachloroethylene as "*likely to be carcinogenic to humans*"; others disagreed with this classification based on the lack of human relevance of animal tumors and inconclusive epidemiologic evidence.

EPA Response: As discussed in A.3.1, EPA has followed the NRC recommendations and continues to classify tetrachloroethylene as "*likely to be carcinogenic to humans.*"

A.5.3. Mononuclear Cell Leukemia

Public Comments: Several comments were critical of calculating cancer potency based on MCL, highlighting issues of susceptibility and that this endpoint is a poor model for human responses. One commenter was critical of conclusions regarding tetrachloroethylene and autoimmune effects, noting that misclassification of effect and recall bias limited the conclusions that could be drawn from human studies of autoimmunity. One commenter cited a study by the Halogenated Solvents Industry Alliance that is currently under final review as providing a lack of evidence of immune suppression following inhalation of up to 1000 ppm for 28days.

EPA Response: As discussed in Section A.3.1, EPA considered the various viewpoints presented by the NRC, and has revised its presentation of MCL data. Recognizing the difficulty in interpreting the MCL findings, and in the absence of mechanistic, biologic or other data that would rule out the relevance of the F344 MCL for assessing human carcinogenic risk, the observation of MCLs were included in the weight of evidence for assessing carcinogenic hazard to humans. Limitations regarding ascertainment of disease incidence and exposure assessment in population-based studies were addressed in the discussion of autoimmune disease data in the Toxicological Review (see Section 4.6.1.1.2).

A.5.4. Hepatic and Renal Toxicity and Cancer

Public Comments: Several commenters recommended improved transparency and clarity in the presentation of hepatic and renal toxicity carcinogenicity (including hepatocellular tumors and hemangiosarcomas), and carcinogenic MOA information. With respect to hepatic endpoints, one commenter recommended additional transparency with respect to presentation and analyses of the hemangiosarcoma data of JISA [1993)]. Another commenter was critical of the Kjellstrand et al. (1984) study. Regarding the kidney, some commenters stated that the rodent and human data were not comprehensively or critically evaluated. One commenter was critical of the conclusions regarding hepatocellular and renal tumors, noting that they were specific to the rodent species and strains studied.

EPA Response: As discussed in Sections A.3.1, EPA has followed the NRC recommendations and revised its presentation of the renal and hepatic toxicity, carcinogenicity (including hepatocellular tumors and hemangiosarcomas), and carcinogenic MOA information. For liver toxicity, lesser emphasis has been given to the

hepatotoxicity findings in the shorter-term study of Kjellstrand et al. (1984), which has also been more completely and accurately described.

A.5.5. **Selection of Tumor Type for Quantitative Assessment**

Public Comments: Several commenters were critical of the use of MCL for cancer risk estimation, for the reasons discussed above (see A.5.3). Other commenters were critical of all of the rodent tissue endpoints, noting their specificity with respect to species/sex.

EPA Response: As discussed in Section A.3.2, EPA considered the various viewpoints presented by the NRC regarding the use of MCL for cancer risk estimation, and clarified that establishing an upper bound risk estimate of human carcinogenic potency involves multiple factors and considerations. Recognizing the difficulty in interpreting the MCL findings, and in the absence of mechanistic, biologic or other data that would rule out the relevance of the F344 MCL for assessing human carcinogenic risk, the observation of MCLs was included for consideration in estimating carcinogenic potency to humans. Based on an evaluation of all the rodent tumor endpoints with respect to the criteria described above (Section A.3.2), and recognizing the differences in opinion regarding the use of the MCL data, the rat MCL data were selected because they had equal or greater weight as compared to other endpoints across the factors evaluated.

A.5.6. **Mode-of-Action Considerations**

Public Comments: Several commenters were critical of the MOA presentation and conclusions, recommending improved transparency and clarity. With respect to genotoxicity, several recommended a more comprehensive review of the available studies for tetrachloroethylene and its metabolites, including tabular summaries of the available data, a discussion of study strengths and weaknesses, and a summary discussion of the evidence. Several criticized the clarity of the MOA presentation for hepatocellular tumors. Some commenters agreed, while others disagreed, with the conclusion that PPARα is not the MOA for tetrachloroethylene-induced hepatic tumors. Some recommended more explicitly addressing tetrachloroethylene-specific studies, the role of metabolic activation, and alternative MOAs (cytotoxicity and hyperplasia). For renal cancers induced by tetrachloroethylene, several commenters recommended further consideration and discussion of the PPARα activation and sustained cytotoxicity MOAs.

EPA Response: As discussed in A.3.3, EPA has followed the NRC recommendations and undertaken significant revisions to more clearly specify the hypothesized MOAs for each tumor endpoint, and to present and analyze the evidence available to support

conclusions about these hypothesized MOAs. In particular, the genotoxicity section (see Section 4.8) was substantially revised to include text and tabular study summaries of the available genotoxicity studies of tetrachloroethylene and its metabolites, and an overall synthesis section. For mouse liver tumors, EPA has significantly revised the presentation of the PPARα activation MOA and added discussion of epigenetic changes and cytotoxicity and secondary oxidative stress. EPA presents quantitative analyses of TCA, DCA, other known peroxisome proliferators, PPARα endpoints (including PPARα transactivation) and hepatic cancer. Additional emphasis has been given to the deficiencies in the knowledge-base regarding the MOA for tetrachloroethylene. Similarly, with respect to rat kidney tumors, EPA has included text and tabular summaries of the relevant data for the MOA hypotheses (including PPARα activation and sustained cytotoxicity).

A.5.7. **Low-Dose Extrapolation**

Public Comments: Several commenters did not support use of linear low-dose extrapolation for cancer dose-response analysis, instead supporting a (threshold) non-linear dose-response analysis (or approach) based on hypothesized MOAs (particularly, PPARα activation for liver and kidney). Several commenters were critical of the range of potencies based on uncertainties in PBPK modeling. In particular, some noted that other factors in addition to PBPK models should be considered, while others recommended selection of a point estimate within the proposed range.

EPA Response: As described in Section A.3.4, EPA has followed the NRC recommendations and retained linear low-dose extrapolation from the POD below the observed range. In addition, EPA has followed the NRC recommendations and evaluated multiple options for improving the model fit in the observed range for data sets showing supra-linear dose-response shapes. As discussed in Section A.3.4, the additional analyses resulted in better characterization of the available data sets for cancer risk estimation.

A.5.8. **Physiologically Based Pharmacokinetic Models**

Public Comments: Several commenters addressed the dose metrics and PBPK models used in risk estimation. Regarding the dose metric, some commenters endorsed the selection of total metabolism; another commenter remarked that dose metrics for cancer risk estimates do not address the distribution or elimination of metabolites likely involved with carcinogenic process. One commenter disagreed that $BW^{3/4}$-scaling is appropriate for interspecies extrapolation because 1) EPA has not established that a metabolite causes cancer; and 2) the unknown

metabolite could be a highly reactive intermediate. Several commenters were critical of the PBPK models used, with some suggesting inclusion of the Clewell et al. (2005) model, one recommending inclusion of Covington et al (2007), and another recommending the use of only Clewell et al. (2005) and Gearhart et al. (1993). Another commenter suggested using the upper 95th confidence limit of the fraction metabolized in the Chiu and Bois (2006) analysis (i.e., 61% at a modeled exposure concentration of 0.001 ppm). Some commenters noted limitations of the available PBPK models for predicting GSH conjugation pathway metabolism. Some commenters disagreed with some conclusions regarding the oral and dermal metabolism of tetrachloroethylene, the rates of metabolism through the GSH pathway conjugation, the metabolism of TCA to DCA, the bioavailability of TCA, and the presentation of and selection among the available PBPK models. These commenters also recommended additional clarity in the presentation of these issues.

EPA Response: As discussed in Section A.3.6., EPA has followed the NRC recommendations and developed a "harmonized" PBPK model (Chiu and Ginsberg, 2011), including implementation of the NRC advice to separate metabolism into three pathways (oxidation, GSH-conjugation with further β-lyase metabolism, and GSH-conjugation with further β-lyase-independent metabolism). The harmonized PBPK modeling analysis showed that the GSH conjugation pathway in humans remains highly uncertain and/or variable (yielding an approximately 3000-fold range in human estimates), and that additional data are needed to better quantify that pathway in humans (see Section 3.5). Therefore, the assessment does not rely on quantitative estimates of GSH pathway metabolism provided by the new PBPK model. Instead, the quantitative risk estimates presented in the revised assessment rely on estimates of blood tetrachloroethylene, oxidation of tetrachloroethylene, and route-to-route extrapolation information derived from this harmonized model. These dose metric estimates from harmonized model are robust and consistent with prior models and, thus, insensitive to model choice. EPA also revised its presentation of metabolism (see Section 3) and dose metric selection (see Section 5), as well as presentation of an empirical analysis of the contribution of TCA to tetrachloroethylene-induced hepatic tumorigenesis (see Appendix C).

Given the current understanding of tetrachloroethylene metabolism and cancer mode(s) of action, EPA maintains that $BW^{3/4}$-scaling of metabolites (oxidative metabolites for hepatocellular tumors, GSH conjugates for kidney tumors) for extrapolation to human cancer risk is supported by the principles previously outlined by U.S. EPA (1992). In this

revised assessment, risks extrapolated using tetrachloroethylene AUC in blood as the dose metric were not scaled by $BW^{3/4}$, also consistent with U.S. EPA (1992).

A.5.9. Uncertainty Analysis

Public Comments: Some public commenters were critical of the the uncertainty analysis presented by EPA, recommending a clear and concise summary of the limitations and uncertainties in the data and analyses instead. Others commenters recommended expansion of EPA's uncertainty analysis to include additional quantitative analyses.

EPA Response:

EPA has followed the NRC recommendations and retained tabular presentation highlighting EPA's choices and their effects on the determination of the upper bound of the risk estimate. As discussed in Section A.3.7, EPA agrees with NRC that its approach to uncertainty analysis reflects the current state of practice. In addition, as discussed in Section A.3.7, EPA also has followed the NRC recommendations and extended the quantitative evaluation of different models to all candidate data sets so as to more fully array the uncertainties at the point of departure.

B. STUDY DESIGN CHARACTERISTICS OF TETRACHLOROETHYLENE EXPOSURE AND CANCER EPIDEMIOLOGICAL STUDIES

B.1. COHORT STUDIES

Tetrachloroethylene cohort studies have been organized by occupational sector with summay of study design, exposure-assessment approach and statistical methodology. Table B-1 provides summaries of the study characteristics of each paper or group of papers.

B.1.1. Dry Cleaner and Laundry Worker Studies

B.1.1.1. Andersen et al. (1999)

Andersen, A.; Barlow, L.; Engeland, A.; Kjaerheim, K.; Lynge, E.; Pukkala, E. (1999). Work-related cancer in the Nordic countries. Scand J Work Environ Health, 25, 1-116. http://www.ncbi.nlm.nih.gov/pubmed/10507118

Summary: This cohort study examined work-related cancer in Denmark, Finland, Norway, and Sweden. The Danish, Finnish, and Norwegian cohorts were identified through the 1970 Censuses, and the Swedish cohort was ascertained through the 1960 Census. Each of the country-specific cohorts consisted of those individuals who were between 25 and 64 years of age and still alive on January 1, 1971. Overall, the four cohorts included 10,101,711 people, of which 2,346,134 were Danish, 2,115,691 were Finnish, 1,792,817 were Norwegian, and 3,847,069 were Swedish. Follow-up began in 1971 and ended with death, emigration, or end of follow-up, whichever came first. The follow-up protocol for each country was as follows: Denmark: 1971−1987 and linked for identifying deaths and/or emigration with the Central Population Register; Finland: 1971−1990 and linked with Statistics Finland; Norway: 1971−1991 and linked with the Central Population Register; and Sweden: 1971−1989 and linked with the cause-of-death register. Incident cancer cases were obtained through the national cancer registries in each country. Of the more than one million cases, 228,456 were from Denmark, 197,305 were from Finland, 207,068 were from Norway, and 397,433 were from Sweden.

The censuses contained information on demographics as well as occupations and industries that was obtained through descriptions provided by the heads of households for all economically active members. These descriptions were then coded according to the Nordic Occupational Classification in Finland, Norway, and Sweden. Denmark coded their inhabitants' occupations according to their own standards. The researchers then recoded all jobs based on a set of 54 common occupational groups based on Nordic Occupational Classification standards and included 1 group for those who were economically inactive at the time of the census. This

scheme was used to evaluate occupation as a proxy for exposure. Group number 51, Code 95 consisted of launderers and dry cleaners and included 29,333 (0.3%) cohort members. There were 9,873 (0.4%) within the Danish cohort, 4,949 (0.2%) within the Finnish cohort, 4,061 (0.2%) within the Norwegian cohort, and 10,450 (0.3%) within the Swedish cohort. This occupational group contributed a total of 519,844 person-years, which were distributed as follows: 159,156 in Denmark, 94,302 in Finland, 78,086 in Norway, and 187,580 in Sweden. Overall, there were 3,254 incident cancer cases among the laundering and dry-cleaning worker population. Of these, 964 occurred in Denmark, 429 in Finland, 545 in Norway, and 1,316 in Sweden.

Age-standardized incidence ratios and their corresponding 95% CIs were calculated for launderers and dry cleaners for all cancer sites, and for cancers of the pancreas, lung and bronchus, cervix, kidney, nervous system, and lymphopoietic tissues (non-Hodgkin lymphoma and multiple myeloma), stratified by country. Expected numbers of cases were determined using the cancer incidence rates for each country's study population. A Poisson distribution was assumed for all confidence intervals (CIs) whose standardized incidence ratios were calculated with 100 cancer cases or fewer. Strengths of the study include the compulsory nature of the 1970 Census in all four countries, the 95−99% accuracy in cancer incidence data depending on the country, and the linkage of census, mortality, and emigration, and cancer incidence data based on personal identifiers. Limitations of the study include the lack of lifetime occupational histories and the inability to differentiate between launderers and dry cleaners in the analyses.

B.1.1.2. Blair et al. (2003)

Blair, A.; Petralia, S. A.; Stewart, P. A. (2003). Extended mortality follow-up of a cohort of dry cleaners. Ann Epidemiol, 13, 50-56. http://dx.doi.org/10.1016/S1047-2797(02)00250-8

Summary: This study extended the follow-up of an earlier cohort (Blair et al., 1990) of dry-cleaning workers for the purpose of providing more information on mortality and cancer risk among those occupationally exposed to dry-cleaning solvents. The cohort was identified through the dues records from the Local No. 161 (St. Louis) of the Laundry, Dry Cleaning, and Dye House Workers' International Union. This particular union was composed entirely of dry cleaners. The cohort consisted of male and female members who entered the union between 1945 and 1978, worked for at least 1 year, and had demographic information (race, sex, date of birth, date of entry) available. Of the 11,062 union members identified, 5,369 met inclusion criteria. Blair et al. (1990) followed-up subjects through January 1979, and Blair et al. (2003) began in January 1979 and ended in December 1993, an addition of 14 years. Person-years were calculated starting at entry to the union or in 1948, whichever came later, and ended with death

or December 1993, whichever came first. Deaths were identified through the National Death Index and all were coded according to the International Classification of Diseases (8th revision) standards.

Dues records were used to obtain demographic and employment information. When demographics were not accessible through this mechanism, attempts were made to identify this information through driver's license records, social security files, health care finance administration records, and credit bureaus (Blair et al., 1990). Tasks within the dry cleaning occupation were used to assess exposure. Exposure indices were determined for four different categories of jobs within the dry cleaning occupation: (1) cleaners who run the machines and handle the clothes were deemed to have the highest exposure and assigned a time-weighted index of 40 (based on an 8-hour day); (2) pressers, sewers, and counter workers who worked where the dry cleaning occurred and were deemed to receive the bulk of their exposures through the air and were assigned a time-weighted average exposure index of 7; (3) counter workers who were employed at pick-up stations were determined to have minimal exposure and assigned an index of 0; (4) maintenance workers who had high, short-term exposures were assessed to have a time-weighted average exposure of 7. Although the authors did not report the numbers of exposed within each category, there were 220 deaths from cancer among those with little/no exposure (index of 0) and 316 deaths from cancer among those with medium/high exposure (index of 7 or 40). Standardized mortality ratios (SMRs) and 95% CIs were estimated for all causes of death, stratified by the initial follow-up period, the extended follow-up period, and the full follow-up period. Expected SMRs were determined using U.S. population 5-year age and mortality statistics. SMRs were also presented by exposure score—little or no exposure and medium/high exposure—and by date of union membership, before 1960 or after 1960, a time corresponding to widespread use of tetrachloroethylene for cleaning clothes. At the end of the follow-up period in 1993, 43.8% of the cohort members were identified as deceased. The authors did not report any strengths of their methodology; limitations include the lack of information on potential confounders, the lack of detail on job history within the industry, the study's inability to determine what proportion of their cohort were exposed to tetrachloroethylene, the inability to attribute risk to occupational versus lifestyle factors, and potential misclassification due to the use of death certificates in determining the cause of death, and the notably limited ability to examine liver cancer due to disease misclassification biases.

B.1.1.3. Cano and Pollán (2001)

Cano, M. I. and Pollán, M. (2001). Non-Hodgkin's lymphomas and occupation in Sweden. Int Arch Occup Environ Health, 74, 443-449. http://dx.doi.org/10.1007/s004200100248

Summary: This study used a historical cohort design to follow 2,881,315 Swedish men and women from 1971 to 1989 to determine whether workers associated with certain occupations had a higher risk of non-Hodgkin lymphoma. The researchers conducted the follow-up by linking the Swedish cancer environment register, which provided information on cancer cases, as well as demographic variables from the 1960 and 1970 Censuses, with a population register, which housed information on occupation and residence in 1970 and occupation in 1960. Incidence rate numerators were calculated using the Swedish cancer environment register, while rate denominators were calculated using the population register. Person-years were counted starting in 1971 until either that individual's date of death or 1989. A total of 278 occupations in men and 263 occupations in women were counted.

A total of 7,610 non-Hodgkin lymphomas were reported in the study cohort, with 5,391 cases in men and 2,219 in women. Among male cases, 11 fell within the launderers and dry cleaners occupational category (Code 943), and 22 were considered textile workers (Code 701). There were no women classified as launderers/dry-cleaners or textile workers in this study. The analysis consisted of the calculation of age-standardized incidence rates, standardized incidence ratios, as well as relative risks, and their associated 95% CIs. Age-standardized incidence rates were developed for each occupation for the entire time period and used the standard European population as a reference. Standardized incidence ratios were calculated for the 10 main occupational sectors, as well as each occupation, stratified by 5-year age groups and 5-year calendar-year period. Log-linear Poisson models were used to compare occupations against the overall cohort, adjusted for geographical area. Relative risks for each occupation and of the 10 main occupational sectors were also calculated and adjusted for age, period, and geographical category and using the other occupations in the general cohort as a reference. A strength of this study is its inclusion of 1960 Census data leading to an improved definition of exposure; a limitation was its lack of control for other potential confounders beyond demographic information.

B.1.1.4. Chow et al. (1995)

Chow, W. H.; McLaughlin, J. K.; Malker, H. S.; Linet, M. S.; Weiner, J. A.; Stone, B. J. (1995). Esophageal cancer and occupation in a cohort of Swedish men. Am J Ind Med, 27, 749-757. http://dx.doi.org/10.1002/ajim.4700270509

Summary: This study aimed to generate and refine hypotheses regarding occupational risks for esophageal cancer by examining the esophageal cancer incidence by occupation and industry in Sweden. The cohort was identified from the Swedish Cancer Environment Registry, which linked employment and cancer information for all individuals registered in the 1960 Census and the National Swedish Cancer Registry. The linkage was performed using personal identifiers. The authors do not report the final cohort size. The follow-up period was from 1961 to 1979. There were three cases of laundry workers, though exposure prevalence could not be estimated because the authors did not report the total laundry worker population. Standardized incidence ratios were calculated for the entire time frame, with expected numbers of cases based on the 5-year birth cohort- and sex-specific rates for esophageal cancer in the general Swedish population during that same time period. Only those occupations that had at least 500 individuals were examined. Statistical significance was evaluated assuming a Poisson distribution. A strength of this study is its extended follow-up period, and a limitation was the small number of exposed laundry worker cases.

B.1.1.5. Ji et al. (2005a, b), Ji and Hemminki (2005a, b, c) , Ji and Hemminki (2006)

Ji, J.; Granström, C.; Hemminki, K. (2005a). Occupation and bladder cancer: a cohort study in Sweden. Br J Cancer, 92, 1276-1278. http://dx.doi.org/10.1038/sj.bjc.6602473

Ji, J.; Granström, C.; Hemminki, K. (2005b). Occupational risk factors for kidney cancer: a cohort study in Sweden. World Journal of Urology, 23, 271-278. http://dx.doi.org/10.1007/s00345-005-0007-5

Ji, J. and Hemminki, K. (2005c). Occupation and upper aerodigestive tract cancers: A follow-up study in Sweden. J Occup Environ Med, 47, 785-795. http://dx.doi.org/10.1097/01.jom.0000165798.28569.b5

Ji, J. and Hemminki, K. (2005b). Occurrences of leukemia subtypes by socioeconomic and occupational groups in Sweden. J Occup Environ Med, 47, 1131-1140. http://dx.doi.org/10.1097/01.jom.0000174302.63621.e8

Ji, J. and Hemminki, K. (2005a). Variation in the risk for liver and gallbladder cancers in socioeconomic and occupational groups in Sweden with etiological implications. Int Arch Occup Environ Health, 78, 641-649. http://dx.doi.org/10.1007/s00420-005-0015-1

Ji, J. and Hemminki, K. (2006). Socioeconomic/occupational risk factors for lymphoproliferative diseases in Sweden. Ann Epidemiol, 16, 370-376. http://dx.doi.org/10.1016/j.annepidem.2005.09.002

Summary: These six studies used a cohort obtained through the Swedish Family-Cancer Database to examine the potential relationship between occupation and various cancers. The database linked national censuses (1960, 1970, 1980, and 1990), mortality data, cancer incidence

data, and an administrative family register. The database was updated at two different time periods (2002 and 2004) with information from the Swedish Cancer Registry. The update in 2002 covered the period 1961−2000, and the update in 2004 covered the period 1958−2002. The cohort consisted of 1,644,958 men who were employed at the time of the 1960 Census and 1,154,091 women who were employed at the time of the 1970 Census. Follow-up began at immigration or at one of the following dates: January 1961 for those in the 1960 Census, January 1970 for those in the 1970 Census or for those who reported the same occupation in both the 1960 and 1970 Censuses, or January 1980 for those who reported the same occupation in all three censuses. Follow-up ended with cancer diagnosis, death, emigration, or December 2000. Occupation was assessed as a proxy for exposure, with relevant census information (employment status, job title, work industry) coded according to Nordic Occupational Classifications. These codes corresponded to 53 occupational groups, which included launderers and dry cleaners. Overall, there were 9,255 (0.6%) male and 14,974 (1.3%) female launderers and dry cleaners. Standardized incidence ratios were calculated for each occupation in each census subcohort (1960, 1960−1970, and 1960−1970−1980). Expected numbers of site-specific cancer were estimated from 5-year-age, 10-year-period, and 6 group socioeconomic status-specific standard incidence rates. Corresponding 95% CIs were estimated assuming a Poisson distribution. Strengths of these studies include their population-based design, extended follow-up period, and utilization of three different censuses. Limitations to the studies include the inability to directly control for smoking as a potential confounder, the exception was bladder cancer (Ji et al., 2005a), the low power resulting from a small proportion of exposed cohort members that reported the same occupation in more than one census, and the high proportion of women without occupational data in the 1960 Census, which made comparisons with more than one census difficult. Also, Ji et al. (2005b) and Ji and Hemminki (2006) limited their study to those over the age of 30 years, which may have biased the external validity of the study because the findings could not be generalized to the ≤30 population.

Ji et al. (2005a) examined the relationship between occupation and first primary bladder cancers using the information from the 2002 database update. Overall, 24,041 men and 3,405 women developed bladder cancer, which included 157 male launderers and dry cleaners from the 1960 Census. There were 67 cases among male launderers and dry cleaners in both the 1960 and 1970 Census, and 19 cases among male launderers and dry cleaners in the 1960, 1970, and 1980 Censuses. The results for female launderers or dry cleaners were not reported. Two different standardized incidence ratios were calculated for occupations stratified by gender. The first estimate was adjusted for age and period, and its corresponding 95% CI was adjusted for age, period, and socioeconomic status. In order to account for the effect of smoking on bladder cancer, all standardized incidence ratios were divided by 35%, which was based on a a

difference in bladder and lung cancer risks for smoking 20 cigarettes per day developed by the International Agency for Research on Cancer (IARC, 2004). This estimated a second, smoking-corrected standardized incidence ratio as well as a smoking-corrected 95% CI. All estimates were stratified by gender.

Ji et al. (2005b) examined the relationship between occupation and first primary kidney cancer, including parenchymal cancer, pelvic cancer, and unspecified cancer. This study utilized the data from the 2002 update. There were 61 cases (51 renal parenchyma, 7 renal pelvis, and 3 unspecified) among male launderers from the 1960 Census and 92 cases (79 renal parenchyma, 6 renal pelvis, and 7 unspecified) among female launderers from the 1970 census. There were 26 cases (21 parenchyma, 3 renal pelvis, 2 unspecified) that occurred among women who reported being launderers in both the 1960 and 1970 Censuses and 3 cases (1 parenchyma, 1 renal pelvis, 1 unspecified) among those who reported being launderers in the 1960, 1970, and 1980 Censuses. All standardized incidence ratio estimates were adjusted for age, time period, and socioeconomic status and stratified by gender.

Ji and Hemminki (2005a) assessed risk factors for first primary upper aerodigestive tract (lip, tongue, month, pharynx, and larynx) cancers using the 2002 database update. There were 83 cases (9 lip, 9 tongue, 13 mouth, 24 pharynx, 28 larynx) that occurred among male launderers in the 1960 Census, 32 cases (2 lip, 3 tongue, 6 mouth, 10 pharynx, 11 larynx) among male launderers who were in both the 1960 and 1970 Censuses, and 13 cases (0 lip, 2 tongue, 2 mouth, 6 pharynx, 3 larynx) among male launderers who were in the 1960, 1970, and 1980 Censuses. Among the female launderer population in the 1970 Census, there were 30 upper aerodigestive cancers (10 lip, 2 tongue, 7 mouth, 6 pharynx, 5 larynx). The results for female launderers in multiple censuses were not reported. All standardized incidence ratio estimates were adjusted for age, period, and socioeconomic status and stratified by gender.

Ji and Hemminki (2005b) examined socioeconomic and occupational risks on leukemia by histologic type after the database's 2004 update. This study was limited to cohort members aged 31 or older and diagnosed with primary leukemia, including chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and polychythemia vera (PV). There were 47 cases of leukemia, of which 19 were CLL, seven AML, and five CML, among male launderers and dry cleaners from the 1960 cohort and 80 cases of leukemia, of which (32 were CLL, 20 AML, and two CML, among female launders and dry cleaners from the 1970 cohort. The results for men and women employed as launderers and dry cleaners for more than one census were not reported. Standardized incidence ratios were calculated for six socio-economic groups reported in the 1960 Census, adjusted for age and period, as well as for each occupational group, adjusted for age, period, and socioeconomic status. All estimates were stratified by gender.

Ji and Hemminki (2005c) examined the relationship between occupation, socioeconomic status, and liver and gallbladder cancers using information from the 2002 database update. Overall, 7,620 men and 4,041 women developed liver and gall bladder cancer (4,211 men and 1,126 women with primary liver cancer), which included 53 male launderers and dry cleaners from the 1960 Census and 86 female launderers and dry cleaners from the 1970 Census (25 men and 25 women with primary liver cancer). All standardized incidence ratio estimates were adjusted for age and socioeconomic status and stratified by gender.

Ji and Hemminki (2006) looked at the socioeconomic and occupational risks for lymphoproliferative diseases, including non-Hodgkin lymphoma, chronic lymphatic leukemia, and multiple myeloma, after the database's 2004 update. This study was limited to cohort members aged 31 and older who were diagnosed with primary lymphoproliferative diseases, including non-Hodgkin lymphoma (NHL), CLL, and multiple myeloma (MM). There were 59 cases of NHL, 19 cases of CLL, and 29 cases of MM among male launderers and dry cleaners from the 1960 Census. Among female launderers and dry cleaners, there were 67 cases of NHL, 18 cases of CLL, and 36 cases of MM in the 1960 Census, 64 cases of NHL, 32 cases of CLL, and 31 cases of MM among those in the 1970 Census, and 12 cases of NHL, 8 cases of CLL, and 9 cases of MM among those from both the 1960 and 1970 Censuses. Standardized incidence ratios were calculated for six socio-economic groups reported in the 1960 Census, adjusted for age and period, as well as for each occupational group, adjusted for age, period, and socioeconomic status. All estimates were stratified by gender.

B.1.1.6. Lindbohm et al. (2009)

Lindbohm, M. L.; Sallmén, M.; Kyyrönen, P.; Kauppinen, T.; Pukkala, E. (2009). Risk of liver cancer and exposure to organic solvents and gasoline vapors among Finnish workers. Int J Cancer, 124, 2954-2959. http://dx.doi.org/10.1002/ijc.24309

Summary: This cohort study of economically active Finns born between 1906 and 1945 examined the relationship between job title reported on the 1970 Census and primary liver cancer incidence between 1971 and 1995. The cohort consisted of 1.2 million economically active men and women born between 1906 and 1945 who participated in the Finnish Population Census of 1970. There were 2,474 liver cancers diagnosed between 1971 and 1995 of which 9 occurred in launderers (2 male, 7 female). Exposure was defined as longest held occupation reported on the 1970 Census and assigned to subjects using industry code (850 for launderers) or as cumulative exposure to "organic solvents" using the Finnish job exposure matrix (FINJEM) for every 5-year birth cohort and 5-year calendar period. The exposure for each birth cohort was assumed to start in the year when the average age of the birth cohort was 20 or at 65 years of age, whichever came first, because occupational histories were not available. The annual average exposure was

the product of the proportion of exposed and the mean level of exposure in that occupation. A lag period was incorporated in the cumulative estimate by omitting exposure from the 10 last years. For launderers, averages of 10 ppm in 1945−1959 and 5.3 ppm in 1960−1984 were assumed. In Finland, for the later time period, this would likely be for tetrachloroethylene because this was the predominate solvent used in dry cleaning, accounting for roughly 85% of all solvents at that time (Johansen et al., 2005; Kauppinen et al., 2009; Lynge et al., 2006).

Standardized incidence ratios and 95% CIs were calculated by gender using a Poisson regression, with expected number of cancer cases estimated using site-specific cancer incidence rates of the larger Finnish population. Statistical analyses controlled for alcohol consumption, smoking, and socioeconomic status. A strength of the study includes the use of census information and the ability of statistical analysis to account for potential confounding from smoking, alcohol consumption, and socioeconomic status. The few liver cancer deaths and low-exposure prevalence and the classification of exposure based solely on census-reported information rather than a full lifetime of employment are limitations.

B.1.1.7. Lynge and Thygesen (1990), Lynge et al. (1995)

Lynge, E; Thygesen, L. (1990) Primary liver cancer among women in laundry and dry-cleaning work in Denmark. Scand J Work Environ Health 16(2):108−112.

Lynge, E; Carstensen, B; Anderson, O. (1995) Primary liver cancer and renal cell carcinoma in laundry and dry-cleaning workers in Denmark. Scand J Work Environ Health 21(4):293−295.

Summary: These studies used a retrospective cohort design to examine the relationship between work in dry-cleaning shops where tetrachloroethylene was the main solvent used and cancer in Denmark. The cohort consisted of 10,600 Danish men and women aged 20 to 64 years who were registered in the 1970 Census as "laundries, cleaning and dyeing." This encompassed industry Code 860 (laundries, cleaning, and dyeing) and occupational Codes 411 (laundry worker, ironer) and 380 (factory hand), as well as those who reported themselves as self-employed or family workers. There were 2,434 (23%) self-employed dry cleaners or launderers, 830 (7.8%) family workers, 6,837 (64.5%) laundry workers or ironers, and 499 (4.7%) factory hands. Overall, there were 2,886 laundry and dry-cleaning shops in Denmark in 1970, of which 695 were known dry-cleaning and dyeing shops where dry cleaning was the predominant activity.

Lynge et al. (1990) studied the cancer incidence within the cohort during a 10-year follow-up after the 1970 Census. The census data were linked to the Danish Cancer Registry for the period 1970 to 1980, and 24 cancer sites were examined. There were a total of 510 observed cancer cases. Standardized incidence ratios and their corresponding 95% CIs were calculated

assuming a Poisson distribution if the observed number of cases was ≤30 and a normal distribution if the number was >30. Expected numbers were estimated by multiplying the person-years at risk within each 5-year age group with the site-specific incidence rates that were estimated for the full 1970 Census cohort. The authors do not report any strengths of their methodology; limitations include the study's inability to separate laundries from dry-cleaning shops and the lack of a sufficient period for cancer latency.

Lynge and Thygesen (1995) used a nested case-control study to differentiate the laundry workers from the dry cleaners in their examination of liver and renal cell carcinoma within this cohort. The cohort was followed from 1970 through 1987 for death, emigration, and incident cancer. During this period, there were a total of 17 liver cancer cases and 16 renal cell carcinoma cases. Controls were randomly selected from within the cohort and matched to cases on gender, 5-year age group, and occupation. In order to be included in the study, controls were required to be alive and living in Denmark at the time of the case's diagnosis; no other exclusion criteria were adopted. There were five controls matched to each case, and the final sample consisted of 33 cases (17 liver and 16 renal cell carcinoma) and 165 controls (85 liver and 80 renal cell carcinoma). Occupation was assessed as a proxy for exposure. The identification numbers of each of the 198 participants were unencrypted to obtain personal addresses, which were then used to retrieve the original census forms. These forms contained descriptions of the occupations and workplaces and allowed the researchers to recode each individual as either a launderer or a dry cleaner. The authors do not state if this assessment occurred blindly. Overall, none of the liver cancer cases, 20 (24%) liver cancer controls, 3 (18%) renal cell carcinoma cases, and 20 (29%) renal cell carcinoma controls worked as dry cleaners in 1970. Conditional logistic regression was used to calculate relative risks and their corresponding 95% CIs. A strength of this study is its ability to examine dry cleaners separately from laundry workers. Limitations include the low-exposure prevalence, the lack of adjustment for alcohol and smoking as possible confounders, the classification of exposure based solely on a census form rather than a full lifetime of employment, and the use of controls with diseases potentially associated with dry-cleaning exposure.

B.1.1.8. Pukkala et al. (2009)

Pukkala, E.; Martinsen, J.; Lynge, E.; Gunnarsdottir, H.; Sparén, P.; Tryggvadottir, L., . . . Kjaerheim, K. (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries. Acta Oncol, 48, 646-790. http://dx.doi.org/10.1080/02841860902913546

Summary: This cohort study, the Nordic Occupational Cancer Study, of 15 million subjects, aged 30−64 years in the 1960, 1970, 1980/1981, and/or 1990 Censuses in Denmark Finland, Iceland, Norway, and Sweden assessed cancer incidence through 2005 using national cancer registries. Occupational title as recorded on census records was used as a surrogate for exposure, and the investigators examined 54 broad occupational categories identified from Nordisk Yrke Klassifisering (NYK) and the International Standard Classification of Occupations (ISCO). In total, 43,496 dry-cleaners and laundry workers (n = 8,744 men, n = 34,752 women), defined by NYK and ISCO Codes 95 (http://astra.cancer.fi/NOCCA/). Both tetrachloroethylene and trichloroethylene were potential exposures to dry cleaners and launderers. Tetrachloroethylene used in Finland was less than in the other Nordic countries in 1975−1994 (Kauppinen et al., 2009). A future effort of this project is an examination of cancer incidence and 20 agents, including tetrachloroethylene and trichloroethylene (Kauppinen et al., 2009).

Follow-up began on January 1 of the year after the first available census, and person-years were counted until the date of emigration, death, or to December 31 of the following years: 2003 (subjects from Denmark and Norway), 2004 (subjects from Iceland), 2005 (subjects from Finland and Sweden). The study examined 49 cancer sites and 27 diagnostic subgroups during the 13−45 year follow-up period. Standardized incidence ratios and their corresponding 95% CIs were calculated for each site-specific cancer and occupational title with expected number of site-specific cancers calculated from separate countrywide incidence rates. Statistical analyses did not include examination of duration of employment, in this case, appearing as a dry-cleaner or laundry worker on more than one census.

This is a large study with follow-up to account for a cancer latent period of ≥15 years, and a strength is linkage with national population registries and cancer registries. The large number of dry-cleaners and laundry workers is an advantage; however, occupational title as dry-cleaner and laundry worker is broad, with subjects having differing potential to exposure intensities and to multiple solvents. Despite the large number of subjects with occupational title of dry-cleaner and laundry worker, statistical power may be compromised from the low-level detail of the exposure-assessment approach for these reasons.

B.1.1.9. Ruder et al. (1994, 2001), Calvert et al.

Ruder, A. M.; Ward, E. M.; Brown, D. P. (1994). Cancer mortality in female and male dry-cleaning workers. J Occup Med, 36, 867-874. http://www.ncbi.nlm.nih.gov/pubmed/7807267

Ruder, A. M.; Ward, E. M.; Brown, D. P. (2001). Mortality in dry-cleaning workers: An update. Am J Ind Med, 39, 121-132. http://dx.doi.org/10.1002/1097-0274(200102)39:2<121::AID-AJIM1000>3.0.CO;2-H

Calvert, G. M.; Ruder, A. M.; Petersen, M. R. . Mortality and end-stage renal disease incidence among dry cleaning workers. Occup Environ Med. http://dx.doi.org/10.1136/oem.2010.060665

Summary: This retrospective cohort study examined the relationship between occupational exposures and mortality in a cohort of dry cleaners and updates earlier studies (Calvert et al., In Press; Ruder et al., 1994, 2001). An examination of end-stage renal disease incidence (ESRD) was presented in (Calvert et al., In Press) using the Renal Management Information System (REMIS) maintained by the U.S. Centers for Medicare and Medicaid Services. The cohort was obtained from union dry-cleaning records in California, Illinois, Michigan, and New York and included anyone employed for at least 1 year prior to 1960 in a dry-cleaning shop that used tetrachloroethylene. Attempts were made to verify the solvent exposure records with visits to the shops themselves. Follow-up of vital status was to 1990 (Ruder et al., 1994), 1996 (Ruder et al., 2001), and 2004 (Calvert et al., In Press). Of the cohort of 1,704 workers in the current follow-up analysis, 618 (36%) worked only in shops that used tetrachloroethylene as the primary solvent cleaner, and 1,086 (64%) worked at shops where the primary cleaner (tetrachloroethylene or Stoddard solvent) could not be verified or where other solvents were known or suspected to be used instead of tetrachloroethylene. (Calvert et al., In Press)found four subjects in Ruder et al. (2001) had missing birthdates, and these subjects were not included in their latest cohort follow-up. Calvert et al. , additionally, was less successful than Ruder et al. (2001) at obtaining causes of deaths; 8% of deaths were not obtained in the latest follow-up compared to 3% in Ruder et al. (2001). As of 2004, 322 deaths had occurred.

Tetrachloroethylene exposure was estimated by duration of employment in the dry-cleaning shops (1 to 5 years or more than 5 years) and by latency periods (time since first employment was less than 20 years or 20 or more years). Person-years were calculated from either January 1, 1940, or after 1 year of employment in a unionized tetrachloroethylene shop, whichever came later, through their death, the date they were lost to follow-up, or the end of 2004, whichever came earlier. SMRs and their corresponding 95% CIs were calculated for each cause of death in the full cohort, for selected causes of death by duration of employment and time since first employment, and for selected causes of death by the tetrachloroethylene-only subcohort (618 workers) and the mixed cohort (1,704 workers) separately. The expected number of deaths was estimated using national rates. SMRs and their 95% CIs for each of the four regions were also estimated using both county and national rates, though these data were not shown. The National Death Index was used to obtain information on deaths that occurred in the cohort.

Subjects employed since 1977, the date REMIS was first available, were followed for ESRD incidence to 2004. A total of 1,296 subjects—494 in the tetrachloroethylene

cohort—were followed with 30 incident cases of ESRD identified. Standardized incidence ratios and their corresponding 95% CIs were calculated for each ESRD type by the tetrachloroethylene-only subcohort and the mixed cohort separately. The expected number of deaths was estimated using all incident cases of ESRD available in REMIS as the numerators and U.S. Census data as the denominators.

A strength of this study is its estimation of tetrachloroethylene exposure based on duration and intensity. A limitation of the study is likely exposure-measurement error introduced through inability to update work histories after 1982, potentially underestimating duration, and lack of information on exposure intensity. Both aspects would tend to result in nondifferential bias that would dampen risk estimates. Additionally, a full latent period has not passed for the cohort, only 2% of the cohort had died at the end of follow-up in 2004, and only one-half of the cohort had a latent period of ≥20 years. This is also valid for analysis of ESRD incidence as the latent period is less than that for mortality. Another limitation is the lack of individual subject information on smoking and alcohol consumption as potential confounders, although the authors noted that the estimates for certain cancers were higher than what they would be if smoking was the only significant factor, and potential for multiple solvents exposures with subjects whose first employment date was before 1960.

B.1.1.10. Sélden and Ahlborg (2011)

Seldén, A. I. and Ahlborg, G. (2011). Cancer morbidity in Swedish dry-cleaners and laundry workers: Historically prospective cohort study. Int Arch Occup Environ Health, 84, 435-443. http://dx.doi.org/10.1007/s00420-010-0582-7

Summary: This study examined cancer incidence in a cohort of 9,440 Swedish dry-cleaning workers launderers, dry cleaners, and pressers identified by employers as working in laundries or dry-cleaning shops during 1973 and 1983 for a study of pregnancy outcomes (Ahlborg, 1990a) . In mid-1980, a questionnaire was mailed to all washing establishments recorded in the Swedish Postal Address Registry. Of the 1,254 employers that received the questionnaire, 475 (37.9%) of the employers responded to the questionnaire and identified 10,389 employees. Data from 14 companies were lost from the original study, leaving workers from 461 companies for the cancer incidence study. The size of companies participating in the study varied from small family businesses to large establishments. In addition to seeking information on employee identities, the questionnaire sought details of production volumes, washing techniques, and details of any chemicals used; no tetrachloroethylene exposure information was provided on individual employees. Study authors verified subjects fulfilled inclusion criteria of Ahlborg (1990a) and this study, excluding subjects who did not fulfill criteria.

Exposure assignment to three categories was carried out using company-provided information on type of business: tetrachloroethylene or PER subgroup, laundry subgroup, or other. The PER subgroup was composed of employees of dry cleaner and laundries with a proportion of dry-cleaning with tetrachloroethylene only; the laundry subgroup included employees in laundry establishments, while the "other" subgroup contained employees of businesses using a combination of chemicals for dry cleaning in addition to tetrachloroethylene (chlorofluorocarbons, white spirit, naphtha, or trichloroethylene). Tetrachloroethylene had been used in Sweden almost exclusively for dry-cleaning since the 1950s. Historical industrial monitoring data indicated exposure levels on the order of 100−200 mg/m^3 in the 1970s, with tetrachloroethylene concentrations decreasing by 50% from 1980 to 1985, and an 8-hour TWA rarely exceeding 50 ppm (Ahlborg, 1990a; Johansen et al., 2005; Seldén and Ahlborg, 2011).

Of the 10,389 subjects reported by the companies and who were employed at least 1 month, 677 were excluded for either not fulfilling the original inclusion criteria or other reasons and 272 were lost in the identification process. Overall, 9,440 subjects (2,810 men and 6,630 women) were followed for cancer incidence from January 1, 1985 to until 85 years of age, death, emigration or to December 31, 2006, whichever can first. A total of 1,106 incident cancers were identified from the Swedish Cancer Registry, 723 of which occurred in subjects categorized in the PER exposure subgroup. Site-specific standardized incidence ratios and their 95% CIs were estimated using expected numbers of cancers estimated from cancer incidence rates of the Swedish population. Additionally, SIR and 95% CIs are reported separately for each exposure category, as well as by employment duration for subjects in the PER and laundry categories.

This study differs from other included in this summary of Swedish or all-Nordic dry cleaners and launderers in that it is based on employer-reported instead of census-reported information. A strength of the study is the over 20-year follow-up. Also, the authors provide some information to evaluate potential confounding from smoking and alcohol. Ahlborg (1990a, b) collected smoking information on some of the women who also participated in the pregnancy outcome study and reported a prevalence of daily smoking before conception of 66−70%, higher than reported for women attending Swedish prenatal care centers in the early 1980s and for national data (Ahlborg and Bodin, 1991; Seldén and Ahlborg, 2011). The higher prevalence of smoking among women may potentially confound observations for smoking-related site-specific cancers such as lung and bladder. With respect to alcohol consumption, a previous survey of women in the pregnancy outcome study found a higher prevalence of "high" consumption compared to women attending prenatal care centers (Ahlborg, 1990b; Ahlborg and Bodin, 1991; Seldén and Ahlborg, 2011). Selden and Ahlborg (2011) do not identify the average age of the cohort. As some subjects in the cohort were included in a study of pregnancy outcomes, this is

not an "old" cohort, and expected cancer rates would be lower than for a cohort composed of more aged subjects. Limitations identified by Selden and Ahlborg (2011) included lack of quantitative exposure data, lack of a full occupational history, and low tetrachloroethylene exposures. The expected lower background cancer rates and low tetrachloroethylene exposures would lower the study's statistical power.

B.1.1.11. Travier et al. (2002)

Travier, N.; Gridley, G.; De Roos, A. J.; Plato, N.; Moradi, T.; Boffetta, P. (2002). Cancer incidence of dry cleaning, laundry and ironing workers in Sweden. Scand J Work Environ Health, 28, 341-348. http://www.ncbi.nlm.nih.gov/pubmed/12432988

Summary: This cohort study examined cancer incidence in Swedish launderers, dry cleaners, and pressers using a linked register that included the 1960 and 1970 Censuses, the Swedish national cancer registry, and the national register of causes of death. Person years were counted starting January 1971 until cancer diagnosis, death, or loss to follow-up December 1989, whichever came first. All individuals with second primary neoplasms were excluded. The authors did not report the total number of individuals included in the cohort. Launderers and dry cleaners comprised Nordic Classification of Occupation Code 943, and pressers were Code 944; laundry, ironing, and dyeing comprised Swedish Industrial Code 880 in 1960 and Code 9520 in 1970.

Exposure was classified into five categories: Group 1, launderer, dry cleaner, or presser occupation employed in the laundry, ironing, or dyeing industries in either the 1960 or 1970 Censuses (543,036 person years); Group 2, launderer, dry cleaner, or presser occupation employed in the laundry, ironing, or dyeing industries in both the 1960 and 1970 Censuses (46,934 person years); Group 3, launderer, dry cleaner, or presser occupation employed in other industries at the time of both censuses (18,960 person years); and, Group 4, other occupational titles employed in laundry, ironing, or dyeing industry (13,395 person years); and, Group 5, not employed in relevant industries or occupations during both censuses (69,540,184 person years).

Multivariable Poisson regressions were used to calculate the relative risks and 95% CIs of cancer for each category of exposure, adjusted for age, calendar period, geographic region, urban setting, and gender. These analyses were also stratified by gender and adjusted for age, calendar period, geographic region, and urban setting. Travier et al. (2002) further assessed temporal changes in solvent use, portraying relative risks by age in 1960 and noted subjects under 40 years of age in 1960 presumably used mainly tetrachloroethylene and carbon tetrachloride. A strength of this study is its detailed analysis of observed associations.

Limitations of this study include its low power and the use of self-reported occupational and industrial codes to classify exposures.

B.1.1.12. Wilson et al. (2008)

Wilson, R.; Donahue, M.; Gridley, G.; Adami, J.; El Ghormli, L.; Dosemeci, M. (2008). Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden. Am J Ind Med, 51, 83-99. http://dx.doi.org/10.1002/ajim.20522

Summary: This study used a retrospective cohort design to examine if incident bladder and renal pelvic cancers share similar occupational risk factors. It tested the hypothesis that bladder and renal pelvis cancers were similarly elevated in each occupation and industry category. The cohort consisted of 4,197,684 Swedish men and women employed during either the 1960 or the 1970 Census and still living at the start of 1971. Person years were counted starting January 1, 1971, and ending with a cancer diagnosis, emigration, death, or December 31, 1989, whichever came first. Cancer information was obtained from the Swedish Cancer-Environment Registry for the study period 1971 to 1989. Overall, there were a total of 70,083,912 person-years of follow up, with a mean time of 16.7 years. Within the cohort, there were 1,374 incident renal pelvis cancers and 21,591 incident bladder cancers.

Occupation as noted on the 1960 and 1970 Censuses was assessed as a proxy for chemical exposures, including tetrachloroethylene. Job titles reported in the censuses were coded according to the National Swedish Classification of Occupations and Industries standards, for which laundry and dry-cleaning workers were occupation Code 943, and the laundry, ironing, and dyeing was industry Code 880 in 1960 and Code 9250 in 1970; 25,249 men and women (0.6% of the cohort) were employed in this industry, for which there 110 observed bladder cancer cases (55 female and 55 male) and 11 observed renal pelvic cancer cases (8 female and 3 male). A job exposure matrix was also used to assess exposure to indoor work and low physical activity, among others.

Standardized incidence ratios and their associated 95% CIs were calculated for each occupation and industry using expected site-specific cancer incidence of rates of the total employed Swedish population. Strengths include the large sample size, use of well-validated registries, adequate follow-up, and high case ascertainment. Limitations to the study include its lack of adjustment for confounders including smoking, possible misclassification of exposure based on job title in 1 or 2 census years, and the lack of occupational history for each participant.

B.1.2. **Other Occupational Cohorts**

B.1.2.1. Anttila et al. (1995)

Anttila, A.; Pukkala, E.; Sallmen, M.; Hernberg, S.; Hemminki, K. (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. J Occup Environ Med, 37, 797-806. http://www.ncbi.nlm.nih.gov/pubmed/7552463

Summary: This cohort study assessed the incidence of cancer among employees who were biologically monitored by the Finnish Institute of Occupational Health (FIOH) between 1965 and 1983 in comparison to the total Finnish population. The cohort consisted of workers who had their blood and urine assessed for trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane due to their employment in occupations that exposed them to hazardous substances. Tetrachloroethylene was monitored in the blood of workers between 1974 and 1983, and median blood tetrachloroethylene concentrations were 0.7 μmol/L in males and 0.4 μmol/L in females. There were, on average, 3.2 blood tetrachloroethylene measurements per individual. In addition to the measurement information, the FIOH database provided data on demographics, date and time of sampling, workplace, solvent code, result, specific activity, and the laboratory in which the sample was analyzed. Approximately 600 codes of workplaces or sampling laboratories were included in the database.

Follow-up was conducted automatically with the Finnish Cancer Registry and began in January 1967 or on the date of first measurement of the solvent, whichever was later, and ended at emigration, death, or December 1992, whichever was first. Death and emigration were ascertained through the Population Register Center; mortality was also followed-up using cause-of-death data from the Central Statistical Office of Finland for the period 1956 to 1991. Of the 11,534 biological measurements taken between 1965 and 1983, 10,743 (93.1%) were linked to personal identifiers, which corresponded to a total of 3,976 workers. After excluding those who could not be completely identified or were not alive at the start of follow-up, the final sample consisted of 3,974 individuals who contributed a total of 71,800 person-years. Follow-up time averaged 18 years, with 27,547 person-years within the period 10−19 years after entry into the cohort and 5,877 person years within the period ≥20 years. There were 849 (21.4%) workers monitored for exposure to tetrachloroethylene, and they contributed a total of 11,958 person-years.

The study examined 29 cancer sites during the 26-year follow-up period, which were selected on the basis of their known or suspected association with the solvents. Of these, 8 sites (pancreas, lung/bronchus, cervix uteri, kidney, nervous system, non-Hodgkin lymphoma, multiple myeloma, and all cancer sites) were specifically evaluated with respect to tetrachloroethylene and contributed 31 observed cancer cases during the follow-up period of

1974 to 1992. Standardized incidence ratios and their corresponding 95% CIs were calculated for all halogenated hydrocarbons, trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane separately, with expected numbers of site-specific cancers calculated from incidence rates of the Finnish population. Significance was evaluated with the Mantel-Haenszel chi-square test under the assumption that the observed cases followed a Poisson distribution. Exposure duration was not examined for tetrachloroethylene subjects, given the few site-specific cancer cases. Strengths of the study include its use of the same source for the calculation of observed and expected cases, as well as its linkage with Finnish registries, which provided complete ascertainment of death, emigration, and cancer incidence. Limitations include the study's low power for its analysis of tetrachloroethylene, incomplete registration in earlier years, low tetrachloroethylene concentrations (for comparison, Ferroni et al. [1992] reported median blood tetrachloroethylene and atmospheric monitoring of dry cleaners of 874 μmol/L and 15 ppm, respectively), the study's inability to infer lifetime exposure based on blood tetrachloroethylene, and the potential for multiple solvents exposures.

B.1.2.2. Boice et al. (1999)

Boice, J.; Marano, D.; Fryzek, J.; Sadler, C.; McLaughlin, J. (1999). Mortality among aircraft manufacturing workers. Occup Environ Med, 56, 581-597. http://dx.doi.org/10.1136/oem.56.9.581

Summary: This cohort mortality study conducted follow-up to evaluate cancer and other diseases among aircraft workers. The cohort was identified through work history cards, personnel files, and retirement records and consisted of individuals employed at Lockheed Martin aircraft manufacturing factories for at least 1 year from January 1960 onwards. Those with missing work history information or incorrect dates were excluded. The follow-up period began January 1, 1960 or after 1 year of employment and ended with death, age 95 years, or December 1996, whichever came first. The vital status of each cohort member at the end of the follow-up period was obtained through a variety of methods, which included California death tapes, the National Death Index, Pension Benefit Information Files, Social Security Death Index, Health Care Financing Administration files, California Department of Motor Vehicles records, employment work history cards, pension and retirement records, and obituaries from 1960 to 1996. Vital status could not be ascertained for 11,533 (15%) of cohort members and were assumed to be alive. This assumption was examined using a random sample of 700 subjects and demonstrated that approximately 95% of this sample was alive, and if representative of all subjects with missing vital status information, overall, lost to follow-up was estimated to be 0.7% of the cohort. The published paper lacks information to evaluate whether the random sample was representative of all subjects lacking vital status. Of the 113,204 aircraft workers,

77,965 (68.9%) were included in the study and contributed a total of 1,889,795 person-years of follow-up. The average follow-up per cohort member was more than 20 years.

Exposure was assessed through walk-through surveys of the closed factories or similar factories, interviews with long-term employees, and industrial hygiene files or other historical documents. From job code, job title, and job change information, the researchers were able to group occupations with similar work activities, identifying job titles that may have indicated chemical exposure. All administrative and technical jobs were classified as having "no significant chemical exposure" and removed from the analysis. All factory-related jobs were categorized based on a number of chemical exposures and a job exposure matrix, to assign tetrachloroethylene exposure defined as routine (part of daily activities), intermittent (not routine or on a daily basis), or minimal to no exposure. Limited data on tetrachloroethylene levels were available, with few measurements before 1970 although tetrachloroethylene was used in vapor degreasing starting in 1966 after TCE was discontinued until the early 1990s (Marano et al., 2000). Air sampling revealed that long-term air exposures to tetrachloroethylene measures from 1987−1988 were 3 ppm (median) and 9.5 ppm (mean) [range: 0.06−27 ppm], and short-term air exposures measured from 1978−1988 were 56 ppm (mean) and 17 ppm (median) [range: 1.7−150 ppm]. Similarly, many factory workers were exposed to multiple substances. For example, 4,421 (59%) subjects were also exposed to chromate, 2,262 (42%) were also exposed to TCE, 5,830 (18%) were also exposed to mixed solvents, and 298 (24%) were also exposed to asbestos. Among the factory worker subcohort, 2,631 (5.8%) employees were assessed as having been exposed to routine levels, and another 3,199 (7.1%) subjects were exposed to intermittent levels of tetrachloroethylene. The workers that were routinely exposed contributed a total of 51,214 person-years at risk and had 476 observed deaths (all causes).

SMRs and their corresponding 95% CIs were calculated for routine exposed subjects assuming the observed number of deaths followed a Poisson distribution. Expected numbers of deaths among the Caucasian population were based on race, age, calendar year, and sex-specific rates among the general population of California, while expected numbers of deaths among the non-Caucasian population were based on the general population rates of the United States. Poisson regression was used to estimate relative risks and their corresponding 95% CIs for a combined grouping of routine and intermittent exposed subjects for duration of exposure, adjusted for date of birth, date first employed, date of finishing employment, race, and sex. Tests of linear trend were also performed to examine the potential effect of exposure duration for subjects with routine or intermittent tetrachloroethylene exposure potential. In all analyses, the referent population consisted of all factory workers with incidental or no exposure. The strengths of this study included its large size, although only 4% of the cohort was identified with routine tetrachloroethylene exposure potential, extended (>37 years) follow-up period, exposure

assessment using a job exposure matrix, and use of an internal referent group in analyses examining exposure duration. Limitations include the study's lack of adjustment for smoking, lack of control for the healthy worker effect, and its finding that the assumption of living vital status for approximately 7% of the cohort was incorrect. This bias would lead to an inflation of the expected number of deaths due to the fact that they were assumed alive at the end of the study period. Additionally, the inclusion of subjects with intermittent exposures who likely have low-exposure potential may reduce the study's detection sensitivity. This may also introduce differential bias in duration exposure-response analyses if intermittently exposed subjects had longer employment duration than routinely exposed subjects. Marano et al. (2000) noted the number of subjects with intermittent tetrachloroethylene exposure potential was 1.5 times larger than the number of subjects assigned routine tetrachloroethylene exposure potential.

B.1.2.3. Bond et al. (1987; 1990)

Bond, G.; McLaren, E.; Cartmill, J.; Wymer, K.; Sobel, W.; Lipps, T.; Cook, R. (1987). Cause-specific mortality among male chemical workers. Am J Ind Med, 12, 353-383. http://www.ncbi.nlm.nih.gov/pubmed/3674026

Bond, G.; McLaren, E.; Sabel, F.; Bodner, K.; Lipps, T.; Cook, R. (1990). Liver and biliary tract cancer among chemical workers. Am J Ind Med, 18, 19-24. http://www.ncbi.nlm.nih.gov/pubmed/2378367

Summary: This nested case-control study, conducted as a follow-up to a cohort mortality study (Bond et al., 1987), investigated liver and biliary cancer deaths of male employees working at Dow Chemical's Midland/Bay City production, research, and headquarters units. The initial cohort was identified through work history records and consisted of men and women employed for 3 or more days between 1940 and 1982. Overall, the cohort consisted of 48,521 men and women, of whom 96% were Caucasian, 77.7% were male, and 56.9% were paid by the hour (Bond et al., 1987). Cases were identified through a review of death certificates and consisted of all male, hourly employees who died between 1940 and 1982. Of the 6,259 cohort members identified, 44 (0.7%) (11 primary liver cancer, 14 gallbladder/bile duct cancer, and 19 unspecified liver cancer) were considered eligible for and included in this study. The source of death certificates was not identified by the authors, and it is not known whether they were obtained through pension records or the National Death Index. Controls were randomly chosen from among the cohort of male workers. Of the 21,437 hourly, male subjects, a random sample of 1,888 (8.8%) was selected as controls. Bond et al. (1990) do not identify if controls were matched to cases on age, time period of first employment or end employment, or vital status.

Dow's work history records were used to determine the employee's work area (administration, manufacturing, unknown manufacturing) as well as their possible exposure to

tetrachloroethylene and 10 other chemical agents. Overall, 6 (13.6%) cases and 213 (11.3%) controls were potentially exposed to tetrachloroethylene during their time at Dow. The Mantel-Haenszel method was used to estimate risk ratios for work areas and chemical exposures separately, adjusted for birth year; Miettinen's method was used to calculate corresponding 95% CIs. Additional adjustment for period of hire produced similar results; as a result, only those analyses controlling for birth year were presented. Individual analyses were conducted for primary liver cancer and gall bladder/bile duct cancer separately. This study is of low prevalence of tetrachloroethylene exposure, unable to determine whether the cancer was primary or secondary in almost half of the cases, lacked information and statistical adjustment for alcoholism as a potential confounder, is based on pension records or deaths known to the employer, and deaths among nonpensioned employees are not used to identify deaths, used a living control population, and may have misclassified exposure and disease given the use of information on death certificates. Additionally, the study lacks description of source and process for assigning tetrachloroethylene exposure potential. The authors do not report any strengths of their methodology.

B.1.2.4. Chang et al. (2003; 2005), Sung et al. (2007; 2008)

Chang, Y.; Tai, C.; Yang, S.; Chen, C.; Shih, T.; Lin, R.; Liou, S. (2003). A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan. Ann Epidemiol, 13, 652-660. http://dx.doi.org/10.1016/S1047-2797(03)00038-3

Chang, Y.; Tai, C.; Yang, S.; Lin, R.; Sung, F.; Shih, T.; Liou, S. (2005). Cancer incidence among workers potentially exposed to chlorinated solvents in an electronics factory. J Occup Health, 47, 171-180. http://www.ncbi.nlm.nih.gov/pubmed/15824483

Sung, T.; Chen, P.; Jyuhn-Hsiarn Lee, L.; Lin, Y.; Hsieh, G.; Wang, J. (2007). Increased standardized incidence ratio of breast cancer in female electronics workers. BMC Public Health, 7, 102. http://dx.doi.org/10.1186/1471-2458-7-102

Sung, T.; Wang, J.; Chen, P. (2008). Increased risk of cancer in the offspring of female electronics workers. Reprod Toxicol, 25, 115-119. http://dx.doi.org/10.1016/j.reprotox.2007.08.004

Summary: After tetrachloroethylene and other substances were detected in the soil and groundwater surrounding a closed Taiwanese electronics factory (Bechtel Environmental Inc., 1990 and Target Environmental Services Inc., 1995), a series of retrospective cohort studies were conducted to examine the potential effect of employment in the factory. Strengths of all of these studies are their large size and linkage with national data sets to assure that all cases had been retrieved. Limitations include the use of employment in the factory as a proxy for exposure, and subjects will have varying exposure potential to tetrachloroethylene.

Chang et al. (2003; 2005) identified the cohort through the Bureau of Labor and Insurance's records for the years 1973 to 1997. To ensure completeness of the cohort, the researchers also determined which employees had been hospitalized through labor-insurance hospitalization data and obtained a list of those associated with the United Labor Association. The cohort consisted of 86, 868 individuals (16,133 men and 70,735 women) who contributed a total of 1,380,354 person years. The average follow-up time was 14.3 years for men and 16.3 years for women; the average age of cohort members was 39.3 years. The cohort included both white- and blue-collar workers.

Chang et al. (2003) linked the cohort with the National Mortality Database for their 13-year follow-up from 1985 to 1997. Person-years were counted starting when an individual entered the cohort or on January 1, 1985, whichever came later, and ended with either that person's death or December 31, 1997. The cohort experienced 1,357 deaths, 316 (24%) of which were due to cancer. All cause mortality rate was 1.56%, and all cancer mortality rate was 0.36%. The analysis consisted of the calculation of SMRs. The number of deaths was stratified by their underlying cause and compared with the expected numbers using the general Taiwanese population as a reference. In order to better understand any dose-response relationships, the cohort was stratified twice. First, it was stratified based on duration of employment: $\leq$1 year, >1 year but $\leq$5 years, and >5 years. Then it was stratified based on the calendar year: 1985−1990 and 1991−1997. Duration of employment consisted of the period of employment between the start and end of labor insurance coverage. Assumptions were made regarding the duration of employment for those individuals with missing data. Limitations include reliance on mortality rates from registration data sources, too brief of a follow-up time to allow for a sufficient cancer latent period, data on employment were incomplete, and the cohort was very young despite the mortality endpoint.

Chang et al. (2005) examined the cancer incidence from 1968 to 1992 by linking the cohort with the National Cancer Registry, National Morality Registry. Follow-up time was calculated between the latter of employment start date or January 1, 1979, until the first of cancer diagnosis, death, or December 31, 1997, with assumptions made regarding duration for those with missing start or end dates. Overall, 998 individuals developed cancer. Standardized incidence ratios were calculated comparing this exposed cohort to incidence rates in the general population of Taiwan by age, calendar year, and sex. Latency periods of <3 months, 6 months, and 1, 5, and 10 years were used. Trends were examined by duration of employment (<1 year, 1 through $\leq$5 years, 5 through $\leq$10 years, and 10+ years) and period of employment (1979−1984, 1985−1990, and 1991−1997). Limitations include the study's reliance on registration data, which meant that exposure could not be quantified, and the results were not adjusted for potential confounders, such as smoking, alcohol consumption, reproductive history, or diet. The lack of

company personnel records prevented verification of the completeness of cohort identification, as well as the need by the author's to make assumptions regarding length of employment. The study was unable to assess potential individual exposures, and the cohort included white-collar employees with limited potential exposure to organic solvents, which may reduce the study's detection ability. Finally, the young average age of cohort subjects and short duration of follow-up may reduce the study's sensitivity given low background cancer rates and inadequate latent period.

Sung et al. (2007) tested the hypothesis of increased breast cancer among female workers in the factory. Using a retrospective design, the cohort was identified through employment records from the Bureau of Labor Insurance and consisted of women employed between 1973 and 1992 who worked for at least 1 day and whose cancer diagnosis occurred after employment began. Of the 64,000 women employed during this time, 63,982 (99.97%) were eligible for and included in the study, contributing a total of 1,403,824 person-years. Vital statistics information was obtained from the Ministry of the Interior; cancer diagnoses were retrieved from the Taiwan National Cancer Registry for the period 1979 to 2001 and linked with the cohort through employee identification numbers. There were 29 cancer sites (oral, salivary, nasopharynx, esophagus, stomach, small intestine, colon/rectum, liver/bile ducts, gall bladder, pancreas, peritoneum, trachea/bronchus/lung, other respiratory, breast, cervix uteri, other uterus, ovary/fallopian tube/broad ligament, other genital, kidney/urinary organs, bladder, skin, brain, other nervous system, thyroid, bone, connective tissue, other/unspecified sites, leukemia, and all sites) examined, and depending on the type of cancer, the latency periods were 5 years (thyroid and leukemia), 15 years (breast and cervix uteri), or 10 years (all other cancer sites). Employment in the factory was assessed as a proxy for exposure; duration of employment (1 month; 1, 5, 10, 15, 20 years) was calculated based on the date that labor insurance started and the date that employment ended. In the event of missing employment information, two assumptions were made: (1) if the date of labor insurance was missing, this was assessed as the earliest possible age (14 years); (2) if the date that employment ended was missing, this was assessed as the date the factory closed in 1992. Periods of exposure were classified according to government regulations that were issued in 1974, 1976, and 1978, as well as documents that discussed factory violations with regard to proper ventilation. Pre-1974 was considered to be the time of highest exposure, and there were 8,461 (13.2%) women who began working during this time. Standardized incidence ratios and their corresponding 95% CIs were calculated assuming a Poisson distribution for each cancer site separately. Additional standardized incidence ratios and 95% CIs were calculated for breast, cervical, colorectal, and thyroid cancer stratified by calendar year (pre- or post-1974) as well as duration of employment. *t*-Tests were used to compare women with breast cancer who were employed either before or after 1974 on age at diagnosis,

age at first employment, and length of employment. Limitations included the lack of detailed exposure information for both the factory and individuals within the cohort, the lack of control for possible confounders, and the lack of detailed information related to the early 1970s.

Sung et al. (2008) investigated any possible link between maternal employment and childhood cancer among first live born children. The factory employment records for all women employed between 1973 and 1992 were obtained from the Bureau of Labor Insurance and linked to the Taiwan Birth Registration database for the period 1978 to 2001. Children were required to be first born singletons. Of the 103,506 children born to 47,348 women between 1978 and 2001, 40,647 children were eligible for and included in the study, contributing a total of 639,051 person-years. Demographics were obtained through the National Birth Registry and included information on birth date, sex, single/multiple pregnancy, gestational age, and birth weight, as well as parents' birth dates, education, marital status, and maternal parity. The children's identification numbers were linked with the National Cancer Registry for the period 1979 to 2001 to ascertain how many were diagnosed with cancer. Employment at the factory during the periconceptional time period was assessed as a proxy for exposure to tetrachloroethylene and the other substances previously found in the soil and groundwater around the factory (Bechtel Environmental Inc., 1990 and Target Environmental Services Inc., 1995). Periconceptional exposure was defined as having been employed at the factory during 3 months prepregnancy and 3 months after conception. Conception was calculated by subtracting the length of gestation and an additional 14 days from the date of birth. Overall, there were 8,506 (20.9%) exposed children who contributed a total of 155,121 person-years. There were 11 cases of cancer (1 liver, 2 bone, 1 skin, 1 testis, 6 leukemia) in the exposed group and 36 cases (3 buccal cavity/pharynx, 1 liver, 1 bone, 3 connective/soft tissue, 1 skin, 2 breast, 2 ovary, 1 testis, 5 brain/other nervous system, 4 multiple myeloma, 9 leukemia, and 4 others) in the nonexposed group. Poisson regression was used to calculate rate ratios and their corresponding 95% CIs, adjusted for maternal age and education level, sex, and year of birth. Strengths of this study include its use of an internal, nonexposed comparison group, which reduced the potential for confounding and selection bias. Also, the researchers compared their list of cancer cases to the death registry to verify that all cases had been retrieved. Limitations include the study's inability to link exposures to individuals, and the study's inability to separate the effects of different chemicals.

B.1.2.5. Spirtas et al. (1991), Blair et al. (1998), Radican et al. (2008)

Spirtas, R.; Stewart, P. A.; Lee, J. S.; Marano, D. E.; Forbes, C. D.; Grauman, D. J., . . . Cohen, J. L. (1991). Retrospective cohort mortality study of workers at an

aircraft maintenance facility: I. Epidemiological results. Br J Ind Med, 48, 515-530. http://dx.doi.org/10.1136/oem.48.8.515

Blair, A.; Hartge, P.; Stewart, P. A.; McAdams, M.; Lubin, J. (1998). Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: Extended follow-up. Occup Environ Med, 55, 161-171. http://dx.doi.org/10.1136/oem.55.3.161

Radican, L.; Blair, A.; Stewart, P.; Wartenberg, D. (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow-up. J Occup Environ Med, 50, 1306-1319. http://dx.doi.org/10.1097/JOM.0b013e3181845f7f

Summary: A retrospective cohort mortality study of workers at Hill Air Force Base in Utah was conducted with four aims: (1) to determine whether working at the aircraft maintenance facility was associated with an increased risk of death; (2) to evaluate, in detail, mortality risks associated with exposure to trichloroethylene; (3) to determine whether any raised risks for specific causes of death were associated with specific chemical exposures; and (4) to generate hypotheses for future research by evaluating the relation between various diseases and specific chemicals. Individual earnings records from the National Personnel Records Center were used to identify the cohort, which consisted of male and female civilian employees who had worked at the base for at least 1 year between 1952 and 1956. Of the 14,457 eligible workers, 14,425 (99.8%) had official personnel folders that were able to be retrieved. These files contained demographic information, as well as complete occupational histories, and were used to create a "job dictionary" with 43,000 job titles. Industrial hygienists assessed exposure through walkthrough surveys of the base, interviews with employees, industrial hygiene files, job descriptions, and other historical documents including worker compensation files, telephone books of the facility, organization charts, technical orders, and position descriptions (Spirtas et al., 1991). Then, position descriptions with job titles and shops/departments were used as the basis for evaluating chemical exposures. Any job that could not be linked to specific solvents was coded as "mixed solvent" exposure, which consisted of 16 chemicals including tetrachloroethylene (Stewart et al., 1991). Tetrachloroethylene consisted of a dichotomous (yes/no) classification (Radican et al., 2008; Spirtas et al., 1991). Tetrachloroethylene was primarily used to clean fabric in the parachute shop, replacing carbon tetrachloride in the late 1950s. In the accompanying paper in exposures at Hill Air Force Base, Stewart et al. (1991) do not present industrial hygiene monitoring data on tetrachloroethylene concentrations; however, Gold et al. (2008) noted, the arithmetic means for personnel measurements were 13 ppm for <1-hour samples and 1.4 ppm for >1-hour samples for degreasing jobs in the aircraft and parts industry. Stewart et al. (1991) identified 851 (5.9%) subjects in the Hill Air Force Base cohort as ever exposed to tetrachloroethylene (Stewart et al., 1991).

Observations for tetrachloroethylene and site-specific cancers are limitedly reported in these studies given the study's primary focus on trichloroethylene exposure. Risk estimates for tetrachloroethylene are presented for multiple myeloma and non-Hodgkin lymphoma in Spirtas et al. (1991) and for breast cancer (women), multiple myeloma, and non-Hodgkin lymphoma in Radican et al. (2008). Blair et al. (1998) did not present risk estimates for tetrachloroethylene.

Spirtas (1991) conducted a follow-up of this cohort through 1982. The data in the official personnel folders were supplemented with vital status information, which was ascertained through the Social Security Administration, the U.S. Office of Personnel Management, official personnel folders, Veterans Administration records, motor vehicle bureau records, the National Death Index, interviews with base personnel, and state vital statistics offices. Death certificates were retrieved for all cohort members that died during the follow-up period, and the underlying cause of death was assessed by a nosologist. Follow-up began in 1953 or 1 year after the start of employment, whichever came later. Person-years at risk were stratified by race, sex, 5-year age group, and calendar era. Person-years of exposure were calculated starting 1 year from the date of first exposure or January 1953, whichever came later. Of those who were exposed to any chemical or solvent and died from multiple myeloma, two (33.3%) women and no men were exposed to tetrachloroethylene; of those who were exposed to any chemical or solvent and died from non-Hodgkin lymphoma, two (20%) women and two (9.1%) men were exposed to tetrachloroethylene. SMRs for the cohort of all white civilian employees at Hill Air Force Base and for the TCE subcohort were estimated using Utah death rates as the basis for determining the expected number of deaths. Corresponding 95% CIs were calculated assuming the observed deaths followed a Poisson distribution. Estimates for the full cohort were adjusted for age, sex, and calendar period. These estimates were then stratified by gender and adjusted for age and calendar period only. All calculations were performed on the Caucasian population only, which included those of unknown race. Strengths of this study include its size, analysis of both genders, and use of a variety of mechanisms to assess exposure. Limitations include the lack of adjustment for smoking and employees' exposure to multiple chemicals.

Blair et al. (1998) aimed to better understand the potential relationship between disease risk and trichloroethylene and other organic solvents/chemicals. The follow-up period was extended to December 1990 and conducted through linkage of the cohort with the National Death Index and the Utah Tumor Registry. Person-years for the mortality analyses began January 1, 1953 or 1 year after first employment and ended December 31, 1990, or date of death. Person-years for incidence analyses began January 1, 1973, and ended December 31, 1990, or the date of cancer diagnosis. Deaths were classified according to the International Classification of Diseases rules. Exposure was assessed using company personnel records from the first job to the end of 1982. Individuals were evaluated as having ever (or never) been exposed to

chemicals. All cause mortality in the cohort was 40%, and all cancer mortality was 7%. Overall, of those who died from non-Hodgkin lymphoma, 40 (81.6%) were exposed to any solvent; of those who died from multiple myeloma, 24 (75.0%) were exposed to any solvent; and of those who died from breast cancer, 28 (57.1%) were exposed to any solvent and died from breast cancer. Relative risks and SMRs were estimated based on mortality in Utah. Rate ratios were calculated for mortality and cancer incidence and compared between the exposed and the unexposed using Poisson regression. Regression models adjusted for the following covariates: date of birth, calendar year of death, and sex. The authors do not report strengths of this study. Limitations include the lack of information on tetrachloroethylene, the lack of mutually exclusive exposures, and lack of data on potential lifestyle confounders.

Radican (2008) extended the follow-up period to gain additional information about the health risks associated with workplace exposures. The cohort was linked with the National Death Index using personal identifiers and followed up for the period 1991 to 2000, an addition of 10 years from Blair et al. (1998). Of those women who were exposed to any solvent and died from breast cancer, 1 (2.6%) had been exposed to tetrachloroethylene. Of those who had been exposed to any solvent and died from non-Hodgkin lymphoma, 5 (10%) men and 2 (16.7%) women had been exposed to tetrachloroethylene. Of those who had been exposed to any solvent and died from multiple myeloma, 3 (10%) men and 2 (25%) women had been exposed to tetrachloroethylene. Of those who had been exposed to any solvent and died from nonmalignant respiratory diseases, 46 (9%) men and 4 (51%) women had been exposed to tetrachloroethylene. Cox proportional hazards regression was used to estimate hazard ratios and their corresponding 95% CIs using age as the time variable and race as the covariate. Analyses were stratified by gender. The researchers also examined mortality using the Cox proportional hazards model for a previously conducted study using a different follow-up period to compare the hazard ratios between the two different statistical approaches. This was not performed for tetrachloroethylene, though. Strengths of the study include its size, long follow-up, limited reporting bias due to exposure assessment before the outcome was known, and its use of an internal comparison group to minimize the healthy worker effect. Limitations include the small number of tetrachloroethylene-exposed deaths and reduced statistical power, the inability to estimate risk of one exposure while controlling for exposures to other chemicals, and the potential misclassification of exposure based on job descriptions and other historical information.

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
I.A. Dry-cleaner and laundry worker studies					
Andersen et al. (1999)	Danish, Finnish, and Norwegian cohorts from 1970 Censuses, Swedish cohort from 1960 Census, men and women, 25−64 yr, alive on January 1, 1971; cancer cases from national cancer registries in each country; demographics, occupations, industries from census descriptions provided by the heads of households for all economically active members Proxy—launderers and dry cleaners All cancers (incidence)	Full cohort: 10,101,711, Denmark: 2,346,134, Finland: 2,115,691, Norway: 1,792,817, Sweden: 3,847,069	Follow-up started 1971 and ended with death, emigration, or end of follow-up; Denmark, 1971−1987, linked with Central Population Register; Finland, 1971−1990, linked with Statistics Finland; Norway, 1971−1991, linked with Central Population Register; Sweden, 1971−1989, linked with cause-of-death register	Census descriptions coded according to Nordic Occupational Classification in Finland, Norway, Sweden; Denmark coded according to own standards; researchers then recoded all jobs based on a set of 54 occupational groups based on Nordic Occupational Classification standards; Group 51, Code 95: launderers and dry cleaners 29,333 (0.3%) cohort members, Denmark: 9,873 (0.4%), Finland: 4,949 (0.2%), Norway: 4,061 (0.2%), Sweden: 10,450 (0.3%); Launderers and dry cleaners: 519,844 person-years; Denmark, 159,156; Finland, 94,302; Norway, 78,086; Sweden, 187,580	SIRs, 95% CIs, stratified by cancer site, country, adjusted for age; expected numbers of cases from cancer incidence rates for each population; Poisson distribution assumed for all CIs whose SIRs had <100 cases

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Blair et al. (2003)	Cohort : from dues records of Local No. 161 (St. Louis) of Laundry, Dry Cleaning, Dye House Workers' International Union; male and female dry cleaners, entered union from 1945−1978, worked ≥1 yr; dues records for demographic, employment information, also driver's license records, social security files, health care finance administration records, credit bureaus; excluded if no demographic information; proxy—dry-cleaning tasks All cancers (mortality)	11,062 members identified, 5,369 met inclusion criteria	Extended from Blair et al. (1990), which ended January 1979; started January 1979, ended December 1993 (14 yr); person-years start at entry to union or 1948, whichever later and ended with death or December 1993, whichever came first; deaths from National Death Index	Exposure indices for jobs within dry cleaning: (1) run machines and handle clothes (highest exposure), TWA = 40; (2) pressers, sewers, counter workers, TWA = 7; (3) counter workers at pick-up stations (minimal exposure), TWA = 0; (4) maintenance workers (high, short-term exposures), TWA = 7; entire follow-up period (1948−1993): 220 deaths from cancer among those with little/no exposure (index = 0), 316 deaths from cancer among those with medium/high exposure (index = 7 or 40)	SMRs and 95% CIs to examine relationship between cancer and other causes of death among dry cleaners; Expected numbers based on general U.S. population 5-year age and mortality statistics; 44% deceased at end of entire follow-up period
Cano and Pollan (2001)	Swedish men and women aged 25−64 yr in 1970 Census, employed and counted in 1960, followed 1971−1989. Over 200 occupational codes examined including " launderers and dry cleaners" Non-Hodgkin lymphoma cancer incidence	2,881,315	Followed 1971−1989 or date of death; Swedish Cancer Environment Register linked to population register	Job title reported on 1960 and 1970 Censuses. Eleven of male cases were launderers and dry cleaners (occupational Code 943); no female cases classified as launderers or dry cleaners	Log-linear Poisson models to compare occupations with cohort, adjusted for geographical area; RRs for sectors, occupations, adjusted for age, period, and geographical category

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Chow et al. (1995)	Swedish Cancer Environment Registry, which linked employment and cancer information for all individuals registered in the 1960 Census and National Swedish Cancer Registry; linkage was performed using personal identifiers Esophageal cancer incidence	Not reported	Follow-up: 1961 to 1979	Job title reported on 1960 Census; 3 cases among laundry workers	SIRs, expected numbers based on 5-year birth cohort- and sex-specific rates for esophageal cancer in general Swedish population during time period; only occupations with ≥500 individuals examined; significance evaluated assuming Poisson distribution
Ji et al. (2005a, b); Ji and Hemminki, (2005b) (2005a, c, 2006)	Cohort: Swedish males and females in Family-Cancer Database linked national censuses; cancer incidence data from Swedish cancer registry (1961−2000) [Ji, et al.,(2005a: bladder cancer) Ji, and Hemminki, (2005b: kidney cancer; 2005a: upper aerodigestive tract cancer) (2005b; c: liver and gallbladder cancer)] Additionally, subjects ≥31 yr age and cancer incidence 1961−2002 [(Ji and Hemminki, 2005b: leukemia; 2006: lymphoproliferative diseases)]	1,644,958 employed men (9,255 dry cleaners and launderers) in 1960 Census and 1,154,091 employed women (14,974 dry cleaners and launderers) in 1970 Census	Follow-up from 1961 (1960 Census), 1970 (for 1970 Census or those with same job in 1960 +1970 Censuses), or 1980 (for those with same job in 3 censuses) through 2000 or 2002	Relevant census information (employment status, job title, work industry) coded according to Nordic Occupational Classifications; codes merged into 53 occupational groups, including launderers and dry cleaners; 9,255 (0.6%) male, 14,974 (1.3%) female launderers and dry cleaners	SIRs for each occupation, stratified by gender: (1) adjusted for age period, SES [aerodigestive tract cancers, leukemia/lympho-proliferative diseases, kidney cancer, liver and gall bladder cancer]; (2) smoking-corrected SIR and smoking-corrected 95% CI (based on IARC, 2004) [bladder cancer]

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Lindbolm et al.(1989)	Cohort: Finnish males and females participating in the 1970 National Population Census; cancer incidence data from Finnish Cancer Registry Liver cancer incidence	1.2 million men and women who were born between 1906 and 1945	Follow-up from 1971−1995	Industry Code 850, and cumulative exposure for organic solvent class. Cumulative exposure based on exposure for each birth cohort, starting when average age of birth cohort was 20 to end of observation period or age 65 yr and included a 10-yr lag period. If exposure took place before 1960, FINJEM estimated use for 1945−1959 period, otherwise estimated for 1960−1984 period used	SIRs for each occupation, stratified by gender from Poisson regression models adjusted for alcohol consumption, smoking, and socioeconomic status; (smoking and alcohol consumption by occupation obtained for FINJEM from the annual surveys of the Finnish population in 1978−1991)
Lynge and Thygesen (1990)	Cohort: Danish men and women, 20−64 yr, registered in 1970 Census as engaged in laundry and dry-cleaning work; linked to Danish Cancer Registry Site-specific cancer incidence	Cohort: 10,600	Follow-up: 1970−1980 (Lynge and Thygesen, 1990)	Industry Code 860 (laundries, cleaning, and dyeing), occupational Codes 411 (laundry worker, ironer) and 380 (factory hand), and those who reported as self-employed/family workers; 2,434 (23%) self-employed dry cleaners/launderers, 830 (7.8%) family workers, 6,837 (64.5%) laundry workers/ironers, 499 (4.7%) factory hands, 2,886 laundry/dry-cleaning shops in 1970, 695 where dry cleaning was the known predominant activity	SIRs, 95% CIs, assuming Poisson distribution if observed cases ≤30 and normal distribution if >30; expected numbers from multiplying person-years at risk within each 5-year age group with site-specific incidence rates for full 1970 cohort (Lynge and Thygesen, 1990)

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Pukkala et al. (2009)	Cohort: Men and women in 1990 Census or prior census in five Nordic countries (Denmark, Finland, Iceland, Norway, Sweden); dry cleaners and launderers occupational title; incident cases from national cancer registries Site-specific cancer incidence	15 million subjects total, 43,496 dry cleaners and launderers	Person-years started January 1 after the first available census and ended with deaths, emigration, or at end of 2003−2005, whichever came first. (depended on country)	Dry cleaner and launderer (Code 95) according to Nordisk Yrke Klassifisering and International Standard Classification of Occupation	SIRs and 95% CIs; expected number of deaths using national rates
Ruder et al. (1994) (2001); Calvert et al.,	Cohort: from union dry-cleaning records in California, Illinois, Michigan, New York; employed ≥1 yr pre-1960 in dry-cleaning shops using PCE; verified records with visits to shops; National Death Index for deaths that occurred in cohort (site-specific cancer mortality) or REMIS for end-stage renal disease incident cases.	1,704 workers (mortality) 1,296 (end-stage renal disease incidence)	Person-years started January 1, 1940, for mortality or January 1, 1977, for renal disease incidence or after 1 year of employment in unionized shop, whichever came later, and ended with death, loss to follow-up, or end of 2004, whichever came first.	PCE exposure estimated by duration of employment in dry-cleaning shops (1−5 yr or >5 yr) and latency periods (time since first employment <20 yr or 20+ yr); 618 (36%) worked only in shops that only used PCE; 1,086 (64%) worked at shops where PCE use is unable to be verified or where other solvents are known/suspected to be used instead	SMRs (for deaths) and 95% CIs; expected number of deaths estimated using national rates; estimates for each of 4 regions used county and national rates for expected numbers though data not shown SIRs (for end-stage renal disease types) and 95% CIs; expected number of deaths estimated using REMIS rates and national population estimates

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Selden and Ahlborg (2011)	Cohort: men and women identified by employer as working between 1973−1983 in dry-cleaning and laundry establishments for a previous study of pregnancy outcome (Ahlborg, 1990a), incident cancers from Swedish National Cancer Registry Site-specific cancer incidence	10,389 employed ≥1 mo identified by employers; 9,440 included in follow-up	Person years started January 1985 and ended with cancer diagnosis, death, emigration, or end of observation period on December 2006, whichever came first.	Jobs assigned to three exposure categories: PCE (dry cleaners or laundries with proportion of dry-cleaning with PCE), laundries (laundering only, no dry cleaning), "other" (dry cleaning with PCE and other solvents)	SIR and 95% CI using site-specific cancer incidence rate of Swedish population
Travier et al. (2002)	Cohort: Men and women reporting work as launderers, dry cleaners, and pressers in 1960 or 1970 Swedish Census, incident cancers from Swedish national cancer registry; all with second primary neoplasms excluded Site-specific cancer incidence	Authors did not report total number included in cohort; 543,036 person-years from 1960 Census and 46,933 person-years from 1970 Census	Person years started January 1971 and ended with cancer diagnosis, death, or loss to follow-up, or December 1989, whichever came first.	Jobs coded by Nordic Classification of Occupations and Swedish Industrial codes; Group 1, launderer, dry cleaner, or presser occupation employed in the laundry, ironing, or dyeing industries in either 1960 or 1970; Group 2, launderer, dry cleaner, or presser occupation employed in the laundry, ironing, or dyeing industries in both 1960 and 1970; Group 3, launderer, dry cleaner, or presser occupation employed in other industries; Group 4, other occupational titles employed in laundry, ironing, or dyeing industries; Group 5, not employed in relevant industries or occupations	Multivariable Poisson regressions, adjusted for age, calendar period, geographic region, urban setting, gender. Analyses also stratified by gender, adjusted for age, calendar period, geographic region, urban setting, and by age in 1960 (<40 yr, 40−59 yr, >59 yr), adjusted for gender, age, calendar period, geographic regions, and urban setting

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Wilson et al. (2008)	Cohort: Swedish men and women employed during 1960 or 1970 Census and still alive in January 1971; cancer information from Swedish Cancer-Environment Registry for 1971−1989 Proxy—laundry, ironing and dyeing industries, laundry workers and clothes pressing occupations Renal pelvis cancer incidence, bladder cancer incidence	4,197, 684 cohort members	Person years began January 1, 1971, and ended with cancer diagnosis, emigration, death, or December 31, 1989, whichever came first. 70,083,912 person-years of follow-up, mean: 16.7 yr	Job titles in censuses coded according to National Swedish Classification of Occupations and Industries standards, laundry workers: occupation Code 943 and clothes pressing: occupation Code 944. Laundry, ironing, and dyeing: industry Code 880; 110 bladder cancer cases and 11 renal pelvic cancer cases with this industry code. Job exposure matrix to assess exposure to indoor work, low physical activity, etc. 25,249 (0.6%) employed in industry Code 880. 16,512 (0.4%) employed in occupation 943, laundry worker	SIRs and 95% CIs for each occupation and industry using expected site-specific cancer incidence rates of total employed Swedish population

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
I.B. Other occupational cohort studies					
Anttila et al. (1995)	Workers with blood:urine biological monitoring; most of TCE in urine; PCE in blood 1974−1983; demographics, date/time sampling, result, workplace, solvent code from FIOH database; excluded if not identified or deceased at start of follow-up Site-specific cancer incidence (pancreas, lung/bronchus, cervix uteri, kidney, nervous system, non-Hodgkin lymphoma, multiple myeloma, and all cancer)	11,534 measurements from 1965−1983, 10,743 (93.1%) linked to personal identifiers, which corresponded to 3,976 workers. Final sample: 3,974 subjects; 849 workers with blood PCE measurements	Follow-up started January 1967 or date of first measurement; ended with emigration, death, or December 1992, whichever came first; used Finnish Cancer Registry, Population Register Center, Central Statistical Office of Finland; overall: 71,800 person-years, averaged 18 yr	Blood measurements: median 0.7 μmol/L in males, 0.4 μmol/L in females, average 3.2 measurements/individual; 849 (21.4%) workers monitored for exposure to PCE, contributed 11,958 person-years; duration not examined for PCE, given its few site-specific cancer cases	SIRs for 8 sites, 95% CIs, expected numbers of cancers from incidence rates of Finnish population; Mantel-Haenszel chi-square test for significance, assuming observed cases followed Poisson distribution

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Boice et al. (1999)	Cohort: from work history cards, personnel files, retirement records, employed at aircraft manufacturing factories ≥1 yr from 1960 onwards; exclusions: missing work history or incorrect dates; vital status from California death tapes, National Death Index, Pension Benefit Information Files, Social Security Death Index, Health Care Finance Administration files, California Department of Motor Vehicles records, employment work history cards, pension and retirement records, obituaries from 1960−1996; if no vital status information found, assumed alive JEM for PCE exposure Site-specific cancer mortality	113,204 employees, 77,965 (68.9%) included in study	Follow-up: started January 1, 1960 or after 1 year employment and ended with death, age 95 yr or December 1996, whichever came first. 1,889,795 person-years of follow-up; average of >20 yr per person	Exposure assessed via walk-through surveys of factories, interviews with employees, industrial hygiene files/other historical documents; based on job code, job title, job change information; factory jobs only assessed as routine (daily), intermittent (not daily), minimal/no exposure; duration (<1, 1−4, ≥5 yr) based on dates of employment for each job; overall: 5,830 (7.5%) exposed to PCE; 2,631 (5.8%) routine exposure, 3,199 (7.1%) intermittent exposure, 51,214 person-years at risk	SMRs, 95% CIs, assuming observed deaths followed Poisson distribution, expected number of deaths among Caucasians based on race, age, calendar year, sex-specific California rates; expected number of deaths among non-Caucasian based on general U.S. population rates; Poisson regression for duration, adjusted for date of birth, date first employed, date of end of employment, race, sex; tests of trend to examine duration of exposure

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Bond et al. (1990)	Dow Chemical's Midland/Bay City production, research, and headquarters units Nested case-control; cohort: from work history records, 48,521 men and women employed 3+d; Cases: from death certificates, men who died from 1940−1982. Controls: randomly selected from among the cohort of male employees Proxy—factory employment Primary liver cancer, cancer of gallbladder/bile ducts, cancer of liver not specified	44 (0.7%) liver and biliary tract deaths eligible for and included in study; 1,888 (8.8%) controls selected randomly from cohort (*n* = 21,437 males) Final sample: 44 cases, 1,888 controls	Follow-up period: 1940−1982	Work history records for exposure by work area and exposure to 11 chemicals, including PCE; 6 (13.6%) cases, 213 (11.3%) controls exposed to PCE	Mantel-Haenszel for RRs, adjusted for birth year; Miettinen's method for 95% CI; primary liver cancer and gall bladder/bile duct assessed separately but not presented; duration work exposure failed to reveal any significant trends
Chang et al. (2003; 2005); Sung et al. (2007; 2008)	Cohort: from Bureau of Labor and Insurance's records Proxy—employment in electronics factory in Taiwan Cancer, mortality	Various (see below)	Various (see below)	Various (see below)	Various (see below)

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Chang et al. (2003)	Cohort: identified from 1973−1997, men and women, average age of cohort members: 39.3 yr; linked with National Mortality Database; compared with labor-insurance hospitalization data Site-specific cancer mortality	86, 868 individuals (16,133 men and 70,735 women) who contributed 1,357 deaths, 316 (24%) due to cancer. All-cause mortality rate was 1.56%, and all cancer mortality rate was 0.36%	Person-years started when entered cohort or January 1, 1985, whichever later, and ended with death or December 31, 1997, whichever came first; total of 1,380,354 person-years; average follow-up time: 14.3 yr for men and 16.3 yr for women	Duration of employment: period of employment between the start and end of labor insurance coverage, with assumptions made for those with missing data	SMRs, stratified by underlying cause of death, expected numbers based on general Taiwanese population as a reference. For dose-response assessment, cohort stratified by duration employment: ≤1 year, >1 year but ≤5 yr, >5 yr and calendar year: 1985−1990, 1991−1997
Chang et al. (2005)	Cohort: identified from 1973−1997, men and women, linked with National Cancer Registry and National Mortality Database; compared with labor-insurance hospitalization data Site-specific cancer incidence	86,868 (16,133 men and 70,735 women) who contributed a total of 1,380,354 person years; 998 incident cancer cases	Follow-up: started January 1, 1979, or date of employment, whichever later, and ended with cancer diagnosis, death, or December 31, 1997, whichever came first	Duration of employment: <1, 1−5, 5−10, and 10+ yr; assumptions made for those with missing start or end dates Period of employment: 1979−1984, 1985−1990, 1991−1997	SIRs comparing exposed to incidence rates in general population of Taiwan by age, calendar year, and sex; trends examined by duration and period of employment Latency periods: <3 mo, 6 mo, and 1, 5, and 10 yr

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Sung et al. (2007)	Cohort: identified from 1973−1992, women worked for 1+ d, cancer diagnosis after employment began; Vital status from Ministry of Interior; cancer diagnoses from Taiwan National Cancer Registry and linked with cohort from 1979−2001 Site-specific cancer incidence: 29 cancer sites	64,000 women employed, 63,982 (99.97%) eligible for and included in the study, contributing 1,403,824 person-years	Follow-up: 1979−2001	Duration of employment (1 mo, 1, 5, 10, 15, and 20 yr) based on date labor insurance started and employment ended; for missing employment information: (1) if missing date labor insurance, and assumed earliest possible age (14 yr); (2) if date employment ended missing assumed factory closure in 1992. xposure by dates of government regulations: pre-1974 had the highest exposure 8,461 (13.2%) women who started working pre-1974	SIRs and 95% CIs, assuming a Poisson distribution for each cancer site; SIRs and 95% CIs for breast, cervical, colorectal, thyroid cancers, stratified by pre- or post-1974, duration of employment; *t*-tests for breast cancer among those employed pre- or post-1974 latency periods: 5 yr (thyroid/leukemia), 15 yr (breast/cervix uteri), 10 yr (all others)
Sung et al. (2008)	Cohort: identified from 1973−1992, women who worked in a factory, linked to the Taiwan Birth Registration Database from 1978−2001; only first born singletons, demographics from National Birth Registry, children linked with National Cancer Registry from 1979−2001 Childhood cancers	103,506 children born to 47,348 women from 1978−2001, 40,647 children eligible for and included in the study, contributing 639,051 person-years; 11 cancer cases among exposed, 36 cancer cases among nonexposed	Follow-up: 1979−2001	Periconceptional exposure defined as employed at factory during 3 mo prepregnancy and 3 mo after conception; conception calculated by subtracting length of gestation +14 d from the date of birth 8,506 (20.9%) exposed children who contributed a total of 155,121 person-years	Poisson regression for RRs and 95% CIs, adjusted for maternal age, maternal education level, sex, year of birth

Table B-1. Summaries of characteristics of cohort studies (dry-cleaner and laundry workers, and other cohorts) (continued)

Reference	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Spirtas et al. (1991); Blair et al. (1998); Radican et al. (2008)	Cohort: male/female civilian employees, worked 1+ yr at base from 1952−1956, identified from individual earnings records Personnel folders, vital status data from Social Security Administration, U.S. Office of Personnel Management, veterans administration records, motor vehicle records, National Death Index, interviews, state vital statistics; death certificates for cohort members who died during follow-up, underlying cause of death assessed by nosologist Mortality: MM, NHL, breast cancer, nonmalignant respiratory diseases	14,425 with personnel files (99.8% of 14,455 eligible); analysis restricted to 10,461 men and 3,605 women classified as Caucasian.	Follow-up began 1953 or after 1 year of employment Follow-up study through 1982 (Spirtas et al., 1991) or 2000 (Radican et al., 2008)	Job exposure matrix based on industrial hygienists, walkthrough surveys of base, interviews with employees, industrial hygiene files, job descriptions, historical documents. Job titles/shops used as basis for evaluating exposures, which for PCE consisted of ever/never classification; jobs unable to be linked to solvents coded as "mixed solvents". 10,256 ever exposed to mixed solvents, 851 ever exposed to PCE. Of those exposed to any chemical/solvent and died from MM, 2 (33.3%) women, 0 men exposed to PCE; of those who were exposed to any chemical/solvent and died from NHL, 2 (20%) women, 2 (9.1%) men exposed to PCE	SMRs MM and NHL and PCE. All calculations on Caucasian population only, including unknown race (Spirtas et al., 1991) Cox proportional hazards regression for hazard ratios and 95% CIs using age as time variable and race as covariate, stratified by gender (Radican et al., 2008); RR for breast cancer, MM, NHL, nonmalignant respiratory diseases, and PCE

JEM = job-exposure matrices; RR = relative risk.

B.2. CASE-CONTROL STUDIES

Tetrachloroethylene case-control studies have been organized by (1) multiple cancer site studies and (2) single cancer site studies. Tables B-2 and B-3 provide summaries of the study characteristics of each paper or group of papers.

B.2.1. Multiple Cancer Site Studies

A number of case-control studies of multiple cancer site studies have been conducted by a single research group. These studies are discussed in this section given common methodologies among the studies. The studies are organized by region (British Columbia and Montreal in Canada, Massachusetts in the United States, New Zealand, Germany, and four Nordic countries (Denmark, Finland, Norway, and Sweden).

B.2.1.1. British Columbia (Canada)

B.2.1.1.1. Band et al. (1999), MacArthur et al. (2009)

Band, P.; Le, N.; Fang, R.; Threlfall, W.; Gallagher, R. (1999). Identification of occupational cancer risks in British Columbia. Part II: A population-based case-control study of 1516 Prostatic cancer cases. J Occup Environ Med, 41, 233-247. http://www.ncbi.nlm.nih.gov/pubmed/10224589

MacArthur, A.; Le, N.; Fang, R.; Band, P. (2009). Identification of occupational cancer risk in British Columbia: A population-based case-control study of 2,998 lung cancers by histopathological subtype. Am J Ind Med, 52, 221-232. http://dx.doi.org/10.1002/ajim.20663

Summary: A registry-based case-control study was undertaken to examine occupational risk factors for cancer in British Columbia. Cases were identified through the British Columbia Cancer Registry from 1983 to 1990 and consisted of men aged 20 or older with histologicallyconfirmed cancer. All cases were mailed a self-administered questionnaire inquiring about lifetime job descriptions, including duration and period of employment, as well as occupation and industry titles. Participants were also asked about their ethnic origin, education, lifetime smoking habits, and alcohol consumption. Data were collected for each cancer site until 1,000 completed questionnaires were returned for that site or until December 31, 1990. If the patient was deceased, the spouse or closest living relative was asked to complete the questionnaire. A total of 25,726 eligible cases were contacted, and 15,463 (60%) participated by returning the questionnaire. Occupations and industries were used as a proxy for exposure and coded according to the Canadian Standard Occupational Classification (SOC) and the Canadian

Standard Industrial Classification (SIC). Laundries and dry cleaners comprised SIC Code 972. The authors did not report the SOC code for dry cleaners. For each occupation and industry, estimates for "ever" (whether or not a job within the given occupation or industry was ever held) and "usual" (job with the longest held lifetime employment in a given occupation or industry) occupations and industries were calculated. Strengths include complete ascertainment of cases and occupational histories, adjustment for confounders, and examination of lung cancer subtypes. Limitations include the lack of information on occupational exposures, small numbers of exposed cases, self-reported lifestyle characteristics, and possible bias due to the use of other cancer cases as controls. There may also be nonrepresentativeness of controls between early and late responders due to the fact that the survey for each cancer site ended at 1,000 cases.

Band et al. (1999) used the data to conduct a matched case-control study examining the occupational risks associated with prostate cancer in British Columbia. Cases consisted of patients with histologically confirmed prostate cancer who returned the questionnaire. A total of 1,519 (9.8%) of the cases in the larger study were prostatic cancer cases. Controls were selected from among the other cancer sites within the larger study, excluding lung cancers and cancers of unknown primary sites, and were matched to cases based on age and year of diagnosis. The final sample consisted of 1,516 cases matched to at least 1 of 4,994 controls. Proxy respondents represented 19.9% of cases and 19.3% of controls. Overall, there were 7 (0.5%) cases who reported "ever" employment and 2 (0.1%) cases who reported "usual" employment in the laundries and cleaners industry. The authors do not report the number of controls that reported "ever" or "usual" employment. Conditional logistic regression was used to estimate odds ratios and 90% CIs for each occupation and industry separately for each of two estimates of exposure, adjusted for education, alcohol consumption, smoking duration, and respondent to questionnaire.

MacArthur et al. (2009) evaluated the occupational risks for lung cancer. Of the 5,528 eligible, incident lung cancer cases, 2,998 (54.2%) returned the questionnaire. Controls consisted of all other cancer cases, excluding those with unknown primary sites (708 other cases) and were matched to cases based on age and year of diagnosis. Laundries and dry cleaners comprised Code 972 and contained 10 (0.3%) cases of lung cancer (squamous cell carcinoma, adenocarcinoma, and small cell lung cancer). Matched case-control analyses for industries and occupations with at least three cases were performed to calculate maximum likelihood estimates of odds ratios and their corresponding 90% CIs for "ever" and "usual" employment. Lung cancer subtypes (squamous cell carcinoma, adenocarcinoma, small cell lung cancer, large cell lung cancer) were also separately assessed. The estimates for all lung cancers combined were adjusted for smoking, questionnaire respondent, alcohol, and education. Lung cancer subtype estimates were separately adjusted for their own set of covariates. All subtypes were adjusted for questionnaire respondent; squamous cell carcinoma, adenocarcinoma, and large cell lung cancer

were adjusted for alcohol consumption status; adenocarcinoma, small cell lung cancer, and large cell lung cancer were each adjusted for smoking duration (years); squamous cell carcinoma was also adjusted for cigarette pack-years, marital status, pipe smoking status, and cigar smoking status. Adenocarcinoma was also adjusted for ethnicity, and small cell lung cancer's additional covariates included ethnicity and cumulative alcohol score. The final covariate for large cell lung cancer was level of education.

B.2.1.1.1.1. Band et al. (2000)

Band, P. R.; Le, N. D.; Fang, R.; Deschamps, M.; Gallagher, R. P.; Yang, P. (2000). Identification of occupational cancer risks in British Columbia: A population-based case-control study of 995 incident breast cancer cases by menopausal status, controlling for confounding factors. J Occup Environ Med, 42, 284-310. http://www.ncbi.nlm.nih.gov/pubmed/10738708

Summary: This study is a population-based case-control study whose objective was to examine the relationship between occupational risk and hormonal factors in breast cancer. Cases were identified through the British Columbia Cancer Registry and consisted of all women under the age of 75 years who were diagnosed with breast cancer between June 1988 and June 1989. In order to be included in the study, cases needed to be Canadian citizens, residents of British Columbia, English-speaking, and have no prior history of breast cancer. Controls were randomly selected from the 1989 British Columbia Provincial Voters List, matched on age, and had no history of breast cancer diagnosis before June 1989.

Participants were mailed a self-administered questionnaire inquiring about demographics, lifetime smoking, lifetime alcohol consumption, current body weight, weight in late teens, age at menarche, parity, age at first birth, history of breast biopsy before 1987, family history of breast cancer, breastfeeding, birth control, estrogen replacement therapy, and lifetime occupational history, including job descriptions, occupation and industry titles, duration, and period of employment. Of the 1,489 eligible cases, 1,018 (68%) returned the questionnaire; of the 1,502 eligible controls, 1,025 (68%) returned the questionnaire. After matching and excluding those with missing information on statistically significant confounders, a total of 995 cases and 1,020 controls were available for the analysis. Occupations and industries were coded according to the Canadian SOC and the Canadian SIC; dry cleaning was included in SOC Code 6162 and SIC Code 9721. Two surrogates of exposure were assessed: "usual" occupation/industry, defined as the job with the longest held lifetime employment in a given occupation or industry, and "ever" occupation/industry, defined as whether a job was ever held in the occupation or industry in question. Overall, there were 12 (1.2%) cases "ever" exposed and 9 (0.9%) cases with "usual" exposure to the laundry and dry cleaning occupation; there were also 23 (2.3%)

cases with "ever" exposure and 10 (1.0%) cases with "usual" exposure to the power laundries and/or dry-cleaners industry. The authors do not report the controls' exposures.

Conditional logistic regression was used to estimate odds ratios and 90% CIs for all occupations and industries, stratified by menopausal status and "usual"/"ever" occupation. Covariates were individually assessed using a forward methodology. The occupational analyses were adjusted for the following three factors: (1) premenopausal women—cigarette pack-year groups, breast biopsy, and family history of breast cancer in the mother and sisters; (2) postmenopausal women—weights in 1986, family history of breast cancer in a first-degree relative, a history of breast biopsy for benign breast diseases, and cumulative alcohol scores; and (3) all women combined—both the pre- and postmenopausal confounders. Strengths of the study include its population-based design, lifetime occupational history, and stratification by menopausal status. Limitations include a lack of information on actual exposures, small number of cases in each occupational category, chance occurrence, and lack of assessment of duration or intensity of exposure.

B.2.1.1.1.2. Teschke et al. (1997)

Teschke, K.; Morgan, M. S.; Checkoway, H.; Franklin, G.; Spinelli, J. J.; van Belle, G.; Weiss, N. S. (1997). Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens. Occup Environ Med, 54, 443-451. http://www.ncbi.nlm.nih.gov/pubmed/9245952

Summary: This case-control study examined sources of occupational exposure to known or probable carcinogens in British Columbia, Canada, with the aim of alerting regulatory agencies and industrial health professionals about occupations that warranted occupational hygiene exposure measurement and control. Cases were identified through the British Columbia Cancer Agency and consisted of men and women aged 19 years or older with histologically confirmed nasal cavity/sinus or urinary bladder cancers. Nasal cavity/sinus cancer cases were obtained for the time period from 1990 to 1992, and bladder cancer cases were selected between 1990 and 1991. Bladder cancer cases born before 1916 were excluded from the study, as were carcinomas in situ. Controls consisted of British Columbia residents aged 19 years or older. They were randomly selected from the provincial voter list and matched to cases based on age and sex. Any selected controls that were in prison or in a mental health institution by court order were excluded from the study. Of the 54 eligible nasal cancer cases and 195 eligible nasal cancer controls, 48 (88.9%) cases and 159 (81.5%) controls participated in the study. Of the 119 eligible bladder cancer cases and 173 eligible bladder cancer controls, 105 (88.2%) cases and 139 (80.3%) controls participated in the study. The final sample consisted of 153 cases and 298 controls.

Interviews were conducted with all cases and controls using a structured questionnaire administered by a registered nurse who knew of their case or control status. In-person or telephone interviews were conducted with all subjects who lived within a 6-hour (one-way) drive of Vancouver. Telephone interviews were conducted with all participants residing more than 6 hours away (21% cases and 23% controls). Proxy interviews with relatives were conducted if the individual was deceased, did not speak English well, or if he/she could not accurately remember life events. This occurred with 26 (17%) cases and 41 (13.8%) controls. The questionnaire inquired about occupational, residential, medical, smoking, and exposure histories; a blinded industrial hygienist evaluated all completed interviews and asked the nurse to conduct follow-up, asking clarification questions of the participant when necessary. Occupations and industries were first coded according to standard occupational and industrial classifications and then blindly grouped according to a previously established classification system. Assignment into a group was based on whether the occupation or the industry was more likely to determine the individual's exposure. In the event that both the occupation and the industry determined exposure, the occupation was used. After that, all duties and exposures related to each occupation were reviewed to verify the accuracy of all categorizations, and all groups with less than 20 individuals were reviewed to determine if they could be combined with others. In total, 57 occupational groups were developed. Laundry personnel were part of the "other" category for nasal cancer and contained no cases or controls; on the other hand, laundry personnel were included in the "originally suspect" group for bladder cancer and contained five cases (3.3%) and four (1.3%) controls who reported "ever" employment in the occupation.

Exact methods were used to estimate summary odds ratios and their corresponding 95% CIs according to Breslow and Day (1980). In the event that nonoccupational risk factors were found to be positively associated with any of the cancers, the odds ratios and their corresponding 95% CIs were estimated using unconditional logistic regression, adjusted for these risk factors. Latency times of 5, 10, and 15 years were also examined, though the results were not shown. All odds ratios were adjusted for sex, age, and smoking. The influence of duration of employment (6 months to 10 years, and 10 years or more) was also examined but only reported if the estimates affected the results. Occupational groups were then assessed for their need for further surveillance based on a set of criteria. Limitations of the study include its small sample size, the grouping of jobs with different duties and exposures, and the exclusion of carcinomas in situ. The authors do not report any strengths associated with the methodology of their study.

B.2.1.2. Montreal (Canada)

B.2.1.2.1. Siemiatycki et al. (1991; 1987), Aronson et al. (1996), Parent et al. (2000)

Siemiatycki, J. (1991). Risk factors for cancer in the workplace. Boca Raton, FL: CRC Press.

Siemiatycki, J.; Wacholder, S.; Richardson, L.; Dewar, R.; Gérin, M. (1987). Discovering carcinogens in the occupational environment. Methods of data collection and analysis of a large case-referent monitoring system. Scand J Work Environ Health, 13, 486-492. http://www.ncbi.nlm.nih.gov/pubmed/3433050

Aronson, K.; Siemiatycki, J.; Dewar, R.; Gérin, M. (1996). Occupational risk factors for prostate cancer: Results from a case-control study in Montréal, Québec, Canada. Am J Epidemiol, 143, 363-373. http://www.ncbi.nlm.nih.gov/pubmed/8633620

Parent, M. E.; Hua, Y.; Siemiatycki, J. (2000). Occupational risk factors for renal cell carcinoma in Montreal. Am J Ind Med, 38, 609-618. http://www.ncbi.nlm.nih.gov/pubmed/11071683

Summary: Siemiatycki (1991) used a population-based case-control design to examine the possible association between occupational exposures and cancer. Cases were identified from hospitals in Montreal and consisted of male residents of Montreal aged 35 to 70 years who were diagnosed or histologically confirmed with any of the following cancers between 1979 and 1985: esophagus, stomach, small intestine, colon, rectum, gall bladder, pancreas, peritoneum, lung, pleura, skin, prostate, penis, testes, bladder, kidney, eye, lymphoid tissue, and multiple myeloma. Brain cancer, buccal cavity cancer, larynx cancer, and leukemia were excluded; due to limited resources, lung cancer was excluded in Years 2, 3, and 6; rectal cancer was excluded in Years 1 and 2; prostate cancer was excluded in Years 4 and 5. All of the large hospitals in Montreal took part, providing 97% population-based case ascertainment. Of the 4,576 cases identified, 3,730 (81.5%) participated in the interview. Response rates for individual cancers varied between 78% and 85%. Two sets of controls were used. Population-based controls were selected through electoral lists and random digit dialing. Of the 541 chosen from electoral lists, 375 (69.3%) were interviewed. Of 199 eligible participants identified through random digit dialing, 158 (79.4%) participated in the interview. Overall, of 740 population controls selected, 533 (72%) were interviewed. The final sample consisted of 99 esophagus cases, 251 stomach cases, 497 colon cases, 257 rectum cases, 116 pancreas cases, 857 lung cases, 449 prostate cases, 484 bladder cases, 177 kidney cases, 103 melanoma cases, and 215 lymphoma cases. In-person interviews were conducted by trained interviewers with cases and controls through a two-part questionnaire. The first section was structured and inquired about demographics; residential history; lifetime consumption of cigarettes, alcohol, coffee, and tea; consumption of food containing carotene; and height and weight. The second part was semi-structured, so as to

acquire detailed information on each of the jobs held during the man's working lifetime. Occupations and industries were coded according to the Canadian Classification and Dictionary of Occupations 1971 and the SIC Manual, respectively. Exposure was classified by a team of blinded chemists and hygienists, who used a checklist of 294 substances to determine the number of potential exposures for each job. All classifications were based on a three-point scale: the degree to which they believed the exposure had actually occurred (possible, probable, definite), the frequency of exposure in a normal workweek (<5, 5−30, and >30%), and the level of the concentration of the exposure (low, medium, high). Nonexposure was evaluated according to the background levels of that particular substance. The 294 substances were combined with 98 occupations and 77 industries to make a total of 469 occupational circumstances. Exposure was assessed as both direct exposure to tetrachloroethylene and proxy exposure through employment as launderers and dry cleaners. There were 6 (1.2%) cases of colon cancer, 7 (0.8%) cases of lung cancer, and 9 (2.0%) cases of prostate cancer that were "ever" exposed to tetrachloroethylene. Similarly, there were 4 (1.6%) cases of stomach cancer, 5 (1.0%) cases of colon cancer, 5 (2.0%) cases of rectum cancer, 12 (1.4%) cases of lung cancer, 9 (2.0%) cases of prostate cancer, 10 (5.6%) cases of kidney cancer, 3 (2.9%) cases of skin melanoma, and 3 (1.4%) cases of non-Hodgkin lymphoma among those who reported "ever" employment as launderers or dry cleaners. The Mantel-Haenszel method was used to estimate odds ratios and their corresponding 90% CIs for "ever" exposure and "substantial" exposure. All estimates were adjusted for age, family income, and cigarette index. Additionally, stomach cancer was adjusted for birthplace; colon and rectum cancers were adjusted for ethnic origin and beer index; lung cancer was adjusted for ethnic origin, alcohol index, and respondent; prostate cancer was adjusted for ethnic origin, Quetelet index, and respondent; and kidney cancer and skin melanoma were adjusted for ethnic origin. Strengths of the study design include its detailed information on potential confounders and occupational histories, its blind exposure assessment, use of histologically confirmed cases and access to two different control groups. Limitations to the study include the possible misclassification of exposure, the small numbers of exposed, the examination of many chemicals and job categories, and the study's goal to identify risk factors for further investigation.

Aronson et al. (1996) and Parent et al. (2000) used the data from Siemiatycki (1991) to further examine associations with selected cancers. Aronson et al. (1996) examined the association between occupations and prostate cancer. Of the 557 prostate cancer cases, 449 (81%) participated in the interview. The cancer controls included all other cancer cases from Siemiatycki et al. (1991) except lung cancer. The final sample consisted of 449 cases, 1,550 nonprostate cancer controls, and 533 population controls. Overall, 55 (27 substances, 11 industries, and 17 occupations) of the 469 occupational circumstances initially reviewed in

Siemiatycki et al. (1991) were examined in this study. Tetrachloroethylene exposure was classified as "unexposed," "nonsubstantial," or "substantial." There were eight participants with "substantial" exposure, but the authors failed to note whether these were cases or controls, precluding a calculation of exposure prevalence. Unconditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs for exposures using partially adjusted and fully adjusted models. The partially adjusted model controlled for age, ethnicity, socioeconomic status, Quetelet index, and self-/proxy respondent status, while the fully adjusted model included the covariates in the partially adjusted model, in addition to the all-core substances with 30 or more exposed cases. Due to the fact that very few differences were found when analyzing the control groups separately, the majority of the results were reported using the pooled group. In the event that two substances were highly correlated, one was removed from the model.

Parent et al. (2000) examined occupation and renal cell cancer. Of the 227 eligible kidney cases, 177 (78%) were interviewed and 142 of the 177 kidney cancers were renal cell carcinoma. There were a total of 1,900 cancer controls, representing a participation rate of 78%. Occupations and industries were assessed as a proxy for exposure and classified as any exposure and duration of exposure >10 years. The laundry and cleaning industry had a total of four cases (2.8%) that were "ever" exposed to the industry. Fewer than 4 cases were exposed for more than 10 years, and the results were not reported. The authors did not report exposure to tetrachloroethylene in this study, although the predecessor study, Siemiatycki et al. (1991) did. Unconditional logistic regression models were used to calculate odds ratios and their corresponding 95% CIs for each occupation and industry, stratified by any exposure and duration of exposure >10 years. Estimates for any exposure were adjusted for respondent status, age, smoking, and BMI.

B.2.1.3. Massachusetts (United States)

B.2.1.3.1. Aschengrau et al. (1993; 1998), Paulu et al. (1999, 2002)

Aschengrau, A.; Ozonoff, D.; Paulu, C.; Coogan, P.; Vezina, R.; Heeren, T.; Zhang, Y. (1993). Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Arch Environ Health, 48, 284-292. http://www.ncbi.nlm.nih.gov/pubmed/8215591

Aschengrau, A.; Paulu, C.; Ozonoff, D. (1998). Tetrachloroethylene-contaminated drinking water and the risk of breast cancer. Environ Health Perspect, 106, 947-953. http://www.ncbi.nlm.nih.gov/pubmed/9703477

Paulu, C.; Aschengrau, A.; Ozonoff, D. (1999). Tetrachloroethylene-contaminated drinking water in Massachusetts and the risk of colon-rectum, lung, and other cancers. Environ Health Perspect, 107, 265-271. http://www.ncbi.nlm.nih.gov/pubmed/10090704

Paulu, C.; Aschengrau, A.; Ozonoff, D. (2002). Exploring associations between residential location and breast cancer incidence in a case-control study. Environ Health Perspect, 110, 471-478. http://www.ncbi.nlm.nih.gov/pubmed/12003750

Summary: These population-based case-control studies of bladder cancer, kidney cancer, and leukemia evaluated the relationship between various types of cancer and tetrachloroethylene exposure through contaminated drinking water. From 1968 to1980, tetrachloroethylene was used in a vinyl liner for asbestos cement water distribution pipes throughout Massachusetts to improve taste and odor. A substantial amount had been installed in five Upper Cape Cod towns, including Barnstable, Bourne, Falmouth, Mashpee, and Sandwich. In 1980, it was discovered that the tetrachloroethylene, which had been assumed to evaporate during the lining process, had leached into drinking water supplies. Cases were identified from the Massachusetts Cancer Registry and consisted of permanent residents of five Upper Cape Cod towns who were diagnosed with cancer between 1983 and 1986. Controls were identified through three mechanisms: living controls <65 years of age were obtained through random digit dialing, living controls ≥65 years of age were randomly chosen from Health Care Finance Administration lists using stratified sampling, and deceased controls were randomly selected from a Massachusetts Department of Vital Statistics and Research file for the period from 1983−1989. Of the 2,236 controls <65 years, 249 (11.1%) were eligible and contacted; of these, 184 (73.9%) were interviewed. Of the 611 controls ≥65 years, 537 (87.9%) were eligible and contacted; of these, 464 (86.4%) were interviewed. Of the 918 deceased controls, 794 (86.5%) were eligible and ascertained; of these, 723 (91.1%) were interviewed with a proxy respondent. Control groups for each of the cancer sites were selected through a two-step process. First, each cancer site was stratified by age, vital status, year of death (if applicable), and gender. Then, all controls that fell within a stratum with at least one case were chosen. Index years for each control group were determined based on the median year of diagnosis for the case group. Controls that moved to the Upper Cape Cod area after the index year, cases or controls with incomplete residential histories, and controls for which no tetrachloroethylene data were available were subsequently excluded. In-person (14%) and telephone (86%) interviews with participants, conducted by trained interviewers, inquired about a 40-year residential history, demographics, smoking, medical and occupational histories and exposures, bottled water consumption, and usual bathing habits. The articles did not provide estimates of proxy interviews. Cases and controls were similar in race, age, marital status, and religion.

Aschengrau et al. (1993; 1998) assessed exposure through relative delivered dose (RDD) of tetrachloroethylene via contaminated water estimated using Webler and Brown's (1993) algorithm, which was based on a tetrachloroethylene-leaching model by Demond (1982). The algorithm accounted for information about the water pipe that supplied each person's home,

including water flow and pipe characteristics. Inputs were determined using maps from local water suppliers or the Massachusetts Department of Environmental Protection. The exposure for cases and controls was assessed by one individual blinded to the individual's case/control status with a high degree of intraobserver and interobserver agreement. An ordinal estimate of exposure to tetrachloroethylene-contaminated water was defined as the estimated mass of tetrachloroethylene that entered the home through the drinking water during a specified period. The estimates were first categorized as "never exposed" (private wells) and "ever exposed," with the latter further categorized as "low" (up to and including median) and "high" (above the 50th, 75th, and 99th percentiles). The estimates based on Webler and Brown (1993) were recently found to correlate with historically measured tetrachloroethylene levels, demonstrating the algorithm's value in epidemiological research (Spence et al., 2008). RDDs were calculated for those that had more than one exposed residence and were categorized into low ($\leq$50th percentile of cumulative exposure among the exposed women), >50th, >75th, and >90th percentiles.

Aschengrau et al. (1993) evaluated the relationship between tetrachloroethylene-contaminated drinking water and bladder cancer, kidney cancer, and leukemia separately. Cases consisted of men and women of all ages who were diagnosed with incident bladder cancer, kidney cancer, or leukemia. Of the 79 bladder cancer cases, 42 kidney cancer cases, and 44 leukemia cases, 72 (91.1%) bladder cancer, 36 (85.7%) kidney cancer, and 38 (90.5%) leukemia cases were eligible and contacted. Of these, 63 (87.5%) bladder cancer, 35 (97.2%) kidney cancer, and 35 (92.1%) leukemia cases participated in the study. After employing the two-step control selection process and the additional exclusion criteria, the final sample consisted of 61 bladder cancer cases and 852 bladder cancer controls, 35 kidney cancer cases and 777 kidney cancer controls, and 34 leukemia cases and 737 leukemia controls. Industries and job titles were coded according to standard industrial (1987) and occupational (1990) classifications. Occupational exposure to tetrachloroethylene was based on industry and job titles, as well as specific questions posed during the interview. Overall, 34.4% bladder cancer cases, 26.2% bladder cancer controls, 25.7% kidney cancer cases, 25.2% kidney cancer controls, 35.3% leukemia cases, and 25.3% leukemia controls reported occupational exposure to solvents including tetrachloroethylene. Overall, there were 13 (21.3%) bladder cancer cases, 127 (4.9%) bladder cancer controls, 6 (17.1%) kidney cancer cases, 112 (14.4%) kidney cancer controls, 7 (20.6%) leukemia cases, and 94 (12.8%) leukemia controls with any exposure to tetrachloroethylene through drinking water without considering a latency period. Unadjusted odds ratios were estimated for all sites with at least two exposed cases, stratified by bottled water consumption and bathing habits separately. The Fisher exact test was used to estimate corresponding 95% CIs. These analyses were performed with and without the assumption of a latency period of 15 years for bladder and kidney cancer and 5 years for leukemia. Multiple

logistic regression was used to estimate odds ratios adjusted for sex, age at diagnosis for cases or index year for controls, vital status at interview, education, and occupational exposures. Additional potential confounders were included if present in at least three or more cases. This consisted of prior medical treatment with irradiation in the leukemia analysis, usual number of cigarettes smoked, and history of a urinary tract infection or stone in the kidney cancer analysis, and usual number of cigarettes smoked, history of a urinary tract infection or stone, and history of a cancer-associated job in the bladder analysis. Maximum likelihood estimates of the standard errors were used to estimate corresponding 95% CIs. Strengths of this study include its ability to control for a variety of potential confounders, including occupational exposures, and its examination of the effect of latency periods on the different cancers. Limitations to the study include a small bladder cancer sample size to examine the effect of a latency period, unknown levels of exposures, and nonblinded interviews.

Both Aschengrau et al. (1998) and Paulu et al. (2002) examined the relationship between tetrachloroethylene-contaminated drinking water and breast cancer in women diagnosed between 1983 and 1986. Of the 334 breast cancer cases, 295 (88.3%) were eligible, and 265 (89.8%) were interviewed. There were 763 controls identified through the two-step control selection process. After employing the additional exclusion criteria, the final sample consisted of 258 cases and 686 controls.

Aschengrau et al. (1998) reported 36 (14%) exposed cases and 81 (11.8%) exposed controls without considering a latency period. Latency periods of 5, 7, 9, 11, 13, and 15 years were also evaluated. Unadjusted odds ratios and their corresponding 95% CIs examined crude associations and potential modifiers. Multiple logistic regression was used to calculate odds ratios adjusted for age at diagnosis or index year, vital status at interview, family history of breast cancer, age at first live birth or stillbirth, personal history of prior breast cancer and benign breast disease, and occupational exposure to solvents. Maximum likelihood estimates of the standard errors were used to estimate corresponding 95% CIs. A strength of the study is its adjustment for a variety of potential confounders. Limitations include potential for measurement error in exposure estimates, small numbers of women, and possible misclassification due to inaccurate reporting on death certificate of control's address or cause of death.

Paulu et al. (1999) studied the relationship between tetrachloroethylene-contaminated drinking water and colon-rectum, lung, brain, and pancreatic cancer cases between 1983 and 1986. Of the 420 colon-rectum, 326 lung, 42 brain, and 43 pancreatic cancer cases selected, 366 (87.1%) colon-rectum, 272 (83.4%) lung, 40 (95.2%) brain, and 39 (90.7%) pancreatic cancer cases were contacted and eligible. Of these, 326 (89.1%) colon-rectum, 252 (92.6%) lung, 37 (88.1%) brain, and 37 (86.1%) pancreatic cancer cases were interviewed for an overall participation rate of 79%. The final sample consisted of 311 colon-rectum cancer cases and

1,158 colon-rectum cancer controls, 243 lung cancer cases and 1,206 lung cancer controls, 36 brain cancer cases and 703 brain cancer controls, and 36 pancreatic cancer cases and 622 pancreatic cancer controls. Excluding any latent periods, exposure assessments were as follows: colon-rectum cancer had 44 (14.1%) cases and 153 (13.2%) controls; lung cancer had 33 (13.6%) cases and 158 (13.1%) controls; brain cancer had 3 (8.3%) cases and 92 (13.1%) controls; and pancreatic cancer had 3 (8.3%) cases and 81 (13.0%) controls. Due to their low numbers of "ever exposed," unadjusted estimates of odds ratios and their corresponding 95% CIs were calculated for brain and pancreatic cancer cases. Multiple logistic regressions was used to estimate the odds ratios and 95% CIs for colon-rectum and lung-cancer cases, adjusted for age at diagnosis or index year, vital status at interview, sex, and occupational exposure to tetrachloroethylene and other solvents. Colon-rectum cancer was further adjusted for history of polyps, inflammatory bowel disease, and occupational history associated with colon-rectum cancer. Lung cancer was further adjusted for usual number of cigarettes smoked and history of cigar/pipe use, living with a smoker, and occupational history associated with lung cancer. Latency periods of 0, 5, 7, 9, 11, 13, and 15 years were considered in the analyses. Strengths of this study are its adjustment for confounders and consideration of a latency period. Limitations include a lack of measured tetrachloroethylene levels, lack of adjustment for smoking, particularly for lung cancer, and low-exposure prevalence, particularly for brain and pancreatic cancer cases.

Paulu et al. (2002) examined residential location using GIS-coded information. The 40-year residential history obtained during the interview included full addresses and calendar years of residence. If the complete address was unknown, tax assessors' books were used to help identify the geographical location. All participants were then blindly mapped onto an enlarged version of a U.S. Geological Survey map, which was later converted into a digital format. The Upper Cape Cod area was divided into subregions with two methodologies: the first employed fixed, multiscale grids and coded each participant as ever exposed or unexposed for each grid cell; the second used overlapping circles (adaptive k-smoothing) whose sizes were based on the number of nearby cases and controls. Crude and adjusted odds ratios were estimated for both the grid and k-smoothed methodologies, using map choropleths for visualization. These maps facilitate visualization of "hot spots" for microscale residence. Multiple logistic regression was used to estimate odds ratios for breast cancer, adjusted for age, parity, vital status, family history of breast cancer in a first-degree female relative, age at first live birth or stillbirth, and prior history of breast cancer or benign breast disease. No strengths were reported by the authors for this study; a limitation was the study's lack of individual measurements of household tetrachloroethylene exposures.

B.2.1.3.2. Aschengrau et al. (2003), Vieira et al. (2005)

Aschengrau, A.; Rogers, S.; Ozonoff, D. (2003). Perchloroethylene-contaminated drinking water and the risk of breast cancer: Additional results from Cape Cod, Massachusetts, USA. Environ Health Perspect, 111, 167-173. http://www.ncbi.nlm.nih.gov/pubmed/12573900

Vieira, V.; Aschengrau, A.; Ozonoff, D. (2005). Impact of tetrachloroethylene-contaminated drinking water on the risk of breast cancer: using a dose model to assess exposure in a case-control study. Environ Health, 4, 3. http://dx.doi.org/10.1186/1476-069X-4-3

Summary: These population-based case-control studies were conducted as a follow-up to Aschengrau et al. (1998) and Paulu et al. (2002) to examine breast cancer and drinking water exposure. Cases were identified through the Massachusetts Cancer Registry and consisted of women diagnosed with breast cancer between 1987 and 1993, a period after that examined in the earlier studies. In contrast to the two-stage control selection process in earlier studies, controls were selected in three ways: (1) random-digit dialing (women ≤64 years), (2) random selection from a Medicare beneficiary roster (≥65 years), or (3) random selection from among death certificates provided by the Massachusetts Bureau of Health Statistics, Research, and Evaluation. Controls were matched to cases based on age and vital status at the time of identification. The final sample consisted of 672 cases and 616 controls, of which 211 (31.4%) cases and 192 (31.2%) controls were nonproxy respondents. Structured interviews were conducted with participants and next of kin to obtain information on demographics, confounders (age at diagnosis, family history of breast cancer, personal history of prior breast cancer, age at first live birth/stillbirth, occupational exposure to tetrachloroethylene, etc.), potential effect modifiers (bathing habits, bottled water, and water filter use), as well as a 40-year residential history. The authors do not state if these were in-person or blinded interviews.

Aschengrau et al. (2003) further examined the hypothesis that tetrachloroethylene exposure via contaminated drinking water increases the risk of breast cancer. Overall, 672 cases (81% selected and eligible cases) and 616 controls (157 [83%] random-digit dialed, 301 [76%] of Medicare roster, and 158 [79%] deceased) were included in the analysis. RDD of tetrachloroethylene via contaminated water was estimated using Webler and Brown's (1993) algorithm, which was based on a tetrachloroethylene leaching model by Demond (1982). The algorithm accounted for information about the water pipe that supplied each person's home, including water flow and pipe characteristics. Inputs were determined using maps from local water suppliers or the Massachusetts Department of Environmental Protection. The exposure for cases and controls was assessed by one individual blinded to the individual's case-control status with a high degree of intraobserver and interobserver agreement. An ordinal estimate of exposure to tetrachloroethylene-contaminated water was defined as the estimated mass of

tetrachloroethylene that entered the home through the drinking water during a specified period. The estimates were first categorized as "never exposed" (private wells) and "ever exposed," with the latter further categorized as "low" (up to and including median) and "high" (with categorization as >50th, >75th, and >99th percentiles). The estimates based on Webler and Brown (1993) were recently found to correlate with historically measured tetrachloroethylene levels, demonstrating the algorithm's value in epidemiological research (Spence et al., 2008). Overall, there were 155 (23.1%) cases and 136 (22.1%) controls exposed to tetrachloroethylene. Data analysis included the following latent periods: 0, 5, 7, 9, 11, 13, 15, 17, and 19 years. Exposure odds ratios and their corresponding 95% CIs estimated crude associations. Multiple logistic regression was used to estimate odds ratios, adjusted for age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer, age at first live birth or stillbirth, and occupational exposure to tetrachloroethylene. Maximum likelihood estimates of the standard error were used to calculate corresponding 95% CIs.

Viera et al. (2005) further studied the associations between tetrachloroethylene exposure and breast cancer. Due to the fact that the majority of the relevant interview information was only collected from nonproxy cases and controls, proxy interviews were excluded from the analyses, though included in comparisons with the total sample. Nonproxy information obtained through the interviews included the daily consumption of tap water or drinks that used tap water (number of drinks), bottled water consumption, and the temperature, frequency, and duration of showers and baths. Data not collected in the interviews, such as inhalation rate, water flow rate, and air exchange rate, were ascertained from the literature. The authors did not provide references for these obtained rates. In contrast to Aschengrau et al. (2002), this study estimated the personal delivered dose (PDD) for each participant by adding the amount inhaled, dermally absorbed, and ingested together for each exposed residence. Inhalation was estimated from reported temperature, frequency, and duration of baths and showers, as well as from the amount of tetrachloroethylene in the bath/shower air. Dermal absorption was estimated according to Fick's first law and used height and weight data to calculate each participant's surface area. Ingestion was based on the volume of tap water the participant drank. RDDs were reestimated for the nonproxy participants only, and both the RDD and PDD were used to classify each participant into nested exposure levels: ≤50th percentile, >50th, >75th, and >90th percentiles. Latency periods of 0, 5, 7, 9, 11, 13, 15, 17, and 19 years were employed. Without considering a latency period, the full sample contained 155 (23.1%) exposed cases and 136 (22.1%) exposed controls, and the nonproxy sample contained 101 (21.9%) exposed cases and 88 (20.8%) exposed controls. Crude and adjusted analyses were conducted for both the RDD and PDD levels, though adjusted analyses were limited to those with at least three exposed cases and at least three exposed controls. Multiple logistic regression was used to estimate adjusted odds

ratios, controlling for the following confounders, which were identified *a priori:* age at diagnosis or index year, family history of breast cancer, personal history of breast cancer, age at first live birth or stillbirth, and occupational exposure to tetrachloroethylene. Maximum likelihood estimates of the standard errors were employed to estimate corresponding 95% CIs. All nonproxy estimates were subsequently compared to estimates for all subjects. The full sample's adjusted odds ratios further controlled for vital status at interview. A goodness-of-fit test compared the RDD and the PDD to ascertain which was a better measure, and a nonparametric rank test evaluated whether RDD and PDD exposures differed significantly from each other. A strength of this study is its incorporation of personal behaviors in estimating exposure, examination of nonproxy respondents, considered to provide more correct information than proxy respondents and to reduce misclassification bias, and comparison of results from only nonproxy respondents to results of all subjects. Limitations include its use of cumulative exposures, which may mask the effect of intensity of exposure, recall bias for behavioral data, and decreased sample size due to the use of nonproxy respondents only.

B.2.1.4. New Zealand

B.2.1.4.1. Corbin et al. (2011), Dryson et al. (2008), 't Mannetje et al. (2008), McLean et al. (2009)

Corbin, M.; McLean, D.; Mannetje, A.; Dryson, E.; Walls, C.; McKenzie, F., . . . Pearce, N. (2011). Lung cancer and occupation: A New Zealand cancer registry-based case-control study. Am J Ind Med, 54, 89-101. http://dx.doi.org/10.1002/ajim.20906

Dryson, E.; 't Mannetje, A.; Walls, C.; McLean, D.; McKenzie, F.; Maule, M., . . . Pearce, N. (2008). Case-control study of high risk occupations for bladder cancer in New Zealand. Int J Cancer, 122, 1340-1346. http://dx.doi.org/10.1002/ijc.23194

't Mannetje, A.; Dryson, E.; Walls, C.; McLean, D.; McKenzie, F.; Maule, M., . . . Pearce, N. (2008). High risk occupations for non-Hodgkin's lymphoma in New Zealand: case-control study. Occup Environ Med, 65, 354-363. http://dx.doi.org/10.1136/oem.2007.035014

McLean, D.; Mannetje, A.; Dryson, E.; Walls, C.; McKenzie, F.; Maule, M., . . . Pearce, N. (2009). Leukaemia and occupation: A New Zealand Cancer Registry-based case-control Study. Int J Epidemiol, 38, 594-606. http://dx.doi.org/10.1093/ije/dyn220

Summary: The case-control studies of Dryson et al. (2008), Mannetje et al. (2008), McLean et al. (2009), and Corbin et al. (2011) are part of an ongoing series of studies examining the relationship between occupation and cancer in the New Zealand population. Cases were identified through the New Zealand Cancer Registry from 2003 to 2004 in Dryson et al. (2008),

't Mannetje et al. (2008), and McLean et al. (2009)and from 2007 to 2008 in Corbin et al. (2011). Population-based controls were randomly chosen from the 2003 New Zealand Electoral Roll and matched to cases based on age. Of 1,200 potential controls initially mailed letters of invitation, 1,100 had valid addresses. Of these, 660 were able to be contacted and considered eligible to participate. Overall, 473 controls were interviewed, with an overall response rate of 48%. After excluding controls with missing information for key variables, the final sample consisted of 471 controls. Controls in Corbin et al. (in press) were identified from 2003 to 2008 with letters of invitation mailed to 2,000 individuals, 1,878 of whom had valid addresses. Of these, 1,134 replied, and 796 were interviewed (48% response rate). In Dryson et al. (2008), 't Mannetje et al. (2008), and McLean et al. (2009), cases and controls were similar in occupational class, with the exception of the lowest class, which was more prevalent among cases than controls. In Corbin et al. (2011), "ever" smoking was more frequent among cases than among controls, as might be expected in a study of lung cancer, and the frequency of subjects 71 years of age and older was higher among controls than among cases.

In-person interviews were conducted with a trained interviewer whose background was in occupational health nursing. The questionnaire inquired about demographics, smoking, and occupational history, and more detailed information was obtained on all jobs lasting longer than 1 year. Occupation was assessed as a proxy for exposure, and jobs were blindly coded according to the 1999 New Zealand Standard Classification of Occupations and the Australian and New Zealand SIC. The authors do not report who assigned the codes. Occupation Code 8264 consisted of textile bleaching, dyeing, and cleaning machine operators and was considered *a priori* to be high risk. The authors did not refer specifically to dry-cleaners or laundry workers. McLean et al. (2009) noted workers in this occupational group had similar exposures as laundry and dry cleaning occupations. In addition, Corbin et al. (in press) presented analyses separately for occupational titles of dry cleaner and launderer. Unconditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs for occupations and industries considered *a priori* and *a posteriori* to be high risk. All estimates were adjusted for 5-year age group, sex, smoking ("ever," "ex," "never"), Maori ethnicity, and occupational status. Semi-Bayes adjustments were performed to minimize the risk of false positive results due to multiple comparisons. These adjustments were performed using an estimate of the variation that was determined *a priori*. Strengths of the study design include its population-based design, near complete coverage of both incident cancers and the general population, and adjustment for smoking. Additionally, interviews were conducted in person and obtained detailed occupational histories. The limitations of the study include the lack of an exposure profile, information on duration or length of employment for only certain occupations or chemicals, and possible selection bias due to the low-response rates of cases and controls, though McLean et al. (2009)

noted the similarity between the distribution of occupations in the national census and the sample. Additional limitations include the study's low exposure prevalence and possible exposure misclassification due to the use of broad occupational categories.

Dryson et al. (2008), 't Mannetje et al. (2008), and Corbin et al. (2011) included men and women aged 25 to 70 years who were diagnosed with either bladder cancer or non-Hodgkin lymphoma. The authors did not state if the cases were histologically confirmed. Dryson et al. (2008) studied bladder cancer among selected occupations that may contribute to the risk of bladder cancer. Of the 381 cases in Dryson et al. (2008) identified from the New Zealand Cancer Registry, 232 (60.9%) were able to be contacted by mail and eligible to participate. In total, 213 cases were interviewed for the study, with an overall response rate of 64%. The final sample consisted of 213 cases and 471 controls. Approximately 77% of cases and 47% of controls were male. "Current" and "ever" smoking were more prevalent among cases than controls. There were 3 (1.4%) bladder cancer cases and 10 (2.1%) controls that reported employment in the bleaching, dyeing, and cleaning machine occupations.

't Mannetje et al. (2008) aimed to assess whether previously reported associations (Pearce et al., 1985, 1987, 1988)(Reif, 1989) between occupations and non-Hodgkin lymphoma persist, and to identify other occupations that may also contribute to the risk of non-Hodgkin lymphoma in the New Zealand population. Of the 533 cases identified from the cancer registry, 335 (62.9%) were able to be contacted and eligible to participate. In total, 291 cases were interviewed for the study, with a response rate of 69%. The final sample consisted of 291 cases and 471 controls. Approximately 54% of cases and 47% of controls were male, and current smoking was more common among cases than controls. There were 5 (1.7%) cases and 10 (2.1%) controls that reported employment as a textile bleaching, dyeing, and cleaning machine operators.

McLean et al. (2009) studied the relationship between occupation and leukemia (chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, and other forms of leukemia). Cases consisted of men and women aged 20 to 75 years who were added to the registry between 2003 and 2004. The authors did not state if the cases were histologically confirmed. Of the 391 eligible cases, 225 (57%) participated in the interview; 11 (4.9%) of which were proxy interviews with next of kin. The final sample consisted of 225 cases and 471 controls. Approximately 61% cases and 47% controls were male, and a higher proportion of cases were current smokers than controls. Overall, 6 (2.7%) cases and 10 (2.1%) controls comprised the textile bleaching, dyeing, and cleaning machine occupation.

Corbin et al. (2011) examined lung cancer and occupation to support previously identified risk factors and to identify new risk factors. Of 744 eligible lung cancer cases, aged 20−75 years in Corbin et al. (in press), 458 were interviewed (53% response rate). Among those

interviewed, 432 of the 796 cases were by phone, and all interviews were with living subjects. Face-to-face interviews were carried for the remaining 432 control subjects. Overall, 20 cases and 13 controls were employed as textile bleaching, dyeing, and cleaning machine operators, with 3 of these cases and 4 controls identified as dry cleaners. An additional 9 cases and 5 controls were identified as launderers.

B.2.1.5. Germany

B.2.1.5.1. Pesch et al. (2000a; 2000b)

Pesch, B.; Haerting, J.; Ranft, U.; Klimpel, A.; Oelschlägel, B.; Schill, W. (2000b). Occupational risk factors for renal cell carcinoma: Agent-specific results from a case-control study in Germany. Int J Epidemiol, 29, 1014-1024. http://dx.doi.org/10.1093/ije/29.6.1014

Pesch, B.; Haerting, J.; Ranft, U.; Klimpel, A.; Oelschlägel, B.; Schill, W. (2000a). Occupational risk factors for urothelial carcinoma: Agent-specific results from a case-control study in Germany. Int J Epidemiol, 29, 238-274. http://dx.doi.org/10.1093/ije/29.2.238

Summary: Between 1991 and 1995, a population-based case-control study was conducted in five regions of Germany to independently estimate the risk of urothelial cancer and renal cell cancer as functions of exposure to aromatic amines, polycyclic aromatic hydrocarbons (PAHs), and other chlorinated hydrocarbons. Cases were identified through the large hospitals in each of the regions and consisted of German men and women who were diagnosed with histologically confirmed urothelial or renal cell cancer within the 6 months prior to the start of the study. Controls were randomly selected from local residency registries and matched to cases on age, sex, and region. In order to be included in the study, cases and controls were required to be German nationals; there were no age limits during the recruitment process.

In-person interviews with trained interviewers occurred with cases in the hospital within the first 6 months of diagnosis and with controls in their home. A structured questionnaire inquired about demographics, lifestyle, and occupational exposures. The final sample consisted of 1,970 cases (1,035 urothelial cancer and 935 renal cell cancer) and 4,298 controls, with overall response rates of 84% for cases and 71% for controls. Exposure was assessed based on the participant's reported occupational history, exposure to specific agents during tasks, and average amount of time each day exposed. All jobs held for at least 1 year were coded according to the International Standard Classification of Occupations. Lifetime exposure was calculated as the total number of years spent at a specific job title; task- and agent-specific exposures were estimated as weighted sums of years spent at that task or exposed to the agent in question. Job exposure matrices (JEMs) and job-task exposure matrices (JTEMs) were also used for calculating exposure to specific agents, including tetrachloroethylene. These matrices evaluated

the probability and intensity of exposure. The JEM, which assessed exposure based on job title, used both the British (Pannett et al., 1985) and the German (Robra and Seidler, 1994) versions. The JTEM was developed by the researchers and adjusted for both region and time. Both studies used conditional logistic regression to calculate odds ratios and their corresponding 95% CIs for potential confounders, occupations and tasks, and substances separately, adjusted for age, study center, and smoking. Potential confounders were also stratified by gender, and additional analyses were adjusted for age and study center without smoking. Strengths of these studies include population-based selection of controls and the use of a JEM and a JTEM to assess substance exposure. Limitations include the lower response rate of controls compared to cases and the reliance of self-reported information for exposure assessment.

Pesch et al. (2000a; 2000b) estimated the urothelial cancer risk for occupational exposure to aromatic amines, PAHs, and chlorinated hydrocarbons besides other suspected risk factors. This study sample included 1,035 urothelial cancer cases and 4,298 controls. When tetrachloroethylene was assessed using the German JEM, there were 183 (17.7%) cases with medium exposure, 188 (18.2%) cases with high exposure, and 74 (7.1%) cases with substantial exposure. The JTEM approach, however, only identified 37 (3.6%) cases with medium exposure, 47 (4.5%) with high exposure, and 22 (2.1%) with substantial exposure.

Pesch et al. (2000a; 2000b) examined the possible impact of occupation-related agents on renal cell cancer development. The sample in this study consisted of 935 renal cell cancer cases and 4,298 controls. When tetrachloroethylene was evaluated using the German JEM, there were 166 (17.8%) cases with medium exposure, 138 (14.8%) cases with high exposure, and 54 (5.8%) cases with substantial exposure. The JTEM approach, however, identified only 52 (5.6%) cases with medium exposure to tetrachloroethylene, 45 (4.8%) with high exposure, and 18 (1.9%) with substantial exposure.

B.2.1.6. Nordic Countries

B.2.1.6.1. Lynge et al. (2006)

Lynge, E.; Andersen, A.; Rylander, L.; Tinnerberg, H.; Lindbohm, M. L.; Pukkala, E., . . . Johansen, K. (2006). Cancer in persons working in dry cleaning in the Nordic countries. Environ Health Perspect, 114, 213-219. http://dx.doi.org/10.1289/ehp.8425

Summary: This study of a case-case control design examined eight site-specific cancers (non-Hodgkin lymphoma, esophageal, gastric cardia, liver, pancreatic, cervix uteri, kidney, and bladder), and job title, distinguishing between dry-cleaning workers, a proxy for tetrachloroethylene, and other job titles such as laundry workers. The cohort from which cases and controls arose consisted of 46,768 individuals identified as laundry and dry-cleaning workers

in the 1970 Censuses in Denmark, Finland, Norway, and Sweden. All were followed for death, emigration, and incident cancer based on nationwide population, death, and cancer registries. Relevant cancer cases were identified as those that occurred during the period of November 1970 (Denmark) or January 1971 (Finland, Norway, Sweden) through 1997 to 2001. Controls were randomly selected from the cohort and matched based on country, sex, 5-year age group, and 5-year calendar period at the time of diagnosis. All analyses were conducted at the level of the record rather than person because a subject may have appeared as a case or as a cancer control in the study more than once. Out of 4,014 records from 3,883 persons, 131 subjects were considered both as a case and as a cancer control.

Lynge et al. (2006) used job title and occupational task identified in the 1970 Census to identify tetrachloroethylene exposure potential. Differing recordkeeping systems and record availability in each country necessitated a number of approaches for assigning exposure potential to cases and controls; Johansen et al. (2005) provides an in-depth description of available records for Danish subjects. In Denmark and Norway, occupational task identified on the 1970 Census form was available and used to identify subjects as (1) dry-cleaners or other workers in dry-cleaning shops with <10 workers, assumed to have high-exposure potential because of the shared work tasks and physical proximity in small dry-cleaning shops; (2) other workers in dry-cleaning shops; (3) unexposed laundry workers and other persons in dry cleaning, and (4) unclassifiable, a category for subjects with missing employment information. Pension data from Denmark and Finland, as well as a Danish biography of dry-cleaning shop owners, were used to identify length of employment, a proxy for cumulative exposure, between 1964 and 1979, and size of workforce, for self-employed subjects. For subjects from Norway and Sweden, a blinded telephone interview was undertaken, given the lack of storage of the 1970 Census forms. The questionnaire asked about occupational task for job title reported on the 1970 Census form, and if dry cleaning, questions sought answers on employment length, number of employees, solvents used, and personal habits of smoking and alcohol consumption. Interviews were obtained with 148 of 258 of cases (57%) and 293 of 457 controls (64%) in Norway; for which 107 cases subjects (72%) and 123 control subjects (42%) were with proxy respondents. For Swedish subjects, interviews were obtained with 369 of 586 cases (63%) and 454 of 756 controls (60%) controls; for which 284 case subjects (77%) and 177 control subjects (39%) were with proxy respondents.

In total, the study included 1,616 cases and 2,398 controls, with roughly two-thirds (68%) of subjects from Denmark and Sweden. There were 695 (175%) cases and controls who were exposed due to their work as dry cleaners, 183 (5%) exposed through other work in a dry-cleaning shop, and 716 (18%) for whom information on employment and exposure potential could not be obtained and were identified as "unclassifiable." The percentage of subjects

identified as "unclassifiable" varied by country, with no subjects from Denmark, 41% of all subjects from Finland, 2% of all subjects from Norway, and 35% of all subjects from Sweden.

Lynge et al. (2006) provided some exposure monitoring data, particularly for 1964–1979, the period examined in analyses of exposure duration. Although a large variation in exposure levels was observed in 168 samples from Nordic dry-cleaning shops, the median concentrations over this period were relatively stable and appeared to range from 3–12 ppm. Lynge et al. (2006)reported a mean of 24 ppm from 53 samples of ≥60 minutes in length.

Rate ratios (RRs) for dry cleaners versus unexposed controls were estimated using logistic regression. RRs were also calculated for the other persons in dry cleaning and for the unclassifiable persons, although the underlying hypothesis did not include these groups. RRs were estimated for all countries together and for Denmark and Norway together given their lower percentage of unclassifiable subjects compared to that for Finland (41%) or Sweden (35%). The researchers adjusted for the matching criteria, as well as smoking and alcohol use (Norway and Sweden only) in bladder cancer analyses that showed smoking as not greatly affecting observed risk estimates. Strengths of the study include its coverage of the period where tetrachloroethylene was used as the main solvent, its population-based design, its use of a series of nested case-control studies within the cohorts to examine specific cancers, its control for smoking in bladder cancer analysis, and its examination of dry cleaner versus other dry-cleaning tasks. A limitation is a lack of exposure monitoring data on individual subjects as industrial hygiene data from 1964−1979 showed a large variation in tetrachloroethylene concentrations across shops. Additionally, the large number of next-of-kin interviews in cases from Sweden and Norway; a control series which included cases with other cancers of *a priori* interest (8% of case series); assessment of tetrachloroethylene exposure potential for one job, that was held in 1970, versus for the full employment history; and, censoring employment duration to 1979 rather than for the study's full period, to 1998 or 2001 (depending on country) likely introduces misclassification bias. Finally, a large number of subjects from Sweden and Finland had missing information. If differential reporting of job title and occupational tasks was associated with exposure as a dry cleaner and status as a case or control, then a misclassification bias would be introduced. Lynge et al. (2006) explored the magnitude of this potential bias on esophageal cancer estimates, noting if all unclassified subjects were exposed as dry cleaners, observed odds ratio (0.76; 95% CI: 0.34, 1.69) would increase (to 1.19; 95% CI: 0.67, 2.12), and, if unexposed, would decrease (to 0.66; 95% CI: 0.30, 1.45).

B.2.2. Single Cancer Site Studies

B.2.2.1. Bladder Cancer

B.2.2.1.1. Burns and Swanson (1991), Swanson and Burns (1995)

Burns, P. B. and Swanson, G. M. (1991). Risk of urinary bladder cancer among blacks and whites: The role of cigarette use and occupation. Cancer Causes Control, 2, 371-379. http://dx.doi.org/10.1007/BF00054297

Swanson, G. M. and Burns, P. B. (1995). Cancer incidence among women in the workplace: A study of the association between occupation and industry and 11 cancer sites. J Occup Environ Med, 37, 282-287. http://www.ncbi.nlm.nih.gov/pubmed/7796194

Summary: This population case-control study is part of the Occupational Cancer Incidence Surveillance Study examining occupation and 11 cancer sites. Burns and Swanson (1991) examined cigarette smoking and occupational title and bladder cancer, with Swanson and Burns (1995) focusing on occupation and cancer in women. The Metropolitan Detroit Cancer Surveillance System (MDCSS) was used to identify cancer cases at 11 sites (lung, colon, rectum, bladder, esophagus, liver, salivary gland, stomach, eye, melanoma, and mesothelioma) among males and females aged 40 to 84 years, diagnosed between 1984−1991. In all, 2,160 bladder cancer cases and 3,979 cancer controls were interviewed by telephone for response rates of 94% and 95% for cases and controls, respectively. Colon and rectal cancer cases from the registry were selected as controls and not matched to cases based on demographic variables. Of those interviewed, 25% of case series and 27.6% of the controls series were proxy or next-of-kin respondents. The high percentage of proxy interviews may introduce potential for i recall bias of detailed occupational history. The interview gathered information on complete lifetime occupation history, including occupation and industry titles, lifetime smoking history, medical history, residential history, and demographic information. Occupation and industry data were coded according to the three-digit codes of the 1980 U.S. Census Bureau classification. The paper does not identify if occupational coding was carried out blinded to case or control status. Exposure prevalence was low for holding an occupation as dry-cleaning worker, 0.4% for cases and 0.4% for controls, or for working in the dry-cleaning or laundry industry, 0.6% for cases and 0.6% for controls. Association with bladder cancer and occupation was examined using unconditional logistic regression adjusted for cigarette smoking habits, race, gender, and age at diagnosis and usual industry or occupation, defined as the longest period of employment.

B.2.2.1.2. Colt et al. (2004)

Colt, J.; Baris, D.; Stewart, P.; Schned, A.; Heaney, J.; Mott, L., . . . Karagas, M. (2004). Occupation and bladder cancer risk in a population-based case-control

study in New Hampshire. Cancer Causes Control, 15, 759-769. http://dx.doi.org/10.1023/B:CACO.0000043426.28741.a2

Summary: This population case-control study examined a number of risk factors including occupation exposures for primary bladder cancer among New Hampshire residents, aged 25−74 years. To be eligible for the study, subjects were required to have a listed telephone number and speak English. Six hundred eighteen (n = 618) cases diagnosed over a 4-year period, between July 1, 1994 and June 30, 1998, were identified from the New Hampshire Cancer Registry and histologically confirmed; 459 were subsequently interviewed (74% participation rate). Controls, shared with a study of nonmelanoma skin cancer in the period 1993−1995 and frequency matched based on age and sex, were selected from population lists of the New Hampshire Department of Transportation, if <65 years old, and from New Hampshire Centers for Medicare and Medicaid Services. The study augmented the control group, adding controls for bladder cancer cases diagnosed between July 1, 1995 to June 30, 1997. Interviews were carried out with 665 of the 990 potential controls (67% participation rate). Little age difference existed between cases and controls, although cases were more likely than controls to have a history of cigarette smoking, with current smokers twice as prevalent among the cases as controls.

Subjects who agreed to participate in the study underwent a detailed in-person interview, usually at their home, with questions on sociodemographic information, tobacco use, medical history prior to the diagnosis, and lifetime work history. Each job reported in the occupation history was coded according to the Standard Occupation Classification Manual scheme, with codes of 7658 and 7657 for occupations in dry-cleaning and laundry service. For each occupation, bladder cancer risk was estimated separately for men and women for each job held after age 15 using unconditional logistic regression models adjusted for age and smoking status. Additionally, the authors conducted a separate analysis of *a priori* suspect high-risk occupations, that included dry-cleaner and laundry workers. Only five male case and five male controls reported a job title of dry-cleaner and laundry workers, and the study authors did not report the associated odds ratio because of the small numbers. The low-exposure prevalence for dry-cleaning and laundry work, as is typical of population case-control studies, greatly reduces the statistical power of this study to examine bladder cancer.

B.2.2.1.3. Colt et al. (2011)

Colt, J. S.; Karagas, M. R.; Schwenn, M.; Baris, D.; Johnson, A.; Stewart, P., . . . Silverman, D. T. (2011). Occupation and bladder cancer in a population-based case-control study in Northern New England. Occup Environ Med, 68, 239-249. http://dx.doi.org/10.1136/oem.2009.052571

Summary: This population case-control study examined occupation and industry as risk factors for urothelial bladder cancer, among residents of Maine, New Hampshire, and Vermont, aged 30−79 years. A focus of the study was exposure to metal working fluids. All residents newly diagnosed with a histologically confirmed carcinoma of the urinary bladder (including carcinoma in situ) between September 1, 2001 and October 31, 2004 (Maine and Vermont) or between January 1, 2002 and July 31, 2004 (New Hampshire) were eligible for study. Cases were identified through a rapid patient ascertainment in each state using data from hospital pathology departments, hospital cancer registries, and state cancer registries. A total of 1,878 eligible cases were identified with in-person interviews obtained from 1,213 (65%). Further pathologic review determined 43 subjects did not have bladder cancer or had nonurothelial carcinoma, leaving 1,170 cases. Controls were randomly selected from state motor vehicle records, if aged 30−64 years, or Medicare or Medicaid records, if aged 65+ years, and frequency matched to cases by state, sex, and age at diagnosis or control selection. Interviews were carried out with 1,418 controls, 594 identified from driver records (65% of eligible) and 824 identified through Medicare/Medicaid roles (65% of eligible).

Case and control subjects were first mailed a questionnaire with follow-up by a home visit where a trained interviewer administered a computer-assisted questionnaire that sought information on all jobs held for at least 6 months since age 16 years, demographic information, tobacco use, and other exposures. For certain occupations held by subjects, a job-specific questionnaire was administered, soliciting detailed information about exposures of interest. Each job was coded blinded to case or control status to the 1980 SOC and the 1987 SIC scheme. Of the 1,170 cases and 1,418 controls, 1,158 cases and 1,402 controls completed both questionnaires.

For each occupation and industry, bladder cancer risk was estimated separately for men and women for each job using unconditional logistic regression models adjusted for age, race, Hispanic ethnicity, state, smoking status, and employment in a high-risk occupation. A high-risk occupation was defined for men and women separately if odds ratios in the current study were 1.5 or higher and 10 or more subjects were employed in the category examined in statistical analyses. Additionally, the authors evaluated smoking effects, replacing smoking status with smoking duration and found minimal changes in the estimated odds ratios; final statistical models were thus adjusted for smoking status only. Interactions between smoking and occupation were tested, adding cross-product terms to the logistic model. Additionally, the authors examined employment duration for occupations and industries with a positive association for “ever”/“never” employed. Tests of linear trend were performed by treating the median duration of employment among controls for each duration category as a continuous variable, with a value of zero assigned to subjects never holding a job in the subject category.

For occupations with observed risk estimates that increased with increasing employment duration, an examination of initial year of employment and bladder cancer risk was examined.

Strengths of the study include the population-based design, ascertainment of complete occupational histories from direct interview with study participants, blind assignment of exposure, and ability to adjust for smoking, employment in high-risk occupations, and other risk factors. Limitations include the low prevalence of exposure as laundering and dry-cleaning machine operators (0.5% of all cases) and lower participation rate (65%) for cases and controls. However, the authors concluded that because study participation likely did not differ between cases and controls in an exposure-dependant manner, observations would not be biased. Some exposure misclassification is likely, given limited information for some cases and controls, and the lack of information on specific exposures by using job title. Biases are likely nondifferential and lead to dampened risk estimates.

B.2.2.1.4. Gaertner et al. (2004)

Gaertner, R. R. W.; Trpeski, L.; Johnson, K. C. (1995). A case-control study of occupational risk factors for bladder cancer in Canada. Cancer Causes Control, 15, 1007-1019. http://dx.doi.org/10.1007/s10552-004-1448-7

Summary: This population-based case control study of bladder cancer in seven Canadian provinces (Newfoundland, Prince Edward Island, Nova Scotia, Manitoba, Alberta, Saskatchewan, and British Columbia) made use of data collected in the Canadian National Enhanced Cancer Surveillance System. The project collected data on cases of various cancers and controls, with the intent of improving knowledge of environmental factors in cancer development. Cases were identified through each province's cancer registry and consisted of men and women aged 20 to 74 years who were diagnosed with histologically confirmed bladder cancers between 1994 and 1997. Controls were randomly selected from the general population of the seven provinces using simple random digit dialing (Newfoundland and Alberta) or sampling from the provincial health insurance plan database (the remaining five provinces), and frequency matched to cases based on age and sex. Of the 1,499 eligible cases, 887 (59%) completed the mailed questionnaire and participated in the study. The response rate among controls was 62% (n = 2,847) of 4,604 eligible subjects.

The mailed questionnaire sought information on socio-demographics, lifetime smoking history, dietary habits, and occupational history, including information on specific agents. Up to 12 occupations were categorized into SOC codes, and study investigators identified 9 occupations as suspect and of *a priori* interest, including job title of dry cleaner. A total of 9 subjects, 4 cases, and 5 controls, reported "ever" holding an occupation as dry cleaner. Employment duration was calculated from time period reported for each occupational activity

over a subject's lifetime. Unconditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs, for males and females separately, adjusted for age, province, race, current smoking status, ex-smoking, consumption of fruit, fried food, and coffee, and "ever" employed in suspect occupations. The authors did not present observations on employment duration and "ever" holding a job as dry cleaner, likely due to the few exposed subjects. The authors reported strengths of the methodology of their study as use of histologically confirmed incident bladder cancer cases and the extensive information on nonoccupational factors. Limitations include the study's small sample size, recall bias among cancer cases, low-response rate among both cases and controls, and use of occupational title as surrogate for tetrachloroethylene exposure potential.

B.2.2.1.5. Kogevinas et al. (2003)

Kogevinas, M.; 't Mannetje, A.; Cordier, S.; Ranft, U.; González, C.; Vineis, P., . . . Boffetta, P. (2003). Occupation and bladder cancer among men in Western Europe. Cancer Causes Control, 14, 907-914. http://dx.doi.org/10.1023/B:CACO.0000007962.19066.9c

Summary: This study used pooled data from 11 previously conducted European case-control studies to examine the association between risk of bladder cancer and occupational exposures in men. The case-control studies were Claude et al. (1988), Cordier et al. (1993), Gonzalez et al. (1989), Hours et al. (1994), (Jensen et al., 1987), Pesch et al. (2000a; 2000b), Porru et al. (1996), Rebelakos et al. (1985), Serra et al. (2000), and Vineis and Magnani (1985). These case-control studies were published between 1976 and 1996 and included detailed information on occupation as well as smoking. Cases and controls needed to fall within the 30-to-79-year age range. Cases whose interview occurred more than 2 years after diagnosis were also excluded. Of the 4,101 cases in the pooled dataset, 3,346 (81.6%) met these criteria and were included in the analysis. Of the 7,365 controls in the pooled dataset, 6,840 (92.9%) were included in the analysis. Three of the pooled studies used population controls; one used both hospital and population controls; the remaining seven used hospital controls only. Cases and controls were matched on 5-year age group and geographic area. All occupational and industrial information were coded according to ISCO-68 and International Standard Industrial Classification of All Economic Activities (ISIC) rev2 standards, respectively. Launderers, dry cleaners, and pressers fell within ISCO Code 56. A total of 19 (0.6%) cases and 30 (0.4%) controls were launderers, dry cleaners, or pressers. The researchers did not consider this occupation to be at high risk *a priori*, though it was identified in other studies to be at high risk.

Unconditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs, adjusted for 5-year age group, smoking, and study center. The interaction between age and study center was found to be significant and was also included in all

of the models. Attributable risk for those occupations identified as high risk *a priori* was also calculated, though this did not include launderers, dry cleaners, and pressers. A strength of the study is its pooled nature, which allowed for a high power and the ability to determine whether risks are similar in different populations. A limitation is the low-exposure prevalence among both cases and controls.

B.2.2.1.6. Reulen et al. (2007)

Reulen, R.; Kellen, E.; Buntinx, F.; Zeegers, M. (2007). Bladder cancer and occupation: a report from the Belgian case-control study on bladder cancer risk. Am J Ind Med, 50, 449-454. http://dx.doi.org/10.1002/ajim.20469

Summary: This population-based case control study aimed to add to the data on associations between occupation and bladder cancer, thereby strengthening the case for focused research on specific occupational categories. Cases were identified through the Limburg Cancer Registry and consisted of men and women aged 40 to 96 years who were diagnosed with histologically confirmed transitional cell carcinoma of the bladder between 1996 and 2004. Controls were randomly selected from the general population of Limburg through simple random sampling and consisted of Caucasian men and women over the age of 50 years, with no previous history of bladder cancer. The exclusion of individuals less than 50 years of age was due to the researchers' finding that the majority of controls were over 50 years. Of the 2,230 eligible cases, 202 (9.1%) participated in the study. The response rate among controls was 26% and included 390 participants.

In-person interviews were conducted by three trained interviewers in the participants' homes using a structured questionnaire. Information was obtained on socio-demographics, lifetime smoking history, and lifetime occupational history of all jobs held for at least 6 months. Lifetime occupational history was assessed as a proxy for exposure, and all occupations were blindly coded according to the International Standard Classification of Occupations. Domestic helpers, cleaners, and launderers comprised Code 913 and included a total of 14 (6.9%) cases and 20 (5.1%) controls. Unconditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs, adjusted for age, sex, current smoking status, years of cigarette smoking, number of cigarettes smoked per day, and education. An interaction of sex and occupation was also included in the model. Only those occupations with 15 or more participants were reported. The authors do not report strengths of their study methodology. Limitations include the study's small sample size, recall bias among cancer cases, and the low-response rate among both cases and controls.

B.2.2.1.7. Schoenberg et al. (1984a)

Schoenberg, J. B.; Stemhagen, A.; Mogielnicki, A. P.; Altman, R.; Abe, T.; Mason, T. J. (1984b). Case-control study of bladder cancer in New Jersey: I. Occupational exposures in white males. J Natl Cancer Inst, 72, 973-981. http://www.ncbi.nlm.nih.gov/pubmed/6585596

Summary: This population case-control study of New Jersey male residents, 21−84 years of age, examined bladder cancer, including papilloma not specified as benign, and occupation. Newly diagnosed incident bladder cancer cases were identified between 1978−1979 using a mechanism whereby incident cases were reported within 72 hours of diagnosis or by searching hospital pathology records (hospital number and local hospitals not identified in published paper). No overlap occurs between this study and the large National Bladder Cancer Study, which also included cases diagnosed between 1977 and 1978 (Silverman et al., 1990; Silverman et al., 1989a; Silverman et al., 1989b; Smith et al., 1985). Age-stratified random samples of male population controls were identified using random digit dialing, if 21−64 years old or, records of the Health Care Financing Administration, if 65−84 years. Controls were not frequency matched by county. To allow for potential county-specific comparison, additional controls were identified, employed, and stratified by county so that the case-to-control ratio for each age-county group would be at least 1:1. Of the 787 male cases and 1,608 controls meeting the case or control definition, 706 cases (90%) and 1,392 controls (87%) were interviewed; all cases and controls were alive at the time of the interview. Few subjects were non-Caucasian, and analyses were restricted to Caucasian males, 658 cases, and 1,258 controls. Face-to-face interviews were carried out using a structured questionnaire that sought information on demographic, personal, and occupational risk factors. Information on all jobs held ≥6 months was ascertained, and subjects were shown lists of industries, employers, and materials to elicit information not initially recalled. All industry and job title information was coded to the 1970 Census Index System and based upon these codes; 19 employment categories were identified *a priori* as known or suspected occupations or exposures; employment as dry-cleaning workers was one of the 19 categories. Few cases and controls were identified with employment as a dry-clean worker: 7 cases (1.1%) and 10 controls (0.8%), which limited the statistical power of this study to examine bladder cancer and dry-cleaning employment.

Odds ratios and 95% confidence limited were calculated using logistic regression with a model including either 19 exposure terms or, as in the case of employment as a dry-cleaning worker, a term for the specific exposure category. Statistical analyses were adjusted for age and duration of cigarette smoking, placed into four categories. Other covariates such as previous bladder or kidney infection, family history of urinary tract cancer, coffee consumption,

education, and use of artificial sweeteners did not change the odds ratio estimate by more than 10% and, therefore, were not included in the final logistic regression model.

B.2.2.1.8. Smith et al. (1985), Silverman et al. (1990; 1989a; 1989b)

Smith, E. M.; Miller, E. R.; Woolson, R. F.; Brown, C. K. (1985). Bladder cancer risk among laundry workers, dry cleaners, and others in chemically-related occupations. J Occup Med, 27, 295-297. http://www.ncbi.nlm.nih.gov/pubmed/3998883

Silverman, D. T.; Levin, L. I.; Hoover, R. N.; Hartge, P. (1989b). Occupational risks of bladder cancer in the United States: I. White men. J Natl Cancer Inst, 81, 1472-1480. http://dx.doi.org/10.1093/jnci/81.19.1472

Silverman, D. T.; Levin, L. I.; Hoover, R. N. (1989a). Occupational risks of bladder cancer in the United States: II. Nonwhite men. J Natl Cancer Inst, 81, 1480-1483. http://dx.doi.org/10.1093/jnci/81.19.1480

Silverman, D.; Levin, L.; Hoover, R. (1990). Occupational risks of bladder cancer among white women in the United States. Am J Epidemiol, 132, 453-461. http://www.ncbi.nlm.nih.gov/pubmed/2389750

Summary: These studies used data from the National Bladder Cancer Study (Hartage et al., 1984), which was a large case-control study researching the relationship between occupation and bladder cancer. Cases consisted of men aged 21 to 84 years who were diagnosed with histologically confirmed urinary bladder cancer between 1977 and 1978 in 9 Surveillance, Epidemiology, and End Results (SEER) reporting locations (Connecticut, Iowa, New Mexico, Utah, Atlanta, Detroit, New Orleans, San Francisco, and Seattle) and one rapid reporting system for bladder cancer, which was mandated by state law (New Jersey). Controls were randomly selected from within each of the 10 geographical areas and matched to cases based on 5-year age group and sex. Control selection occurred in two ways: men aged 21 to 64 years were randomly digit dialed, and men aged 65 years and older were obtained from a stratified random sample of Health Care Finance Administration lists. The random digit dialing telephone screening yielded an 88% response rate, and the home interview response rates were 73% for cases and 83% for controls (Hartage et al., 1984). In-person interviews were conducted by a trained interviewer within 3 months of diagnosis, reducing the need for proxy interviews. All interviews used a structured questionnaire that inquired about artificial sweeteners, smoking, coffee consumption, medical history, and occupational history for all jobs that lasted at least 6 months from 12 years of age onwards. Job histories were coded according to the U.S. Bureau of the Census Index of Industries and Occupations.

Smith et al. (1985) examined bladder cancer risk among individuals employed as laundry workers and dry cleaners and in other occupations and industries with similar chemical

exposures and compared it with that of workers in occupations or industries that did not expose them to these chemicals. The authors did not report the final number of cases and controls included in the study. Participants were classified into one of three exposure categories: (1) exposed through employment as laundry/dry-cleaning operatives for at least 6 months (103 participants); (2) exposed through chemicals encountered in other occupations or industries (5,776 participants); and (3) unexposed (1,869 participants). Duration of exposure among those in the laundry/dry cleaning occupation was calculated as the total number of years employed in that profession. Logistic regression was used to separately calculate the relative risks of occupational exposure, adjusted for age and sex, and duration of exposure by age, sex, and smoking status. One strength of this study is its large, population-based design with in-person interviews and matched cases and controls. A limitation is its small exposed population.

Silverman et al. (1989a; 1989b) examined high risk occupations for bladder cancer among and Caucasian and non-Caucasian men. The final sample consisted of 2,100 Caucasian male cases, 126 non-Caucasian male cases, 3,874 male controls, and 383 non-Caucasian male controls. Cases and controls were similar on occupational history variables, with the exception of age at first employment where cases were younger than controls. Occupations were subsequently grouped by their potential to have similar exposures, which aggregated 417 census codes into 163 categories. Workers involved in "processing" within an industry were also grouped together in one category within that industry. Dry cleaners, ironers, and pressers were examined as miscellaneous *a priori* suspect occupations and contained 11 (8.7%) non-Caucasian cases and 12 (3.1%) non-Caucasian controls. Exposure prevalence for occupation as dry cleaners, ironers, and pressers is not presented in the published papers for Caucasian cases and controls. The maximum likelihood method was used to estimate odds ratios for occupations. The estimate for the dry cleaner, ironer, and presser occupation was adjusted for smoking and employment in other high risk occupations. The estimates' corresponding 95% CIs were calculated using Gart's interval estimation procedure. Maximum likelihood was also used to estimate odds ratios for duration of exposure as a dry cleaner, ironer, or presser (<5 years, ≥ 5 years), adjusted for smoking and age, and a Mantel-Haenszel procedure was used to evaluate one-tailed significance tests of trend. Finally, population attributable risks and their corresponding 95% CIs were calculated according to Whittemore (1983) and adjusted for age, geographic area, and smoking. Due to the large number of analyses performed, only those occupations for which there were a minimum of 15 exposed cases or controls and who met one of three additional criteria (statistically significant risk, *a priori* category, or summary category) were presented. The authors did not note any strengths of their methodology. A limitation of the methodology is the potential for misclassification of exposure when grouping occupations for the purposes of analysis.

B.2.2.1.9. Steineck et al. (1990)

Steineck, G.; Plato, N.; Gerhardsson, M.; Norell, S. E.; Hogstedt, C. (1990). Increased risk of urothelial cancer in Stockholm during 1985-87 after exposure to benzene and exhausts. Int J Cancer, 45, 1012-1017. http://dx.doi.org/10.1002/ijc.2910450605

Summary: This population case-controls study of males residing in the county of Stockholm 1985−1987 and born between 1911 and 1945 and population controls examined occupational exposures and urothelial cancer. The source for identifying cases is not identified in the published paper. Population controls were identified using random sampling of population registers at four periods during case ascertainment. A total of 320 cases and 363 controls were identified of which 256 cases and 287 controls were alive and completed the interview; participation rates were 80% for cases and 79% for controls. Of the 256 cases, 243 were of the urinary bladder, 5 of the renal pelvis, 5 of the ureter, and 3 of multiple sites. An additional two cases had heavy exposure to aromatic amines and were excluded from the case series.

Occupational history was sought from case and control using a questionnaire with an industrial hygienist blinded to case and control status classifying potential exposure to 38 agents or groups of substances, including 17 categories of aromatic amines. Two cases and two controls reported employment as a dry cleaner or in the dry-cleaning industry, with an exposure prevalence of <1% for either cases or controls. The published paper does not discuss other information obtained from the questionnaire, except smoking, for which a subject was categorized as either a current smoker, former smoker, or never smoker. Some residual confounding is likely given the use of these broad categories rather than pack years. Logistic regression was used to estimate an odds ratio adjusted for birth year and smoking.

B.2.2.1.10. Zheng et al. (2002)

Zheng, T.; Cantor, K. P.; Zhang, Y.; Lynch, C. F. (2002). Occupation and bladder cancer: A population-based, case-control study in Iowa. J Occup Environ Med, 44, 685-691. http://www.ncbi.nlm.nih.gov/pubmed/12134533

Summary: This population case-control study used data from a larger study of drinking water by-products to examine the relationship between occupation and bladder cancer. Cases and controls were identified in two phases. In Phase 1, cases consisted of male Iowa residents without a previous diagnosis of neoplasm, aged 40 to 85 years, and who were diagnosed with one of six cancer sites (brain, kidney, pancreas, colon, rectum, and urinary bladder) between 1986 and 1987. Controls were randomly selected from the Iowa residents, and frequency was matched to all cases based on 5-year age group and sex. Control selection occurred in two ways:

(1) men aged 64 aged years or younger were randomly digit dialed, and (2) men aged 65 years and older were obtained from a stratified random sample of Health Care Finance Administration lists. The control matching frequency to bladder cancer case series was ~2.3:1. Phase 2 of case and control ascertainment occurred between 1988 and 1989. Cases, aged 40 to 85 years, with in situ and invasive bladder cancer (transitional cell carcinoma and papillary transitional cell carcinoma) were identified among Iowa residents between 1998−1989 with controls frequency matched to cases at a ratio of 1:1. The random digit dialing telephone screening yielded an 85% response rate for cases (1,452): 82% for controls younger than 65 years, and 80% for controls ≥65 years. A total of 1,452 case (1,135 men, 317 women) and 2,434 control (1,601 men, 833 women) participated in the study.

In-person interviews were conducted by a trained interviewer within 3 months of diagnosis, reducing the need for proxy interviews. All interviews used a structured questionnaire that inquired about artificial sweeteners, smoking, coffee consumption, medical history and occupational history for all jobs held for 5 years or longer from 16 years of age onwards. Proxies completed the questionnaires for 156 cases who had died or were not competent to participate. All controls except two completed questionnaires in person. Job titles and industries were reported by Standard Industry Classification and SOC Manual schemes using two-, three-, and four-digit codes. The SOC code for occupation in laundering and dry cleaning was 7,658. Zheng et al. (2002) reported three female cases, and one female control held an occupation in dry cleaning and laundering; however, these authors did not report the number of male cases or controls.

Odds ratios and 95% CIs were calculated using unconditional logistic regression adjusted for age, lifetime pack-years of cigarette smoking, and having a first-degree relative with bladder cancer. Other variables such as education, frequency of strenuous or moderate exercise, duration of living in a residence served by chlorinated surface water, population size of places of residence, and other cancer in a first-degree relative were also examined in the statistical analysis but did not result in material change to the observed association and were, therefore, not included in the final logistic regression model. Duration of exposure was examined using a dichotomous grouping of <10 years and ≥10 years employment duration.

Certain characteristics of this study strengthen the interpretation and included use of histologically confirmed cases, use of lifetime job-exposure history, and relatively high-response rates from both cases and controls. On the other hand, observations for dry cleaning and laundering occupation are based on small numbers, limiting the study's sensitivity. Additionally, exposure misclassification may have been introduced because the study did not specifically identify tetrachloroethylene exposure intensity for individual subjects and is likely of a nondifferential direction, which would be expected to attenuate the strength of estimated risks.

Additionally, use of employment duration is a crude surrogate for cumulative exposure, particularly in light of any temporal changes in intensity.

B.2.2.2. Brain Cancer

B.2.2.2.1. Heineman et al. (1994)

Heineman, E. F.; Cocco, P.; Gomez, M. R.; Dosemeci, M.; Stewart, P. A.; Hayes, R. B., . . . Blair, A. (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. Am J Ind Med, 26, 155-169. http://dx.doi.org/10.1002/ajim.4700260203

Summary: This case-control study explored the potential association of brain cancer with specific solvents, including tetrachloroethylene. Cases consisted of Caucasian men who had died of brain or other central nervous system (CNS) tumors between 1978 and 1980 in Louisiana and between 1979 and 1980 in New Jersey and Pennsylvania. Controls were Caucasian men who had died of other causes, excluding cerebrovascular diseases, epilepsy, suicide, and homicide. Controls were matched to cases based on age, year of death, and study area. Both cases and controls were obtained from death certificates. Of the 741 cases and 741 controls selected, next of kin were found for 654 (88%) cases and 612 (83%) controls. Of these, proxy interviews were performed for 483 cases (74% of those contacted) and 386 (63% of those contacted) controls. After excluding cases for which a hospital diagnosis was not reported and controls whose death may have been associated with their occupation (e.g., lung cancer, liver cancer, leukemia, etc.), the final sample included 300 cases and 320 controls.

Blinded, trained interviewers conducted interviews with next of kin regarding possible risk factors for brain cancer as well as all occupations held by the case or control since the age of 15 years. Information collected included job title, tasks, name and location of the company, type of industry, kinds of products, employment dates, and hours worked. A job exposure matrix (Gomez et al., 1994) was used to estimate exposures based on reported occupations and industries. Occupations and industries were coded according to four digit U.S. SIC and SOC codes, respectively. All of the four digit codes were assigned exposure estimates of probability (i.e., low, medium, high) and intensity (i.e, 1, 2, 3) *a priori*. Intensity was defined as an average of the concentration and frequency of exposure. Occupations were also assigned a category. Jobs that fell within Category A, such as dry cleaner operators, had sufficient information to be assessed for exposure, independent of their industry. For jobs that fell within Category B, the probability of exposure depended entirely on the industry, and the intensity was weighted by both the occupation and the industry. Those in Category C had their probability and intensity of exposure fully determined by the industry within which the job fell. Time of employment was

accounted for in the matrix through a decade indicator. There were 111 (37%) cases and 106 (33.1%) controls "ever" exposed to tetrachloroethylene.

The analysis included maximum likelihood estimates of odds ratios and 95% CIs using Gart (1970), adjusted for age and study area. Linear trends were examined using Mantel (1963), and logistic regression was performed to estimate odds ratios and their corresponding 95% CIs, controlling for age, study area, and employment in electronics-related occupations or industries. A lag time of 10 or 20 years was included. A strength of the study is its blinded exposure classification. Limitations include possible misclassification due to inaccurate reports from proxy respondents, although cases and controls were dead, minimizing potential differential reporting between cases and controls by proxy respondents, misclassification of exposure due to the interchangeability of some solvents, and a high proportion of nonrespondents.

B.2.2.3. Breast Cancer

B.2.2.3.1. Peplonska et al. (2007)

Peplonska, B.; Stewart, P.; Szeszenia-Dabrowska, N.; Rusiecki, J.; Garcia-Closas, M.; Lissowska, J., . . . Blair, A. (2007). Occupation and breast cancer risk in Polish women: a population-based case-control study. Am J Ind Med, 50, 97-111. http://dx.doi.org/10.1002/ajim.20420

Summary: This study used data from a large case-control study in Poland to evaluate the risk of breast cancer by occupation and industry. Cases were identified through a rapid case ascertainment system organized by participating hospitals and were newly diagnosed histologically confirmed in situ or invasive breast cancers in female residents of Warsaw and Lódź, between 20−74 years of age, diagnosed 2000−2003. Population controls were identified from the Polish Electronic System of Population Evidence and matched to cases by city of residence and age within 5-year age groups.

A structured questionnaire administered using in-person interviews collected data on demographic, reproductive, and menstrual history; hormone use history; physical activity; occupation history; smoking and alcohol use; diet; cancer history in female relatives; medical and screening history; prenatal exposures; and history of weight and height development. With respect to occupation history, all jobs held at least 6 months, including job title and possible exposure to a list of chemicals potentially associated with breast cancer, were obtained, and industry and occupation codes were assigned according to the SIC Manual and SOC Manual. Of the 2,275 cases (79% response rate) and 2,424 controls (66% response rate) completing the questionnaire, 28 cases and 32 controls were identified as working in the laundry, cleaning, and

garment services industry; exposure prevalence was 1% for cases and 1% for controls. Peplonska et al. (2007) does not report the percentage of subjects with proxy interviews.

Unconditional logistic regression analyses were used to estimate odds ratio and 95% CIs as the measure of association between occupation or industry and breast cancer risk. Multivariate models included adjustment for age, age at menarche (≤12, 13−14, ≥15, missing), menopausal status (premenopausal; postmenopausal), age at menopause among postmenopausal women (<45, 45−54, ≥55, missing), number of full-term births (≤1, 2, ≥3), body mass index (25, 25−30, >30), breast cancer in first-degree relative (yes, no), education (less than high school, high school, some college, professional training, college degree, missing), and city of residence. The influence of oral contraceptive use, marital status, tobacco and alcohol use, age at first full-term birth and breastfeeding, and recreational and occupational physical activity was also evaluated; but, these factors had little impact on risk estimates and were not included in the final models. Additionally, each specific white-collar job, using all other white-collar jobs as the reference group, was analyzed to control for socioeconomic factors that could not be completely captured by adjustment for education level.

Methodological strength of this study includes the size of the studied population and the scope of information on lifetime occupational history that was collected, together with comprehensive data on potential confounders, and effect modifiers including pre- and postmenopausal status. Potential limitations are the small numbers for many occupational groups, multiple jobs, and multiple comparisons.

B.2.2.4. Colon Cancer

B.2.2.4.1. Fredriksson et al. (1989)

Fredriksson, M.; Bengtsson, N. O.; Hardell, L.; Axelson, O. (1989). Colon cancer, physical activity, and occupational exposures. A case-control study. Cancer, 63, 1838-1842. http://www.ncbi.nlm.nih.gov/pubmed/2702592

Summary: This case-control study examined the relationship between occupational exposures and colon cancer in Sweden. Cases consisted of men and women between 30 and 75 years of age who were diagnosed with large bowel cancer adenocarcinoma between 1980 and 1983. Cases were obtained from the Swedish Cancer Registry and needed to be living at the time of the study (1984 to 1986), located within the admissions region of the Department of Oncology in Umeå, and medically able to complete a mailed questionnaire. Controls were selected from the National Population Register, and two controls were matched to each case based on county of residence, sex, and age. Controls were required to be living at the time of the study and medically able to complete the questionnaire. Of the 402 cases and 717 controls

identified, 329 cases and 658 controls met inclusion criteria and were contacted with a mailed questionnaire inquiring about occupational histories, occupational exposures, food and drinking habits, previous diseases, and drug intake. Overall, 312 (94.8%) cases and 623 (94.6%) controls participated in the study.

Occupations were assessed as a proxy for exposure by two physicians and one hygienist, who independently classified exposure as either high or low grade. There were 5 (1.6%) female cases and 5 (0.8%) female controls who reported employment in dry cleaning. The authors did not report any dry cleaning information for men. Mantel-Haenszel methods were used to calculate odds ratios, and Miettinen (1976) was used in the estimation of corresponding 95% CIs. These analyses were performed for all occupations, including dry cleaning, stratified by age and physical activity. The authors note that an advantage to limiting their study to living patients only was the lack of information bias due to proxy responders. Although this is a methodological strength, there is a potential bias created if occupational exposure is associated with survival.

B.2.2.5. Liver Carcinoma

B.2.2.5.1. Austin et al. (1987)

Austin, H.; Delzell, E.; Grufferman, S.; Levine, R.; Morrison, A. S.; Stolley, P. D.; Cole, P. (1987). Case-control study of hepatocellular carcinoma, occupation, and chemical exposures. J Occup Med, 29, 665-669. http://www.ncbi.nlm.nih.gov/pubmed/2821204

Summary: This case-control study studied the relationship between hepatocellular carcinoma and occupational factors and chemical exposures encountered at work or in leisure activities. Cases consisted of men and women aged 18 to 84 years, diagnosed with hepatocellular carcinoma at 5 study centers, including the University of Alabama, Duke University, University of Miami, University of Pennsylvania, and the Harvard School of Public Health. The majority (93.0%) of cases were histologically confirmed, and the remainder were clinically confirmed. Controls consisted of patients admitted to the same hospitals for other conditions that were diagnosed within 3 years of the interview, excluding bronchitis, emphysema, primary liver disease, and the following cancers: lung, oral cavity, esophagus, larynx, bladder, and pancreas. Controls were matched to cases based on gender, age, race, and study center. The final sample consisted of 86 cases and 161 controls. Authors do not report response rates.

Each participant's occupational history related to all jobs held 6 months or longer was ascertained during the interview, and jobs were coded according to SIC and SOC manuals.

There were 0 cases and 4 (2.5%) controls who reported employment in the laundering and cleaning industry. The authors did not report this industry's corresponding code. Conditional likelihood methods were used in logistic regression models to estimate odds ratios and their corresponding 95% CIs. Due to the small numbers of "exposed," the authors did not present the results for the laundry and cleaning industry. The authors do not report strengths of their study. A limitation is the small number of exposed, which precluded the analysis of participants employed in the laundry and dry-cleaning industry.

B.2.2.5.2. Hernberg et al. (1988)

Hernberg, S.; Kauppinen, T.; Riala, R.; Korkala, M. L.; Asikainen, U. (1988). Increased risk for primary liver cancer among women exposed to solvents. Scand J Work Environ Health, 14, 356-365. http://www.ncbi.nlm.nih.gov/pubmed/3212412

Summary: This case-control study examined if previously reported findings of an increased risk of primary liver cancer among women exposed to organic solvents (Hernberg et al., 1984) were a true effect, due to chance, or reflective of an undetected systematic error. Cases consisted of men and women diagnosed with primary liver cancer and reported to the Finnish Cancer Register from 1976 to 1978, and also in 1981. The years 1979 and 1980 were excluded from this study because they were previously examined (Hernberg et al., 1984). Two control groups were used in this study: a control series of randomly selected stomach cancer patients identified from the Finnish Cancer Register in 1977; the other included patients whose hospital autopsy records noted that they had died of a coronary infarction in 1977. Coronary infarction controls were matched to cases on sex, age, and hospital of diagnosis. The authors make no mention of matching between cases and stomach cancer controls. All living patients were excluded from the analyses, as were those with untraceable relatives. Of the 526 cases by proxy who met inclusion criteria, 377 (71.7%) returned the questionnaire. After excluding those for whom a diagnosis could not be confirmed, a total of 344 (65.4%) were included in the analysis. Of the 654 stomach cancer controls and 558 coronary infarction controls who met the inclusion criteria, 476 (72.8%) stomach cancer controls and 385 (69.0%) coronary infarction controls returned the questionnaire. The final sample consisted of 344 cases and 861 controls (476 stomach cancer and 385 coronary infarction).

A questionnaire mailed to proxy-respondents focused on obtaining information on work history, including employers, work sites, jobs held, and calendar years of work. Information on alcohol, tobacco, coffee, tea, medicines, leisure activities, and for women, history of oral contraceptive use, was also obtained. Two occupational hygienists blindly assessed exposure, based on the likelihood of the participants' industries, workplaces, and job titles, including solvents or other agents. Exposures were classified as heavy, moderate, or light; dry-cleaning

exposures were based on 1950 records by the Finnish Institute of Occupational Health that noted tetrachloroethylene exposure ranged from 34−600 ppm during that time. Any exposures that could not be determined by the occupational hygienists were followed up with phone calls to the workplace or the proxy respondent. Two cases (0.6%) were identified with possible chlorinated hydrocarbon exposures: (1) a case assessed as having light, possible exposure to chlorinated hydrocarbons in a laundry facility, and (2) another case estimated to have heavy exposure to chlorinated hydrocarbons during 6 years employed as a dry cleaner. Two coronary infarction controls (0.5%) were determined to have light exposure to tetrachloroethylene as a result of employment in the dry-cleaning industry.

Likelihood-based odds ratios and 90% CIs were calculated according to Cornfield (1956) for the association between primary liver cancer and solvent exposure and for the association between primary liver cancer and heavy/moderate alcohol use. Both were stratified by sex using methods by Gart (1970). A latency period of 10 years was included, and, thus, any exposures that occurred before this time were excluded from the analysis. A strength of the study is its use of a blinded exposure assessment. Limitations to the study include the potential for selection bias due to the number of eligible cases and controls whose proxy respondents could not be found or whose proxy respondents did not return the questionnaire. Moreover, misclassification bias is likely, given the high percentage of proxy respondents. The authors also noted the need for information on previous hepatitis B infection in order to control for it as a potential confounder.

B.2.2.5.3. Houten and Sonnesso (1980)

Houten, L. and Sonnesso, G. (1980). Occupational exposure and cancer of the liver. Arch Environ Health, 35, 51-53. http://www.ncbi.nlm.nih.gov/pubmed/7362270

Summary: This study used a hospital-based case-control design to study the occupational associations of patients admitted to Roswell Park Memorial Institute. The 102 cases were men and women with primary liver cancer between 1956 and 1965. Controls consisted of all other cancer patients admitted to the Roswell Park Memorial Institute during the same time frame. The authors failed to mention how many controls were included in the study. Occupation was assessed as a proxy for exposure, with a total of two cases (2%) employed in the laundry and dry-cleaning industry. The analysis consisted of a chi-square goodness-of-fit test, where the distribution of the cases was compared to controls by each industry. Limitations to the study include the size of the sample; few exposed cases, which decreased the study's detection sensitivity; the use of other cancer patients as controls; self-reported occupational information; and inadequate reporting of study design and results.

B.2.2.5.4. Stemhagen et al. (1983)

Stemhagen, A.; Slade, J.; Altman, R.; Bill, J. (1983). Occupational risk factors and liver cancer: A retrospective case-control study of primary liver cancer in New Jersey. Am J Epidemiol, 117, 443-454.
http://www.ncbi.nlm.nih.gov/pubmed/6837558

Summary: This study used a case-control design to examine occupational associations with liver cancer. Cases were identified through New Jersey hospital records, the New Jersey State Cancer Registry, and death certificates and consisted of men and women living in New Jersey who were diagnosed with histologically confirmed primary liver cancer between 1975 and 1980. The authors do not note any age restrictions in their methodology, though cases were aged 20 years and older. Controls were chosen from among men and women admitted to the same hospitals as the cases, as well as from death certificates, and matched to cases on age, race, sex, county of residence, and vital status. Potential controls were excluded from the study if they had a history of liver cancer, hepatitis, cirrhosis, or other liver disease. Deceased controls whose cause of death was homicide or suicide were also excluded from the study because of the sensitivity of approaching next of kin. Of the 335 eligible cases, 296 were able to be contacted, and of these, 265 (79.1%) were interviewed. Of the 825 eligible controls, 687 were able to be contacted, and of these, 530 (64.2%) were interviewed. Demographics between cases and controls were similar.

In-person interviews were conducted with all participants or their next of kin to obtain information on lifetime residence, smoking habits, alcohol, medical history, and employment since the age of 12 years. There were 254 (95.8%) proxy case interviews and 508 (95.8%) proxy control interviews. Occupations held for at least 6 months were assessed as a proxy for exposure. All industries and occupations were coded according to the Index of Industries and Occupations standards developed by the Bureau of Census. The laundering, cleaning, and other garment services industry included 10 male cases (3.8%) and 8 male controls (1.5%). The authors further examined the laundry/dry-cleaning industry by occupations, though the results are not presented. No information was reported on female employment in the laundry, dry cleaning, or garment service industry.

Mantel-Haenszel methods were used to estimate odds ratios and 95% CIs for males employed at least 6 months in selected industries and occupations. The distribution of subjects by calculated level of alcohol consumption were adjusted for age (women) and age and smoking (men), but risk estimates for occupations and industries were not adjusted for potential confounders. There were no differences in alcohol consumption between cases and controls. The authors did not report any strengths in their study. Limitations include possible misclassification of exposure due to proxy respondents, lack of adjustment for confounders such

as smoking and alcohol consumption, possible misclassification due to inaccurate information on death certificates, and lack of assessment of intensity or duration of exposure.

B.2.2.5.5. Suarez et al. (1989)

Suarez, L.; Weiss, N. S.; Martin, J. (1989). Primary liver cancer death and occupation in Texas. Am J Ind Med, 15, 167-175. http://www.ncbi.nlm.nih.gov/pubmed/2729281

Summary: This case-control study examined the risk of liver cancer among occupations in the petroleum and chemical industry and other potentially high-risk occupations. Death certificates, which listed usual occupation and business or industry, were obtained from the Texas Bureau of Vital Statistics and used to identify cases and controls for the time period from 1969 to 1980. Cases consisted of men aged 20 years or older who were living in Texas and whose underlying cause of death was liver cancer. Of the 1,771 potential cases, 1,742 were eligible and included in the study. The same number of controls were randomly selected from among the 537,000 death certificates, which represented all other causes of death, excluding neoplasms, liver and gallbladder diseases, infectious hepatitis, and alcoholism. Controls were matched to cases based on 5-year age group, race, ethnicity, and year of death.

Occupation was assessed as a proxy for exposure grouped according to the U.S. Census Classified Index on industrial categories. Groupings were partially based on Hoar et al. (1980), who categorized industries by product or exposure. In addition to the petrochemical industry, 22 other industries or product categories with at least 10 individuals were examined, including dry-cleaning services. Occupations within these categories that had at least 10 individuals were also analyzed and included dry-cleaning operators. There were a total of 11 cases and 12 controls employed in the dry-cleaning industry and 4 cases and 8 controls employed as dry-cleaning operators. The published paper does not provide information regarding the total number of controls included in the final sample (although they state that the number of controls and cases are the same), precluding a calculation of exposure prevalence for this study.

The Mantel-Haenszel method was used to calculate odds ratios, adjusted for race and ethnicity. Corresponding 95% CIs were estimated using Miettinen's method. Limitations to the study include the lack of control for potential confounders that were not included in the death certificate information, such as alcohol consumption or hepatitis B infection, as well as the lack of information on exposure and the possible misclassification of exposure based on occupation and industry information provided on the death certificates. The authors do not report any strengths of their study's methodology.

B.2.2.6. Lung and Upper Respiratory Tract Cancers

B.2.2.6.1. Brownson et al. (1993)

Brownson, R. C.; Alavanja, M. C.; Chang, J. C. (1993). Occupational risk factors for lung cancer among nonsmoking women: a case-control study in Missouri (United States). Cancer Causes Control, 4, 449-454. http://www.ncbi.nlm.nih.gov/pubmed/8218877

Summary: This study used a population-based case-control design to evaluate the risk of lung cancer in nonsmokers in relation to their specific occupations. Cases were Caucasian females living in Missouri between 30 and 84 years and diagnosed with primary lung cancer between 1986 and 1991. Cases needed to be either lifetime nonsmokers, ex-smokers who had quit for at least 15 years prior to diagnosis, or ex-smokers that had smoked less than one pack per year. The cases were selected from the Missouri Cancer Registry; hospitals participating in the study were also visited to ensure all cases were documented. Of the 429 cases included in the study, 333 (77%) were histologically confirmed. The 1,021 controls were chosen in two ways: (1) through a sample of state driver's licenses of women under the age of 65 years, provided by the Missouri Department of Revenue; and (2) through a roster of Medicare beneficiaries of women aged 65 to 84 years, provided by the Health Care Finance Administration. Controls were matched to the cases by age group at a 2.2:1 ratio. Of the 650 eligible cases, 618 (95%) participated in the telephone interview, and 429 (69%) of these 618 also participated in the second, in-person interview. Of the 429 cases included in the final analysis, 179 (42%) consisted of interviews with the cases, and 250 (58%) involved interviews with the spouse or another relative. Of the 1,527 eligible controls, 1,402 (92%) participated in the telephone interview, and 1,021 (73%) of these 1,402 also participated in the second, in-person interview. Overall, 30 of the cases and 39 of the controls were employed in the dry-cleaning industry.

Both the telephone and in-person interviews were performed by trained interviewers. The telephone interview inquired about residential history, passive smoke exposure, personal and family health histories, and reproductive health history. The in-person interview consisted of questions related to diet and occupation. Occupational risk factors were determined by 28 questions, which were based on a review of the literature and focused on job title as well as exposure. Subjects reported the years in which they worked at each job or with each exposure. Analysis consisted of the calculation of odds ratios and 95% CIs with multiple logistic regression, adjusted for age, active smoking (for ex-smokers), and history of previous lung disease. In their examination of risk based on duration of employment, the researchers ascertained their cutoff points by achieving an approximate equal distribution of controls in "low" and "high" exposure categories.

Strengths of the study include its large sample size and the fact that it pathologically reviewed all cases. On the other hand, the study's retrospective nature has limitations. For example, there was a substantial difference in the proportion of proxy respondents between the cases and controls. Here, 58% of the case interviews were conducted with surrogates, compared with none of the controls. The authors noted the inclusion of proxy respondents would introduce recall bias that would likely bias risk estimates towards the null. Additionally, the researchers lacked information on the intensity and specific types of occupational exposures these women experienced. Limitations include the study's low statistical power, small sample of histologically confirmed cases, difficulty in assessing passive smoking retrospectively, and that not all cases were eligible to be controls. In this study, 91% of cases under the age of 65 years and 100% of controls had a current driver's license, suggesting that the case population may have differed in some characteristics from the control population.

B.2.2.6.2. Consonni et al. (2010)

Consonni, D.; De Matteis, S.; Lubin, J. H.; Wacholder, S.; Tucker, M.; Pesatori, A. C., . . . Landi, M. T. (2010). Lung cancer and occupation in a population-based case-control study. Am J Epidemiol, 171, 323-333. http://dx.doi.org/10.1093/aje/kwp391

Summary: This large population case-control study, part of the Environment And Genetics in Lung cancer Etiology (EAGLE), was designed to explore various etiologic factors for lung cancer risk factors using an integrative approach that combined epidemiologic, clinical, and molecular data in a clearly defined population setting. Cases and controls were identified from the Lombardy area in Italy and were from 5 cities and 216 municipalities. The study included 1,943 incident lung cancer cases, 35−79 years of age, from 2002−2005, identified from 13 hospitals and 2,116 population controls through population databases (not identified in paper) and frequency matched to case by residence, sex, and age. Cases could have any stage of primary cancer of the trachea, bronchus, and lung as well as morphology that was verified with tissue pathology (67%), cytology (28%), or review of clinical records (5%). Response rates were 92.5% for cases and 99.8% for controls. Controls had higher education and held more jobs compared to cases. All subjects underwent a computer-assisted personal interview and blood sampling (or buccal rinse collection for a small percentage of study subjects), and they completed self-administered questions available on the EAGLE Web site. Lung tissue sample from cases were collected when available. The interview included lifetime history of jobs held for ≥6 months. Industries and job titles were coded blindly by two of the study investigators, following the International Standard Industrial Classification of All Economic Activities and the ISCO. Codes were then translated into occupations as known (List A) or suspected (List B) lung carcinogens. Two (0.2% exposure prevalence) male cases and 3 male controls and 12 (3%

exposure prevalence) female cases and 11 controls were identified as launderers, dry cleaners, or pressers (ISCO Code 560). Odds ratios and 95% CIs were calculated using unconditional logistic regression, separately by gender, with covariates for area, age, smoking pack-years, and number of jobs held. Selected analyses were repeated, adding educational level as a surrogate of socioeconomic status.

Major strengths of the study are the enrollment of incident cases, the large sample size, high participation rates, and face-to-face interviews using a structured questionnaire. Jobs are self-reported, potentially introducing bias; however, the authors noted reliability of self-reported job history is usually considered good. The blind coding of job title could introduce misclassification, a source of nondifferential bias. The low exposure prevalence of dry cleaner, laundry worker, or presser, job titles, particularly among males, in this study reduces its sensitivity.

B.2.2.6.3. Pohlabeln et al. (2000)

Pohlabeln, H.; Boffetta, P.; Ahrens, W.; Merletti, F.; Agudo, A.; Benhamou, E., . . . Jockel, K. H. (2000). Occupational risks for lung cancer among nonsmokers. Epidemiology, 11, 532-538. http://www.ncbi.nlm.nih.gov/pubmed/10955405

Summary: This study used a case-control design to investigate the relationship between occupational exposures and lung cancer in nonsmokers in Europe. A total of 12 study centers in 7 countries (France, Germany, Italy, Portugal, Spain, Sweden, UK) participated. Cases and controls up to the age of 75 years were enrolled in the study between 1988 and 1994. Controls were chosen from the community in six centers, from hospitals in five centers, and from both the community and a hospital in one center. All hospital-based controls had diseases not related to smoking. A nonsmoker was defined as an individual who has smoked less than 400 cigarettes during his/her lifetime. The final sample consisted of 650 nonsmoking cases and 1,542 nonsmoking controls. Cases and controls were similar based on sex, age, and most common histological subtype. With the exception of two centers in Germany and one center in Portugal, whose response rates were below 50%, the response rates ranged between 55% and 95%.

Demographics, diet, smoking exposure, smoking history, and occupational history were collected for each participant through an in-person interview. Industry and occupation were blindly assessed as a proxy for exposure and coded according to ISCO and ISIC standards. All jobs that lasted at least 6 months were assessed according to Ahrens and Merletti (1998), who categorized occupations based on either known (List A) or suspected (List B) associations with lung cancer. Launderers and dry cleaners were classified into List B and included 20 (3.1%) cases and 29 (1.9%) controls. Participants were then divided into one of three exposures: "ever"

List A, "ever" List B/"never" List A, and "never" List A or B (unexposed). Unconditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs of "ever" working in a List A or List B occupation, adjusted for age and center and stratified by gender. The inclusion of occasional smoking, residence, diet, and exposure to tobacco smoking as confounders did not significantly affect the estimates and was not included in the final model. No differences were found when considering the control groups separately, and the pooled results were provided. A strength of this study is its size, and limitations include possible misclassification of smoking status among very light smokers, different response rates among the centers in Europe, and lack of assessment of duration or intensity of exposure.

B.2.2.6.4. Richiardi et al. (2004)

Richiardi, L.; Boffetta, P.; Simonato, L.; Forastiere, F.; Zambon, P.; Fortes, C., . . . Merletti, F. (2004). Occupational risk factors for lung cancer in men and women: a population-based case-control study in Italy. Cancer Causes Control, 15, 285-294. http://dx.doi.org/10.1023/B:CACO.0000024223.91059.ed

Summary: This population case-control study was conducted in two regions in North Italy, included subjects in a large international case-control study of nonsmoker lung cancer, and was coordinated under the International Agency for Research on Cancer (Pohlabeln et al., 2000). Richiardi et al. (2004) reported observations from the two Italian centers on lung cancers, adding the smoking cases and occupational factors. Cases (n = 1,171) were incident primary histologically or cytologically confirmed lung cancers among residents 75 years of age or younger and identified from all hospitals in the study area. Controls (n = 1,569) were randomly selected from the local population registries and were frequency matched ($\geq$1:1 ratio) with cases by 5-year age groups and sex. The case series included a higher proportion of ever smokers, heavy smokers, and lower education compared to the control series. The enrollment period was 1990−1991 (Eastern Venice) and 1991−1992 (Turin). Response rates for Turin and Venice regions, respectively, were 86, 72, 85, and 74% among cases and controls, respectively.

In-person interviews with a standardized questionnaire gathered information on demographic details, active and passive smoking, and lifetime occupational history for all jobs lasting at least 6 months. No information is presented by the authors regarding the number of proxy interviews; however, the paper appears to suggest interviews were carried out directly with subjects. Job title and industry were coded blindly to case-control status using the International Standard Classification of Occupations and the International Standard Industrial Classification. The occupational history of each subject was evaluated for employment in occupations and industries *a priori* known (List A) or suspected (List B) to entail exposure to lung carcinogens; List B included dry cleaner and laundry occupations. Three male cases (0.3% exposure

prevalence) and 9 female cases (5% exposure prevalence) were identified as holding dry cleaner or laundry occupation.

Odds ratios (ORs) and 95% CIs were estimated using unconditional logistic regression with analyses conducted separately for males and females for lung cancer histological types. Covariates included in the models were age, study area, education, cigarette smoking, consumption of other tobacco products, and total number of jobs.

Strengths of this study include the high-response rate and statistical control in analyses examining occupational title for smoking with any residual confounding related to smoking likely of a small magnitude. There was evidence of selection bias related to a higher socioeconomic status among nonparticipant cases and lower among nonparticipant controls compared to participant cases and controls, although the potential bias may be minimal, because education was a covariate in statistical analyses and did not substantially change risk estimates. The exposure-assessment approach based on job and industry titles is limited as a proxy for cumulative exposure with potential for misclassification bias, usually, nondifferential and of a downward direction.

B.2.2.6.5. Vaughan et al. (1997)

Vaughan, T. L.; Stewart, P. A.; Davis, S.; Thomas, D. B. (1997). Work in dry cleaning and the incidence of cancer of the oral cavity, larynx, and oesophagus. Occup Environ Med, 54, 692-695. http://www.ncbi.nlm.nih.gov/pubmed/9423585

Summary: This study used data collected from two population-based case-control studies to examine whether employment in the dry-cleaning industry and its associated exposure to tetrachloroethylene increased the risk of upper aerodigestive tract cancers. The authors do not provide any references for the studies. Cases were identified through the Fred Hutchinson Cancer Research Center, a population-based cancer registry encompassing 13 counties in Washington state, and consisted of male and female residents within the three largest counties. Cases were between 20 and 74 years of age and diagnosed with cancer of the oral cavity or pharynx, larynx, esophagus, or gastric cardia between 1983 and 1987 or with adenocarcinoma of the esophagus or gastric cardia between 1987 and 1990. The authors do not state if the cancer cases were histologically confirmed. Response rates were 85.2% for the oral cavity, 80.8% for the larynx, and 82.9% for the esophagus and gastric cardia. Cases of nonepithelial and nonspecified cancers were excluded, as were cases without telephones on the date of their diagnosis. Controls were selected through random digit dialing and matched to cases based on 5-year age group and sex. Of those contacted, 95.4% were screened, and 80.3% of those eligible were interviewed. The final sample included 1,130 cases (491 oral cavity, 235 larynx,

109 esophagus squamous cell, and 295 esophagus adenocarcinoma), of which, 10 had two cancers, and 724 controls.

In-person interviews were conducted to gather detailed information on all occupations that lasted at least 6 months, including employer, type of business, job title, typical activities performed, and dates of employment. History of occupational exposure to solvents was also obtained. Information on demographics, and tobacco and alcohol consumption was also obtained. Proxy interviews with next of kin were conducted in 7.2% of the laryngeal cases, 18.7% of the oral and pharyngeal cases, and 33.2% of the esophageal and gastric cardia cases. Exposure to tetrachloroethylene was assessed blindly by estimating the probability that the solvent was used on the job and the 8-hour time weighted average exposure to tetrachloroethylene on the job. The latter was based on findings in the literature but was not validated within this population. Overall, 16 (1.4%) cases (7 oral cavity, 5 larynx, 2 esophagus squamous cell, and 2 esophagus adenocarcinoma) and 8 (1.1%) controls reported "ever" employment in the dry-cleaning industry. Exposure to tetrachloroethylene was determined to be possible among 15 (1.3%) cases (7 oral cavity, 4 larynx, 2 esophagus squamous cell, and 2 esophagus adenocarcinoma) and 8 (1.1%) controls. Probable exposure to tetrachloroethylene was determined for 8 cases (0.7%) and 3 controls (0.4%). Finally, duration of employment (1−9 years and ≥10 years) in the dry-cleaning industry and cumulative exposure to tetrachloroethylene (1−29 ppm/year and ≥30 ppm/year) were assessed, with the latter being the product of the duration and the 8-hour time weighted average.

Conditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs for those employed in the dry-cleaning industry and those exposed to tetrachloroethylene. All estimates were adjusted for age, sex, education, study period, alcohol consumption, and cigarette smoking. Including race among the potential confounders in the analysis did not change the estimates and was not included in the final model. A strength of the study is its detailed occupational history. Limitations included the low prevalence of exposed cases and controls, the high proportion of proxy respondents, and the lack of information on solvents used.

B.2.2.7. Lymphopoietic cancers

B.2.2.7.1. Blair et al. (1993)

Blair, A.; Linos, A.; Stewart, P. A.; Burmeister, L. F.; Gibson, R.; Everett, G., . . . Cantor, K. P. (1993). Evaluation of risks for non-Hodgkin's lymphoma by occupation and industry exposures from a case-control study. Am J Ind Med, 23, 301-312. http://dx.doi.org/10.1002/ajim.4700230207

Summary: This population-based case-control study examines occupational exposures—particularly agricultural exposure—as risk risk factors for non-Hodgkin lymphoma. In Iowa, cases were identified through the Iowa State Health Registry and consisted of Caucasian men who were diagnosed with non-Hodgkin lymphoma between 1981 and 1983. In Minnesota, cases consisted of Caucasian men diagnosed between 1980 and 1982 who were identified from a surveillance of participating network hospitals that covered approximately 97% of the state. The cities of St. Paul, Duluth, Minneapolis, and Rochester were excluded from the study. All identified cases underwent pathology review. Controls included Caucasian men without hematopoietic or lymphatic malignancies who were frequency matched by state, age, and year of death for deceased cases. Controls for living cases who were under the age of 65 years at diagnosis were obtained through random-digit dialing, and those for living cases who were 65 years or older at diagnosis were selected from computerized Medicare files from the Health Care Finance Administration. Controls for deceased cases were chosen from state vital records (death certificates). Of the 715 eligible cases, 622 (87.0%) participated in the interview. A total of 1,245 controls (77% of random digit dialing, 79% of Medicare, and 77% of death certificate) participated in the interview, though the authors do not provide the eligible population. Farmers were excluded from the analysis, leaving a total of 546 cases and 1,087 controls.

In-person interviews were conducted by trained interviewers with a structured questionnaire that inquired about sociodemographic characteristics; agricultural exposures; exposures to chemicals through hobbies; residential, medical, and occupational histories; as well as family history of cancer. Occupational histories were ascertained for all jobs held at least 1 year since the age of 18 years, as well as industry, name of employer, products produced, job title, and duties. There were 184 (29.6%) proxy case interviews and 425 (34.1%) proxy control interviews. Industries and occupations were coded according to SIC and the Dictionary of Occupational Titles (DOT), respectively. Exposure was assessed blindly by an industrial hygienist who used a job-exposure matrix to evaluate probability (4-point scale) and intensity (3-point scale) of exposure. Laundry and garment workers comprised Code 721 and included 16 (2.9%) cases and 14 (1.3%) controls.

Polychomotous unconditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs, adjusted for age, state, direct or surrogate respondent, agricultural use of pesticides, postsecondary education, use of hair dyes, first-degree family member with malignant lymphoproliferative diseases, and tobacco. Analyses were also conducted for the three main types of non-Hodgkin lymphoma (follicular, diffuse, and other) for selected exposures, occupations, and industries. Exposure-response relationships examined the risk of non-Hodgkin lymphoma, or of the subtypes of non-Hodgkin lymphoma, by duration of employment, intensity of employment, and by the probability of exposure. In this instance,

unexposed cases and controls consisted of those not employed in that particular occupation or industry, or those who lacked the exposure of interest. A strength of the study is its use of a job-exposure matrix. Limitations include its low-exposure prevalence, possible misclassification due to limited exposure information, and high percentage of proxy respondents.

B.2.2.7.2. Clavel et al. (1998)

Clavel, J.; Mandereau, L.; Conso, F.; Limasset, J. C.; Pourmir, I.; Flandrin, G.; Hémon, D. (1998). Occupational exposure to solvents and hairy cell leukaemia. Occup Environ Med, 55, 59-64. http://dx.doi.org/10.1136/oem.55.1.59

Summary: This study used a retrospective, hospital-based case-control design to examine the relationship between occupational exposures and hairy cell leukemia in men in France. Cases and controls were obtained from 18 hospitals throughout the country; cases included all patients diagnosed between 1980 and 1990 who were still alive at the time of the study. Controls consisted of patients admitted to the hospitals during this same time frame for other reasons. Due to the researchers' need to find a restricted number of cases in the same age range in each city, controls were predominantly chosen from the orthopedic and rheumatological departments. Control exclusion criteria included patients admitted for malignant disease, diseases related to occupations, and work-related accidents. Cases and controls were matched on birth date, sex, admission date, and residence. Of the 378 cases identified, 278 were considered eligible (i.e., still alive at the time of the study). Of these, 226 (81.3%) participated by returning the questionnaire. Of the 809 eligible controls, 465 (57.5%) participated by returning the questionnaire. Of these, 40 were excluded because the case they were initially matched with either died or did not respond, and they could not be matched to other cases. As a result, 425 (52.5%) of the eligible controls were included in the analysis. Efforts were made to match 2 controls with each case; 30% of cases were matched with 1 control, 56% were matched with 2 controls, and 14% were matched with 3 to 5 controls. The final sample consisted of 226 cases and 425 controls.

Self-administered questionnaires were sent to all participants, inquiring about sociodemographic characteristics, tobacco smoking, lifelong occupations, and leisure activities. Additional questionnaires were sent to participants with suspected occupational exposures. Semi-structured interviews were also conducted to help experts assess exposures for those involved in textile degreasing, among others.

Jobs were coded according to International Labor Organization (ILO) and ISIC standards. Launderers and dry cleaners comprised ILO Code 5.6. There were 1 (0.4%) case and 2 (0.5%) controls who reported employment as launderers or dry cleaners. Exposure was evaluated in two ways. The first consisted of a blinded assessment by two of the study's researchers, which

was based on the consistency of the participant's statements, the type of industry in which they worked, their job title, and the type of exposure. From this information, the researchers were able to classify the type of solvent used as well as the intensity of exposure associated with each job. The second method used a job-exposure matrix that was initially developed for a study by the International Agency for Research on Cancer (Ferrario et al., 1988) to assess exposure to solvents. The matrix used ILO and ISIC codes to classify each job into one of seven categories based on the probability, intensity, and frequency of exposure. These categories included unexposed, possibly exposed/unevaluable, probably exposed (<1/3 of exposed subjects, 1/3−2/3 of exposed subjects, or >2/3 exposed subjects), certainly exposed, and certainly highly exposed.

Conditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs, adjusted for smoking and farming. These estimates were ascertained for job titles, including launderers and dry cleaners, occupational tasks, including degreasing, and the main chemical families of organic solvents. A strength of this study is its use of a job-exposure matrix. Limitations include the study's retrospective recruitment, low response rate, lack of verification of self-reported information, and lack of individual solvent assessment. Also, while the study's inclusion of only living cases may have caused confounding by duration of survival, exposure information was obtained directly by the case, precluding the use of proxy respondents, who often do not provide as accurate information as that obtained directly from subjects. This study was inadequately powered to evaluate dry-cleaning exposures, resulting from the low-exposure prevalence among cases and one reported case as a launderer or dry cleaner.

Interviews were conducted by trained interviewers either in-person or by telephone. Of the 430 cases interviewed, 76% were in-person with the cases themselves, 9% over the telephone with the cases themselves, and 16% were proxy-interviews with next of kin when the case was deceased or too ill to participate. Of the 1,683 controls interviewed, 81% were in-person with the cases themselves, 18% were over the telephone with the cases themselves, and less than 1% were proxy interviews with next of kin. The questionnaire inquired about multiple risk factors, including chemical exposures, which were assessed blindly by the researchers and a toxicologist into 20 categories. For statistical reasons, only those exposures with a minimum of 10 exposed cases were analyzed, and this consisted of aliphatic hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, and pesticides. Chlorinated hydrocarbons included dry-cleaning solvents, though only one case reported exposure to these particular solvents. The questionnaire also inquired about employment in four industries: petroleum, rubber, dry cleaning, and meat processing. Overall, 14 (3.3%) cases and 59 (3.5%) controls reported working for at least 6 months in the dry-cleaning industry.

Unconditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs. Both unadjusted and adjusted odds ratios were calculated for

all-respondents and self-respondents only (excluding proxy-respondents); adjusted odds ratios controlled for race, 10-year age group, education, sex, and study site. The authors do not report strengths of their methodology. Limitations include the study's lack of adjustment for smoking and reliance on self-reported or proxy-reported occupational, which may have introduced recall bias. Misclassification of exposure towards the null was possible, given the discrepancy between those who reported working in the dry-cleaning industry and those who reported exposure to dry-cleaning solvents. Misclassification may have also occurred when participants were required to judge what, if anything, needed to be noted in the "other chemicals" portion of the chemical exposures question. Additionally, frequency, intensity, and duration of exposure were missing, which is mostly due to the fact that the questionnaire was developed to assess different risk factors. The study group was enrolled for the purposes of measuring the effect of gene influences on the immune system, rather than exposure to common chemicals. The study also suffered from a small sample size, impacting the statistical power to examine dry-cleaning exposures.

B.2.2.7.3. Fabbro-Peray et al. (2001)

Fabbro-Peray, P.; Daures, J. P.; Rossi, J. F. (2001). Environmental risk factors for non-Hodgkin's lymphoma: A population-based case-control study in Languedoc-Roussillon, France. Cancer Causes Control, 12, 201-212. http://dx.doi.org/10.1023/A:1011274922701

Summary: This population-based case-control study of NHL evaluated medical, occupational, and environmental risk factors and the occurrence of malignant lymphomas. This study was limited to French men and women aged 18 years or older who were living in Languedoc-Roussillon, which is the French county with the highest incidence of non-Hodgkin lymphoma. Cases were diagnosed with malignant lymphomas between 1992 and 1995 from 19 hospitals and a cancer research center. Controls were randomly chosen from electoral lists in a two-phase approach. First, the municipalities were randomly selected based on their size and the distribution of the population in the county. Second, individuals within each of the chosen municipalities were randomly selected. There were two controls assigned to each case, though the nonelectronic nature of the data prevented matching of cases and controls. Of the 627 eligible cases and 1,962 eligible controls, a total of 517 (82.5%) cases and 1,025 (52.2%) controls participated in an interview between 1992 and 1996. Of the 517 cases, 445 cases (86.0%) presented with NHL and 72 cases (13.9%) with Hodgkin lymphoma. Overall, there were more male cases (56.9%) than male controls (44.8%), and cases were older than controls.

Unblinded interviews were conducted by trained interviewers with cases and controls either in-person or over the phone. The questionnaire inquired about general characteristics,

medical history, occupational history, environmental and occupational exposure to chemicals, occupational exposure to electromagnetic radiation, and smoking. Age at first exposure, duration of exposure, total number of days exposed, and time since first exposure were assessed for each chemical, including dry-cleaning solvents. There were a total of 35 (6.8%) cases and 77 (7.5%) controls exposed to dry-cleaning solvents.

Mantel-Haenszel methods were used for estimating the odds ratios and 95% CIs examining the effect of sociodemographic characteristics. Unconditional logistic regression using a forward stepwise approach was used to estimate odds ratios and 95% CIs for the effect of chemical exposures, occupational exposures to electromagnetic radiation, and cigarette smoking individually on non-Hodgkin lymphoma, adjusted for age, gender, urban setting, and education level. A lag time of 5 years prior to cancer diagnosis was included. Limitations to the study include the recall bias, given all information was self-reported, a high rate of refusal to participate in the control group, leading to potential selection bias, nondifferential misclassification, and the use of a broad category of dry-cleaning solvents that included tetrachloroethylene and other solvents. No strengths were reported by the authors.

B.2.2.7.4. Gold et al. (2010a; 2010b)

Gold, L. S.; Milliken, K.; Stewart, P.; Purdue, M.; Severson, R.; Seixas, N., . . . De Roos, A. J. (2010a). Occupation and multiple myeloma: an occupation and industry analysis. American Journal of Industrial Medicine, 53(8), 768-779. http://dx.doi.org/10.1002/ajim.20857

Gold, L. S.; Stewart, P. A.; Milliken, K.; Purdue, M.; Severson, R.; Seixas, N., . . . De Roos, A. J. (2010b). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents. Occupational and Environmental Medicine, 68(6), 391-399. http://dx.doi.org/10.1136/oem.2009.054809

Summary: This population-based case-control study examined occupation exposures, particularly solvents exposure, as risk factors for multiple myeloma, and was carried out in two SEER sites, Seattle, WA, and Detroit, MI. Incident multiple myeloma cases (ICD-O-2/3, 9731 [plasmacytoma not otherwise specified] and 9732 [multiple myeloma]) eligible to participate were 35−74 years old and were newly diagnosed between 2000 and 2002. Gold et al. (2010a) reported on occupational and industry, with Gold et al. (2010b) reporting findings on 6 chlorinated solvents: tetrachloroethylene, trichloroethylene, 1,1,1-trichloroacetic acid, methylene chloride, chloroform, and carbon tetrachloride. Of the 365 cases eligible to participate, 64 (18%) had died before they could be contacted, 28 (8%) were unable to be located, and 18 (5%) were patients of physicians who refused to participate (71% participation rate). Population controls were selected from a previous case-control study of NHL undertaken at the same time in the same two SEER reporting sites (Chatterjee et al., 2004) and who (1) had

not been previously diagnosed with multiple myeloma, plasmacytoma, NHL, or HIV, (2) were between 35−74 years of age, (3) were identified as residents of the Detroit or Seattle-Puget sound areas between 1998−2002, and (4) spoke English. Controls under 65 years of age were identified using random digit dialing; controls (65−74 years of age) were identified from Medicare roles. Of the eligible 1,133 controls, 481 (52%) participated. Control participation was not associated with study site or generation, but individuals in the 35−50- and 65−74-age groups were less likely to have participated than subjects 51−64 years old.

In-person interviews were conducted using a computer-assisted personal interview program. All interviews were carried out with the case; proxy interviewees could not complete the interview but could aid in recalling details of occupational exposures. Information on all jobs held since the age of 18 years for at least 1 year between 1941, for cases, and 1946, for controls, and the study enrollment dates, was collected. Subjects were additionally administered job-specific questionnaires for 20 occupations with potential solvent exposure. These modules were administered only when participants held the relevant job for at least 2 years. All jobs were coded blinded to case or control status according to the SOC system (Gold et al., 2010a) or assessed for exposure to six chlorinated solvents using job-exposure matrices developed for each decade for specific industries such as the chemical or rubber industries, occupations such as auto mechanics or hair dressers, and tasks such as degreasing, gluing, and painting, through literature reviews for trichloroethylene and tetrachloroethylene (Bakke et al., 2007; Gold et al., 2008). Each job was assigned a score for probability (0−4) based on the percentage of subjects likely to have had exposure, and for jobs with probability scores of 1 or higher, frequency (1−4), and intensity (1−4) scores. All jobs were assigned a score for confidence levels (1−4). Probability was scores as 0 = <1%; 1 = 1 through <10%; 2 = 10 through <50%; 3 = 50 through <90%; 4 + $\geq$ 90%. Frequency was defined as the average hours per week of exposure: 0 = <15 minutes/week; 1 = 15 minutes through <1 hour/week; 2 = 1−10 hours/week; 3 = >10−20 hours/week; 4 = >20 hours/week. The intensity score was the contraction of solvent estimated to have been in the subject's breathing zone over the exposure period (not an 8-hour TWA): 1 = 1−10 ppm, 2 = >10−100 ppm, 3 = >100−200 ppm, 4 = >200 ppm. The confidence level was assigned as 1 = literature contradictory or no information was available; 2 = one metric (probability, frequency, or intensity) was based on the literature or self-report; 3 = two metrics were based on the literature or self-report; and 4 = all metrics based on the literature or directly from self-report. Of the 180 cases and 481 controls interviewed, 9 (5%) cases and 4 (0.8%) controls were identified as "ever" holding job as textile, apparel, and furnishing machine operator or tender, of whom, 5 cases (3%) and 3 (0.7%) controls were dry cleaners. Regarding specific exposures, 29 cases (19%) and 63 (13%) controls were assigned "ever" exposed to

tetrachloroethylene, of whom, 17 (3%) cases and 15 (3%) controls were assigned high cumulative tetrachloroethylene exposure (>7,794 ppm-hours).

Statistical analyses consisted of unconditional logistic regression to estimate odds ratios and their 95% CIs for associations between the risk of multiple myeloma and the exposure surrogate ["ever" employed in occupation or industry (Gold et al., 2010a) or exposed to any of the six chlorinated solvents or to each of the chlorinated solvents (Gold et al., 2010b)]. Other surrogates examined were employment duration, cumulative exposure (for each exposed job, the midpoint of intensity × the midpoint of frequency × total years worked, summed over all exposed jobs), cumulative exposure for all jobs with a probability score of 2 or greater, and all jobs with solvent exposures lagged 10 years. All models adjusted for sex, age, race, education, and SEER site. As a sensitivity analysis, all analyses were repeated, assuming occupations with confidence scores of 1 were considered as unexposed.

A strength of this study is its use of detailed occupational information to improve assessment of solvent exposure compared to analyses based only on job title. Even so, exposure misclassification was likely. Some limitations of this study were relatively low participation rates among cases and controls, the inability to examine race or socioeconomic status, and if associated with occupation and, potentially, solvents exposure, the potential for selection bias, and small numbers of subjects with exposure to individual chlorinated solvents with limited statistical power. Last, the study may reflect relationships between chlorinated solvents and less severe forms of multiple myeloma due to the large proportion of cases who died before they could be contacted or eligible subjects who refused to participate, particularly, if refusal was related to being too ill.

B.2.2.7.5. Hardell et al. (1981)

Hardell, L.; Eriksson, M.; Lenner, P.; Lundgren, E. (1981). Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. British Journal of Cancer, 43(2), 169-176. http://www.ncbi.nlm.nih.gov/pubmed/7470379

Summary: This study used a case-control design to examine the possible relationship between exposure to chemical classes (organic solvents, chlorophenols, and phenoxy acids) and Hodgkin lymphoma and non-Hodgkin lymphoma. Cases consisted of men aged 25 to 85 years with histologically confirmed malignant lymphoma between 1974 and 1978. Living controls were obtained from the National Population Registry and matched to cases on sex, age, and municipality. Potential living controls were excluded if they did not live in the same municipality at the time the case was diagnosed, if they were deceased, or if they had emigrated. Deceased controls were obtained from the National Registry for Causes of Death and matched on

sex, age, municipality, and year of death. Potential deceased controls were excluded if their death had occurred in 1978, was the result of suicide or malignant tumors, or if the date of last employment did not occur within 5 years of the deceased case's last employment. There were initially 8 living controls matched to each living case and 10 deceased controls matched to each deceased case; in each instance, the two controls closest in age to cases were used in the analysis. The final sample consisted of 169 cases (60 with Hodgkin lymphoma and 109 with non-Hodgkin lymphoma) and 338 controls.

Self-administered questionnaires inquired about leisure-time activities, smoking/drug use, exposure to chemicals, and occupational history (including time and place of employment). A blinded individual evaluated each questionnaire and conducted telephone interviews with the participants when information was unclear or incomplete. Exposure to organic solvents, including tetrachloroethylene, was categorized into high grade and low grade (continuous exposure of ≤1 week or repeated, brief exposure for ≤1 month). There were 10 (5.9%) cases and 31 (9.2%) controls who reported exposure to low-grade organic solvents, though the authors do not report if this included tetrachloroethylene. Of the 40 (23.7%) cases and 47 (13.9%) controls who reported high-grade exposure to organic solvents, only 1 (0.6%) case reported exposure to tetrachloroethylene. Chi-square tests based on Miettinen (1969, 1970) were used to calculate chi-square estimates and odds ratios. Corresponding 95% CIs were determined according to Miettinen (1976). Limitations to the study include its inability to independently evaluate the effect of tetrachloroethylene within the chlorinated solvents category and possible misclassification due to self-reported exposures. The authors do not report any strengths of their methodology.

B.2.2.7.6. Kato et al. (2005)

Kato, I.; Koenig, K. L.; Watanabe-Meserve, H.; Baptiste, M. S.; Lillquist, P. P.; Frizzera, G., . . . Shore, R. E. (2005). Personal and occupational exposure to organic solvents and risk of non-Hodgkin's lymphoma (NHL) in women (United States). Cancer Causes Control, 16, 1215-1224.

Summary: This study used a population-based case-control design to examine whether exposures to solvents were associated with the risk of non-Hodgkin lymphoma in women. Cases were identified through the New York State Cancer Registry and consisted of women aged 20 to 79 years living in New York State and diagnosed with non-Hodgkin lymphoma between 1995 and 1998. Any potential cases with a previous history of hematologic cancers or without a valid driver's license were excluded. Two sets of controls were used. Those under the age of 65 years were obtained from an age-stratified random sample of driver's licenses from the New York Department of Motor Vehicles (DMV), and those 65 years and older were identified from Health

Care Finance Administration (HCFA) beneficiary records. All eligible cases and DMV controls were first sent a solicitation letter by the New York Cancer Registry. Only cases and DMV controls that responded to the letter were contacted for an interview. Of the 722 eligible cases, 376 (56%) participated. The participation rates were 30% for DMV controls and 67% for HCFA controls. The authors did not report response rates for cases or controls. The final sample consisted of 376 cases and 463 (248 DMV and 215 HCFA) controls.

Blinded telephone interviews were conducted with both the cases and controls with a structured questionnaire. Nearly 21% of the case interviews and just over 3% of the control interviews were conducted with proxy respondents, in this case, next of kin. This occurred when the participant was either deceased or medically incapable of answering the questions. The median time between the cancer diagnosis and the interview was 1.2 years and ranged between 2 months and 3.3 years. A total of 50 (13.3%) cases and 48 (10.4%) controls reported occupational exposure to degreasers and cleaning solvents, and 7 (1.9%) cases and 8 (1.7%) controls reported occupational exposure to dry-cleaning fluids. To allow for a minimum lag period of 1 year, an index date was determined for each case. Any exposures that occurred after this date were excluded from the analysis.

Unconditional logistic regression estimated odds ratios and 95% CIs for occupational and household exposures to solvents, adjusting for age at index date, family history of hematologic cancer, college education, surrogate status, year of interview, BMI 10 years before interview, average frequency of use of pain-relieving drugs, total number of episodes of systemic antibiotic use, total number of uses of household pesticide products, and duration of work involving pesticide exposures. This study's strength is its questionnaire that examined long-term exposures by asking about the participant's whole personal history. Limitations include its self-reported occupational history and the potential for recall bias in measuring exposures to degreasers/cleaning solvents and dry-cleaning fluids. It also includes a limited number of household products that contained organic solvents, which may have underestimated actual exposure. Recall bias and the low response rate were additional methodological limitations to this study.

B.2.2.7.7. Malone et al. (1989)

Malone, K. E.; Koepsell, T. D.; Daling, J. R.; Weiss, N. S.; Morris, P. D.; Taylor, J. W., . . . Lyon, J. L. (1989). Chronic lymphocytic leukemia in relation to chemical exposures. Am J Epidemiol, 130, 1152-1158.
http://www.ncbi.nlm.nih.gov/pubmed/2589308

Summary: This study used previously collected data from a larger study (Koepsell et al., 1987) to examine the relationship between selected occupations or chemical exposures and

leukemia. Cases were identified through SEER reporting sites in Washington state, Utah, Michigan, and Georgia and consisted of men and women under the age of 80 years who were diagnosed with chronic lymphocytic leukemia between 1977 and 1981. Of the eligible cases, 82.5% responded, and 430 were interviewed. The authors were unclear regarding the number of eligible cases. Three of the cases were excluded because the interview failed to provide any information on chemical exposures. Controls were randomly selected in one of two ways: (1) random digit dialing in Utah, Michigan, and Georgia and (2) area sampling in Washington state. Controls were matched based on sex, race, and/or age, depending on the location. Of the 2,028 eligible controls, 83% were interviewed. The final sample consisted of 427 cases and 1,683 controls.

B.2.2.7.8. Mester et al. (2006), Seidler et al. (2007)

Mester, B.; Nieters, A.; Deeg, E.; Elsner, G.; Becker, N.; Seidler, A. (2006). Occupation and malignant lymphoma: A population based case control study in Germany. Occup Environ Med, 63, 17-26. http://dx.doi.org/10.1136/oem.2005.020453

Seidler, A.; Mohner, M.; Berger, J.; Mester, B.; Deeg, E.; Elsner, G., . . . Becker, N. (2007). Solvent exposure and malignant lymphoma: A population-based case-control study in Germany. J Occup Med Toxicol, 2, 2. http://dx.doi.org/10.1186/1745-6673-2-2

Summary: A multicentre, population-based case control study was conducted in six regions in Germany that is part of a larger multicountry lymphoma case-control study (the EPILYMPH study). Cases were identified through physicians who played a role in the diagnosis and treatment of malignant lymphoma in patients admitted to hospitals in each of the study areas. Cases consisted of German residents (men and women) aged 18 to 80 years who were diagnosed with either non-Hodgkin or Hodgkin lymphoma. Controls were identified from the population registration office and matched to cases based on sex, region, and age. The participation rate among controls was 44.3%; more than half (51%) of those who did not participate cited reasons related to lack of interest. Additionally, in order to be included in the study, cases and controls needed to be familiar with the German language. The final sample consisted of 710 cases and 710 controls.

In-person interviews were conducted with trained interviewers and inquired about the participant's medical history, lifestyle behaviors (smoking, alcohol, etc.) and activities, and occupational history. The occupational history obtained information on dates of employment, title, industry, and tasks associated with each job held for at least 1 year. Any participants who reported potentially hazardous jobs (including dry cleaning) were asked additional questions about their job tasks based on Bolm-Audorff et al. (1989).

Mester et al. (2006) aimed to identify occupations suspected to be associated with lymphoma risk and to generate new hypotheses about occupational risks. Occupation was assessed as a proxy for exposure, with job titles and industries blindly coded by two individuals from the Frankfurt Institute for Occupational Medicine according to ISCO-68 and Statistical Classification of Economic Activities in the European Community. Launderers, dry cleaners, and pressers comprised ISCO-68 Code 56 and included 11 (1.5%) cases and 11 (1.5%) controls. Conditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs, adjusted for smoking and alcohol consumption. Unconditional logistic regression was employed to further examine lymphoma subentities (Hodgkin lymphoma, B-non-Hodgkin lymphoma, T-non-Hodgkin lymphoma, B-non-Hodgkin lymphoma and Hodgkin lymphoma, and other lymphomas), estimating odds ratios and their corresponding 95% CIs, adjusted for age, sex, region, smoking, and alcohol consumption. All estimates were stratified by employment duration (≤10 years or >10 years). Additional analyses examined the effect of a latency period of 10 years by only including exposures that occurred up until 10 years before diagnosis, though the data were not reported. Limitations to the study include the low control response rate, possible misclassification in the assessment of exposure through employment in specific industries and occupations, small numbers of exposed, and lack of control for race/ethnicity or immigration status. The authors do not report strengths associated with the methodology of their study.

Seidler et al. (2007) examined the association between exposure to chlorinated hydrocarbons and lymphoma on an in-depth expert assessment of solvent exposure. Intensity and frequency of exposure was assessed by a blinded, trained industrial physician. Intensity was evaluated as low (0.5−5 ppm), medium (>5−50 ppm), or high (>50 ppm). Frequency was calculated as the percentage of weekly working time exposed and was categorized as low (1−5%), medium (>5−30%), or high (>30%). Confidence in the exposure was classified as possible, probable, or certain, and cumulative exposure (ppm-years) to each solvent for each occupation was also calculated. Overall, there were 36 (5.1%) cases and 31 (4.4%) controls exposed to tetrachloroethylene. Conditional logistic regression was used to calculate odds ratios and 95% CIs, adjusted for smoking and alcohol consumption. The authors reported only those calculations with at least five participants reporting exposures. Tests for trend were analyzed by including specific exposures as continuous variables in the logistic regression model. Unconditional logistic regression was employed to estimate odds ratios and 95% CIs in an unmatched analysis of the most frequent lymphoma subentities (Hodgkin lymphoma, B-non-Hodgkin lymphoma, T-non-Hodgkin lymphoma, B-non-Hodgkin lymphoma and Hodgkin lymphoma, and other lymphomas), adjusted for age, sex, region, smoking, and alcohol. Strengths of the study include blinded exposure assessment, adjustment for potential

confounders, and an expert-based estimate of solvent exposure. A limitation of this study is the low-exposure prevalence.

B.2.2.7.9. Miligi et al. (2006; 1999), Costantini et al. (2008; 2001)

Miligi, L.; Costantini, A. S.; Benvenuti, A.; Kriebel, D.; Bolejack, V.; Tumino, R., . . . Vineis, P. (2006). Occupational exposure to solvents and the risk of lymphomas. Epidemiology, 17, 552-561. http://dx.doi.org/10.1097/01.ede.0000231279.30988.4d

Miligi, L.; Seniori, C. A.; Crosignani, P.; Fontana, A.; Masala, G.; Nanni, O., . . . Vineis, P. (1999). Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. Am J Ind Med, 36, 60-69. http://dx.doi.org/10.1002/(SICI)1097-0274(199907)36:1<60::AID-AJIM9>3.0.CO;2-Z

Costantini, A. S.; Benvenuti, A.; Vineis, P.; Kriebel, D.; Tumino, R.; Ramazzotti, V., . . . Miligi, L. (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian Multicenter Case-control study. Am J Ind Med, 51, 803-811. http://dx.doi.org/10.1002/ajim.20592

Costantini, A. S.; Miligi, L.; Kriebel, D.; Ramazzotti, V.; Rodella, S.; Scarpi, E., . . . Vineis, P. (2001). A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. Epidemiology, 12, 78-87. http://www.ncbi.nlm.nih.gov/pubmed/11138825

Summary: These four publications report on a large, population-based case-control study examining pesticide or solvent exposures and hematolymphopoietic malignancies. The studies were conducted in 12 different parts of Italy (Turin, Ragusa, Siena, Alessandria, Forli, Novara, and Vercelli, as well as Florence, Verona, Imperia, Latina, and Varese provinces), but only 11 of the locations had interviews available for analysis. The authors do not note which study site was excluded. Cases consisted of men and women aged 20 to 74 years who were diagnosed with hematolymphopoietic malignancies between 1991 and 1993. Cases were obtained through surveys with public hospitals in the 12 study areas, as well as regional medical centers or university-affiliated hospitals in Milan, Pavia, Rome, and Bologna to ensure complete collection of cases from all 12 locations. One location (Varese) found all of its cases through the local cancer registry. Controls were randomly selected from the general population of residents in each of the study locations, stratified by sex and 5-year age groups. Of the 3,357 eligible cases, 3,118 were able to be contacted, and 2,737 (88%) were interviewed, including 1,450 non-Hodgkin lymphoma, 365 Hodgkin lymphoma, 652 leukemia, and 270 multiple myeloma cases. Of the 2,391 eligible controls, 2,196 were able to be contacted, and 1,779 (81%) were interviewed.

In-person interviews were conducted to obtain information on education, lifestyle behaviors, occupational history, extraoccupational exposure to solvents and pesticides, hair dye use, lifelong residential history, medical history, and reproductive history. Proxy interviews were conducted with spouses (45%), children (28%), parents (11%), or another relative (16%) for 19% of the cases and 5% of the controls. The occupational history section of the questionnaire was created by industrial hygienists and agronomists and inquired about the participant's full working history as well as exposure to chemicals, solvents, and pesticides. Industrial hygienists from each of the areas blindly assessed occupational exposures, evaluating the probability and intensity of exposures to categories of solvents as well as individual chemicals, including tetrachloroethylene. Probability was rated as low, medium, or high, and intensity was classified as "very low," "low," "medium," and "high." To ensure consistency in assessment, a job exposure matrix was created with the minimum overall consensus for those jobs that were reported most frequently.

Costantini et al. (2001) investigated the associations between occupational exposures and hematolymphopoietic neoplasms. This study used the full sample of 2,737 cases and 1,779 controls within the 11 available study areas. All jobs were coded according to International Standard Classification of Occupations; launderers, dry cleaners, and pressers fell within Code 56. There were 3 (0.2%) male non-Hodgkin lymphoma cases, 1 (0.3%) male Hodgkin lymphoma case, and 2 (0.3%) male leukemia cases who were employed in the dry-cleaning industry. Odds ratios and their corresponding 95% CIs for non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, and multiple myeloma were calculated using the Mantel-Haenszel approach adjusted for age. The results for men were presented and compared with the results for men and women combined. Only those occupations that had a minimum of five exposed cases in at least one gender were presented. The authors did not specifically mention strengths associated with the methodology; a limitation is its use of occupation as a proxy for examining risks associated with chemical exposures.

Miligi et al. (2006) evaluated the association between solvent exposure in the work environment and non-Hodgkin lymphoma, including chronic lymphatic leukemia, and Hodgkin lymphoma. Due to the fact that the industrial hygienists' exposure assessment was only completed in 8 areas, there were 1,719 eligible cases of non-Hodgkin lymphoma, 347 eligible cases of Hodgkin lymphoma, and 2,086 eligible controls. The final sample consisted of 1,428 (83%) NHL cases, 304 Hodgkin lymphoma cases (88%), and 1,530 controls (73%). In-person interviews were conducted with 85% of the non-Hodgkin lymphoma cases, 93% of the Hodgkin lymphoma cases, and 97% of the controls. Intensity of exposure was classified as "very low/low" or "medium/high." There were 18 (1.3%) non-Hodgkin lymphoma cases and 29 (1.9%) controls with "very low/low" exposure to tetrachloroethylene and 14 (1.0%)

non-Hodgkin lymphoma cases and 15 (1.0%) controls with "medium/high" exposure. Duration of exposure was categorized as having lasted <15 years or ≥15 years. There were 10 (0.7%) non-Hodgkin lymphoma cases and 10 (0.7%) controls who reported <15 years of exposure to tetrachloroethylene and 3 (0.2%) non-Hodgkin lymphoma cases and 5 (0.3%) controls who reported 15 years or more. Odds ratios and their corresponding 95% CIs were calculated for non-Hodgkin lymphoma, non-Hodgkin lymphoma subtypes, and Hodgkin lymphoma, individually. All were adjusted for sex, age, education, and area. Strengths of the study include its large sample size and the exclusion of participants who were classified as having a low probability of exposure. Limitations include the potential for misclassification of subjects by individual chemical, the low-exposure prevalence to tetrachloroethylene, the high percentage of proxy interviews among the case series, and the small sample of cases for each lymphoma subtype, which for Hodgkin lymphoma, prevented the examination of potential associations by individual chemical.

Costantini et al. (2008) examined the association between solvent exposure and occurrence of leukemia subtypes and multiple myeloma. The final samples consisted of 586 cases of leukemia (acute myeloid leukemia and chronic lymphatic leukemia) and 1,278 controls collected from 7 of the locations, as well as 236 cases of multiple myeloma and 1,100 controls collected from 6 of the sites. Intensity of exposure was classified as "very low/low" or "medium/high." There were 6 (1.0%) leukemia cases, 17 (1.3%) leukemia controls, 3 (1.3%) multiple myeloma cases, and 15 (1.4%) multiple myeloma controls with "very low/low" exposure to tetrachloroethylene and 7 (1.2%) leukemia cases, 12 (0.9%) leukemia controls, 2 (0.8%) multiple myeloma cases, and 12 (1.1%) multiple myeloma controls with "medium/high" exposure. Duration of exposure was categorized as having lasted <15 years or ≥15 years, though tetrachloroethylene was not specifically reported. Point odds ratios and their corresponding 95% CIs were calculated for leukemia, leukemia subtypes, and multiple myeloma, individually. All were adjusted for gender, age, education, and area. The authors did not report the method used to derive estimates. A linear test for trend was also conducted using the midpoints of all duration categories (0, 7.5, and 35 years). The authors did not note any strengths or limitations of their methodology, although those identified for Miligi et al. (2008) are relevant for this study.

B.2.2.7.10. Schenk et al. (2009)

Schenk, M.; Purdue, M.; Colt, J.; Hartge, P.; Blair, A.; Stewart, P., . . . Severson, R. (2009). Occupation/industry and risk of non-Hodgkin's lymphoma in the United States. Occup Environ Med, 66, 23-31. http://dx.doi.org/10.1136/oem.2007.036723

Summary: This study used a case-control design to examine the relationship between occupation and development of non-Hodgkin lymphoma. Cases were identified through the SEER registry and consisted of men and women aged 20 to 74 years, living in Iowa or selected parts of California, Michigan, or Washington state and diagnosed with histologically confirmed non-Hodgkin lymphoma between 1998 and 2000. Controls were selected in two ways. Those under the age of 65 years were chosen from random digit dialing, and those 65−74 years were chosen through Medicare files. Controls were matched to cases on 5-year age group, gender, and race within each study center. All HIV-positive individuals were excluded from both the cases and controls, as were controls with a previous diagnosis of non-Hodgkin lymphoma. Of the 2,248 eligible cases, 1,728 (77%) were contacted, and 1,321 participated in the interview, yielding a response rate of 59% and a participation rate of 76%. Of the 2,409 eligible controls, 2,046 (85%) were contacted, and 1,057 participated, yielding a response rate of 44% and a participation rate of 52%. After excluding those cases and controls who were never employed or whose occupations were unknown, the final sample consisted of 1,189 cases (293 follicular, 366 diffuse large B-cell lymphoma, 487 other, 43 unknown) and 982 controls.

Initially, all participants were mailed a self-administered questionnaire inquiring about either family and medical history or diet. Then participants were visited in their homes for a computer-assisted interview. All participants were asked about demographics, hair coloring, residential history since 1970, and occupational history (Chatterjee et al., 2004). The occupational history asked about all jobs lasting 6 months or longer and obtained information on location, dates of employment, job title, and number of hours worked (part-time or full-time). Occupation was assessed as a proxy for exposure, and all jobs were blindly assigned occupation and industry codes according to SOC and SIC conventions. Participants were considered exposed if they had ever been employed in a particular occupation or industry and unexposed if they had not. Launderers and ironers were assigned Code 503 and included a total of 12 (1.0%) cases and 3 (0.3%) controls.

Unconditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs, adjusted for age, gender, ethnicity, and study center. Analyses were also performed, stratified by gender and histological subtype separately. Strengths of the study include its population-based sample, the large number of cases, its detailed information on multiple risk factors, as well as its ability to examine this disease by multiple histological subtypes and by gender. Limitations to the study include its small number of exposed participants and low power. The study also fails to examine intensity or duration of exposure and may be subject to selection bias in light of its low participation rate.

B.2.2.7.11. Scherr et al. (1992)

Scherr, P. A.; Hutchison, G. B.; Neiman, R. S. (1992). Non-Hodgkin's lymphoma and occupational exposure. Cancer Res, 52, 5503s-5509s. http://www.ncbi.nlm.nih.gov/pubmed/1394164

Summary: This hospital-based case-control study of non-Hodgkin lymphoma examined occupations and exposures associated with increased risk of all NHLs or of specific NHL histological subtypes. The case series were patients diagnosed with NHL from January 1, 1980, to May 31, 1982, treated at any of nine participating Boston hospitals, and residents of the Boston Standard Metropolitan Statistical Area. A total of 379 NHL histologically confirmed cases were identified, of which, 303 interviews with the living case, next of kin, or parent for ases aged 17 years or younger (80% response rate). A pathology review of the cases confirmed the NHL diagnosis, and this is one of the early studies to classify NHL subtypes according to the Modified Rappaport or Working Formulation Classification, if tumors were nodular or diffuse, or by cell type (B- or T-cell). The control series were randomly selected from residence lists for all Massachusetts towns and, for controls 17 years of age or older, matched to cases based on sex and age. For cases under 18 years of age, possible controls were identified from matching based on the age and sex of a case's parent or guardian and interviewed to determine whether he or she had a child of the same age and sex as the case. Of 423 potential controls, 303 were interviewed (72% response rate). All interviews were carried out with the liver control. No statistically significant differences between cases and controls were found for education, marital status, current family income, and highest family income. Religion was found to differ between cases and controls ($p < 0.05$).

Face-to-face interviews were carried out using a questionnaire that sought information on current or most recent job, job held 15 years previously, major and second major occupation, and exposure to a list of agents that included chlorinated solvents as a category. One-third of cases' responses were from proxy or next-of-kin respondents. Each occupation was categorized by occupation and industry and coded according to the Dictionary of Occupational Titles.
Nine cases (3% exposure prevalence) were identified as holding jobs in laundering, dry cleaning, and leather products fabrication, and 73 cases (24% exposure prevalence) reported exposure to chlorinated solvents.

Statistical analyses were carried out using a hierarchal approach that aggregated histological subtypes into groups with similar histological characteristics and exposure defined as a function of calendar time (1901−1949, 1950−1959, 1960−1969, 1970 and later) or exposure duration (10 years, 20 years). All exposure that showed consistent patterns within histological categories over calendar time or over duration were considered as candidate variables for conditional logistic models with covariates for age and sex.

A strength of the study is its examination of NHL subtypes, although different classification schemes were used, and no attempt was made to harmonize across schemes. The lack of a common scheme to classify NHLs might lead to potential for disease misclassification. Another limitation of the study includes the high percentage of proxy respondents (33% cases, no controls), which may have led to measurement error and misclassification bias in exposure assignment. Last, the statistical analyses, using a hierarchal approach, could identify true positive associations but was not specific, with a greater potential for some false negative findings.

B.2.2.8. Childhood lymphopoietic cancers

B.2.2.8.1. Infante-Rivard et al. (2005)

Infante-Rivard, C.; Siemiatycki, J.; Lakhani, R.; Nadon, L. (2005). Maternal exposure to occupational solvents and childhood leukemia. Environ Health Perspect, 113, 787-792. http://dx.doi.org/10.1289/ehp.7707

Summary: This study used a population-based case-control design to examine the possible relationship between childhood leukemia and maternal exposure to occupational solvents. Cases consisted of children who were diagnosed with acute lymphoblastic leukemia and were being treated in tertiary care centers in Quebec Province, Canada. Between 1980 and 1993, children aged 0 to 9 years were included in the study; between 1994 and 2000, cases were children between 0 and 14 years of age. Controls were selected in two ways. The 1980−1993 controls were obtained from government records indicating all families who had received a stipend for having children living legally in Canada. The 1994−2000 controls were chosen from universal health insurance records for the Quebec Province. Both mechanisms provided the most complete census of children during these time periods. Controls were matched to cases on sex and age at diagnosis. Prospective participants were excluded if children were adopted or lived with foster families, if neither French nor English was spoken, if they did not currently reside in Canada, or if the parents were not available to be interviewed. Of the 848 eligible cases, 790 (93.1%) of parents were interviewed. Of the 916 eligible controls, 790 (86.2%) of parents were interviewed. The final sample consisted of 790 cases and 790 controls.

Telephone interviews with parents were conducted using a structured questionnaire, which inquired about general risk factors, potential confounders, and maternal occupational risk factors. The latter consisted of a complete occupational history (job title, industry, name, address) provided by the mother for the time period, which began when she was 18 years of age and ended with the birth of the child. All jobs held by the mother during the 2 years prior to the birth of the child were further examined using a semi-structured questionnaire to obtain

information on the company's activities, raw materials and machines used, goods produced, responsibilities, working conditions, activities of coworkers, and the presence of solvents and other chemicals. Finally, for all jobs for which there was significant possible exposure, including textile dry cleaners, more detailed questionnaires were used to inquire about the specific tasks, the time spent at these tasks, the specific exposures associated with these tasks, and the environment in which the tasks were carried out.

Exposures were classified by a team of blinded chemists and industrial hygienists. All jobs were coded according to standard Canadian industrial titles (3 digit codes) and job titles (7 digit codes). Then, the team determined whether or not participants were exposed to a list of over 300 chemicals, including tetrachloroethylene, based on the information provided by the respondent, previous information on exposures in that geographical area, and the team's knowledge of exposures in the industry in question. All jobs held in the 2-year time period before the pregnancy were coded separately, based on the team's confidence that the exposure had occurred (possible, probable, or definite), the frequency of the exposure during a normal workweek (<5%, 5−30%, or >30% time), and the level of the concentration (low/background, medium, high). This methodology for exposure assessment has been validated and used in other research publications. All chemicals were assigned 3 digit codes based on Siemiatycki (1991); tetrachloroethylene was Code 243. This study did not provide sufficient detail to determine the number of cases exposed to tetrachloroethylene to calculate a prevalence of exposure. Conditional logistic regression was performed separately for each chemical using two time periods, the 2 years before the child's birth and during pregnancy. Odds ratios and their corresponding 95% CIs were estimated, adjusting for maternal age and level of schooling. A strength of this study is the use of a detailed exposure assessment. Limitations include power due to small sample size and nondifferential misclassification.

B.2.2.8.2. Lagakos et al. (1986), Costas et al. (2002)

Lagakos, S. W.; Wessen, B. J.; Zelen, M. (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts. J Am Stat Assoc, 81, 583-596.

Costas, K.; Knorr, R. S.; Condon, S. K. (2002). A case-control study of childhood leukemia in Woburn, Massachusetts: The relationship between leukemia incidence and exposure to public drinking water. Sci Total Environ, 300, 23-35. http://dx.doi.org/10.1016/S0048-9697(02)00169-9

Summary: Lagakos et al. (1986) had two aims: (1) to assess the association between access to contaminated water and the incidence rate of childhood leukemia, and (2) to determine whether adverse pregnancy outcomes (fetal wastage, low birth weight, stillbirth, birth defects) were correlated with exposure to water from the contaminated wells. Cases were identified

through the state cancer registry and the Dana-Farber Cancer Institute/Children's Hospital cancer registry and consisted of male and female children aged 19 years and younger who were diagnosed with leukemia in Woburn between 1964 and 1983. In total, 20 cases of childhood leukemia were identified. This study was a precursor to a later case-control study of childhood leukemia by Costas et al. (2002).

In 1982, telephone interviews were conducted by blinded, trained interviewers with Woburn residents. Of the 8,109 telephone numbers, 7,134 (88%) were contacted. After excluding for business, second phones, and disconnected numbers, the sample decreased to 6,219 households. Of these, 5,010 (80.6%) were interviewed. The questionnaire used during the interviews inquired about all pregnancies 1960 and 1982, excluding elective and spontaneous abortions, chronic and recurrent child health problems, and the residential history for each family member (current and former) up through, but excluding the current address. Pregnancy information obtained included the date the pregnancy ended, maternal age, and smoking status during pregnancy, offspring vital status at delivery, offspring weight, gender, and congenital anomalies. A 1983 study by Waldorf and Cleary estimated the monthly distribution of water from the contaminated wells for the time the wells were in use (1964−1979). These estimates were used to determine the proportion of annual water supplied by the contaminated wells for each household between 1960 and 1982. Annual exposures for pregnancies were based on the year the pregnancy ended; annual exposures for children were determined starting the first year they lived in Woburn. Cumulative and binary metrics were used to characterize exposure to well water in the study area. Of the 4,396 pregnancies that occurred during the study period and 4,978 children about whom information was obtained, approximately 16% of pregnancies, and 27% of children were estimated to have had some exposure to the contaminated wells.

A Cox hazards regression model was used to estimate whether the distribution of childhood leukemia cases was associated with the contaminated wells. Individual risk sets consisted of children from the survey of adverse pregnancy outcomes and childhood disorders who were matched to cases on year of birth and were residents of Woburn when the case was diagnosed. These risk sets were used to estimate the expected cumulative exposure for each case. Logistic regression using the maximum likelihood method was employed to estimate odds ratios and their corresponding 95% CIs for adverse pregnancy outcomes including spontaneous abortion, perinatal death, low birth weight, and musculoskeletal, cardiovascular, eye/ear, CNS, chromosomal, and oral cleft anomalies separately. Each adverse outcome was adjusted for its own set of risk factors. Overall, these were maternal age during pregnancy, smoking during pregnancy, year pregnancy ended, and mother's pregnancy history, which included prior spontaneous abortion, prior perinatal death, prior low birth weight, and prior musculoskeletal anomaly. A survival time model with age of diagnosis as the time variable was used to estimate

relative risks of childhood disorders, including anemia/blood disorders, allergy/skin disorders, kidney/urinary tract disorders, lung/respiratory tract disorders, neurologic/sensory disorders, learning disabilities, and other disorders separately. These were each adjusted for their own set of risk factors. Overall, these were year the pregnancy ended, age at pregnancy, SES, and sex. A strength of this study is its large sample of pregnancy outcomes and child disorders. A limitation is its use of annual exposure estimates, which may not have been accurate enough to assess intensity of exposure, particularly for pregnancy outcomes. A second limitation included potential bias of omission of families that moved from Woburn prior to 1982. Nonresponse of eligible, omitted households that were not contacted may have introduced bias.

Costas et al. (2002) used a matched case-control design in their follow-up to a Massachusetts Department of Health study (Cutler et al., 1986), which found a cluster of leukemia cases in Woburn, Massachusetts. This study expanded on the initial research by using water distribution models to assign exposure rather than location of residence (Costas et al., 2002) and aimed to determine whether childhood leukemia was associated with exposure to water from Wells G and H (MDPH, 1997). Cases consisted of children who were diagnosed with leukemia before their 19th birthday between 1969 and 1989. Those diagnosed before 1982 were identified through pediatric health professionals and greater-Boston pediatric oncology centers, and those diagnosed from 1982 onwards were obtained through the Massachusetts Cancer Registry. Controls were randomly selected from Woburn Public School records and matched to cases based on race, sex, and date of birth. Two controls were matched to each case. Both cases and controls were required to be Woburn residents at the time of the case's diagnosis. Of 21 eligible cases, 19 (90.5%) participated in the study. Of the 38 controls selected, one was excluded from the study when it became known that they no longer fit the inclusion criteria. The authors do not report response rates for controls. The final sample consisted of 19 cases and 37 controls. Cases and controls were similar on family history of cancer, maternal smoking and alcohol consumption, and potential exposure to 60 Hz electric and magnetic fields.

In-person interviews were conducted with both parents of cases and controls, except for two instances where the father was interviewed via telephone. The maternal questionnaire inquired about demographics, lifestyle characteristics, medical history, environmental and occupational exposures, and use of public drinking water at home. The paternal questionnaire inquired about occupational history and occupational exposures. A detailed residential history was also ascertained for each mother and child for the period 2 years preconception through date of case diagnosis, and all were evaluated for electromagnetic field exposure using a power distribution wire code scheme (Kaune and Savitz, 1994). All estimates were based on well water contaminant levels, which were measured just before the wells' closure in 1979. As a result, exposure was determined by the potential for a residence to receive water from the contaminated

wells rather than the actual concentrations of contaminants. A water distribution model developed by Murphy (1991) was used to estimate water distribution patterns through the creation of exposure index values for each neighborhood in Woburn for each month that the wells were in use between 1964 and 1979. Overall, seven cumulative exposure scores were estimated for each participant for the entire etiologic period, preconception, each trimester, overall pregnancy, and period between birth and diagnosis. Two exposures were assessed for each participant: (1) culative exposure (summed for all months of residence in a particular location), and (2) average exposure (consisted of water exposure data averaged over time). During the full exposure time frame (2 years preconception through case diagnosis), 16 (84.2%) cases and 24 (64.9%) controls had been exposed to water from the contaminated municipal wells. Of these, 7 cases (36.8%) and 13 controls (35.1%) received the most exposure, and 9 cases (47.4%) and 11 controls (29.8%) received the least.

Conditional logistic regression with a proportional hazards model was used to calculate odds ratios and their corresponding 95% CIs. Unadjusted odds ratios examined the relationship between case-control status and effects of maternal alcohol consumption, breastfeeding, paternal grandfather with cancer, paternal employment in a high-risk industry, and public water as primary beverage. Odds ratios for four exposure time periods (2 years preconception through case diagnosis, 2 years preconception, pregnancy, birth to diagnosis) examined "ever" exposure and subcategories within "ever" exposure ("most" or "least") separately. Each was then adjusted for a composite covariate according to Tukey (1991), who controlled for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, and breastfeeding. Trends related to increasing exposure ("never," "least," "most") were evaluated for each exposure time period separately using the chi-square method. Strengths of this study include its adjustment for potential confounders and its use of exposure estimates that were developed through an investigation of the distribution of municipal water throughout the city. A limitation of the study is its lack of information on actual well water contamination levels during the time the wells were in use and the study's small size, which leads to low statistical power and imprecise estimates of risk.

B.2.2.8.3. Lowengart et al. (1987)

Lowengart, R. A.; Peters, J. M.; Cicioni, C.; Buckley, J.; Bernstein, L.; Preston-Martin, S.; Rappaport, E. (1987). Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst, 79, 39-46. http://www.ncbi.nlm.nih.gov/pubmed/3474448

Summary: This case-control study investigated possible etiologic factors for childhood leukemia. Cases were identified through the Los Angeles County Cancer Surveillance Program

and consisted of children aged 10 years or younger at the time of their diagnosis between 1980 and 1984. In order to be included in the study, biological case mothers were required to be available for an interview. Controls were selected in two ways: (1) friends of cases were identified by case mothers and asked to participate, and (2) population-based controls were chosen through random digit dialing when friends were not available. Of the 216 eligible cases, 202 (94%) were able to be contacted. Of them, 159 (79%) mothers were interviewed. There were 154 case fathers also interviewed, of which, 30 cases where mother's provided proxy information on paternal variables. There were five fathers who did not participate in the study. There were 136 control mothers and 130 control fathers who participated in the interview. There were 6 fathers for whom interviews could not be obtained, and 43 of the paternal interviews were by proxy with mothers. The authors do not report control response rates. Controls were matched to cases based on age, sex, race, and Hispanic origin (if race was "white"), though 3 population-based controls were unable to be matched based on sex and 10 were unable to be matched based on race. After further exclusions (4 cases and 5 controls) for incomplete occupational histories, the final sample consisted of 123 case-control pairs for which complete information was available about both parents.

Telephone interviews were conducted by two, nonblinded, trained interviewers using a structured questionnaire that inquired about family and personal medical histories, alcohol and tobacco use, household and personal products, X-ray exposure, and occupational history (job title, industry, time period worked). The maternal questionnaire also asked about medical complications, use of drugs, and diet during the index pregnancy, as well as the child's medical history and exposure to ionizing radiation. The interviews occurred between 1983 and 1985. Industries and occupations were coded according to 1970 U.S. Census classifications and grouped based on potential hydrocarbon exposure. All occupations and exposures within 1 year of conception were excluded. There was 1 (0.8%) case father who reported exposure to tetrachloroethylene in the year before pregnancy, 1 (0.8%) case father who reported exposure during pregnancy, and 2 (1.6%) case fathers who reported exposures after delivery. No control fathers were exposed to tetrachloroethylene. The authors did not report information on maternal exposure to tetrachloroethylene. Conditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs. Limitations of the study include its lack of exposure verification and inability to assess intensity of exposure.

B.2.2.8.4. Shu et al. (1999)

Shu, X. O.; Stewart, P.; Wen, W. Q.; Han, D.; Potter, J. D.; Buckley, J. D., . . . Robison, L. L. (1999). Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. Cancer Epidemiol Biomarkers Prev, 8, 783-791. http://www.ncbi.nlm.nih.gov/pubmed/10498397

Summary: This case-control study examined the association between parental occupational exposure and the risk of childhood acute lymphocytic leukemia. Potential cases and controls were required to meet the following criteria: have a telephone in their place of residence and have their English-speaking, biological mother available for an interview. Cases consisted of children aged 15 years and under who were diagnosed with acute lymphocytic leukemia between 1989 and 1993 by 1 of 37 participating Children's Cancer Group members or institutions from Australia, California, Canada, Colorado, Illinois, Indiana, Iowa, Michigan, Minnesota, Missouri, Nebraska, New York, North Carolina, Ohio, Oregon, Pennsylvania, Tennessee, Texas, Washington state, Washington, DC, Wisconsin, and Utah. Of the 2,081 eligible cases, 1,914 (92%) mothers were interviewed. Controls were chosen through random digit dialing and matched to cases based on age, race, and telephone area code and exchange. Of the 2,597 eligible controls, 1,987 (76.5%) mothers were interviewed. After excluding the 72 cases for whom a matched control could not be found, the final sample consisted of 1,842 cases and 1,986 controls.

Telephone interviews were conducted with case mothers and fathers using a structured questionnaire. The maternal questionnaire inquired about demographics; personal habits; household exposures before and during index pregnancy; exposure to environmental hazards; and occupational, medical, reproductive, and family histories. The paternal questionnaire inquired about personal habits; household exposures; and medical, occupational, and family histories. Of the 2,081 eligible cases and 2,597 eligible controls, fathers were interviewed for 1,801 (86.5%) cases and 1,183 (69.8%) controls, yielding 1,618 matched sets. The majority (83.4% cases and 67.7% controls) consisted of direct interviews with fathers; the remainder were proxy interviews with the mothers.

Maternal occupational histories were collected for all jobs that lasted at least 6 months and occurred between the 2 years prior to the pregnancy and the case's diagnosis, while paternal occupational histories were obtained for all jobs lasting at least 6 months from age 18 years onwards. Both maternal and paternal occupational histories inquired about job titles, industries, duties, dates of employment, and exposure to solvents/degreasers/cleaning agents, plastic materials, paints, pigments/thinners, and oil/coal products. Any self-reported exposures that were not included as part of the exposures listed in the questionnaire were blindly assessed by an industrial hygienist and placed into the established exposure categories. Maternal and paternal dates of employment were used to determine whether an exposure occurred during preconception, pregnancy, or the postnatal period; duration of exposure within each of these time frames was calculated and categorized using the control group's median time as the cutoff. Maternal exposures to tetrachloroethylene occurred anytime in 4 (0.2%) cases and 9 (0.5%) controls, during preconception in 3 (0.2%) cases and 2 (0.1%) controls, during pregnancy in

3 (0.2%) cases and 2 (0.1%) controls, and during the postnatal period in 4 (0.2%) cases and 8 (0.4%) controls. Paternal exposures to tetrachloroethylene occurred anytime in 25 (1.4%) cases and 23 (1.9%) controls, during preconception in 21 (1.2%) cases and 22 (1.9%) controls, during pregnancy in 8 (0.4%) cases and 14 (1.2%) controls, and during the postnatal period in 10 (0.6%) cases and 15 (1.3%) controls.

Conditional logistic regression was used to estimate odds ratios and their corresponding 95% CIs for maternal exposures, adjusted for maternal education, race, and family income. Unconditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs for paternal exposures, adjusted for paternal education, race, family income, age, and sex of the case. Tests for trend were conducted by incorporating the categorical variables of exposure as continuous variables in the models. No strengths were reported by the authors. Limitations included self-reported information on exposure based on a list of specific exposures provided to the participant, the lack of information on intensity or level of exposure, the lack of specific information related to additional exposures that prevented their categorization, low prevalence of maternal tetrachloroethylene exposure, and the high proportion of proxy paternal interviews that likely results in an increased potential for misclassification bias.

B.2.2.9. Neuroblastoma

B.2.2.9.1. DeRoos et al. (2001)

De Roos, A.; Olshan, A.; Teschke, K.; Poole, C.; Savitz, D.; Blatt, J., . . . Pollock, B. (2001). Parental occupational exposures to chemicals and incidence of neuroblastoma in offspring. Am J Epidemiol, 154, 106-114. http://dx.doi.org/10.1093/aje/154.2.106

Summary: This case-control study evaluated the effects of parental occupational exposure on neuroblastoma incidence in offspring. Cases consisted of male and female children aged 18 years or under who were diagnosed with neuroblastoma between 1992 and 1994 and registered in one of 139 participating hospitals in either the United States or English-speaking Canada. Of the 741 eligible cases, 538 (73%) were enrolled in the study. A control was selected for each of 504 cases through random digit dialing and matched to cases based on birth date. Approximately 71% of the eligible controls were recruited, and 74% of the households that were screened participated. After excluding those with missing occupational exposures and all proxy interviews, the final sample consisted of 537 case mothers, 405 case fathers, 503 control mothers, and 302 control fathers.

Telephone interviews were conducted with both mothers and fathers and inquired about demographics as well as lifetime occupational history, which included dates of employment, names of employers, occupations, industries, job titles, specific duties, and hours per week.

Chemical exposure histories were requested for all jobs held within 2 years of the index child's birth. Interviews were conducted with 537 case mothers, 472 case fathers, 503 control mothers, and 445 control fathers, though 67 (14.2%) of the case father interviews and 141 (31.7%) of the control father interviews were completed by mothers as the proxy respondent. All proxy interviews were subsequently excluded from the analyses. Exposure was assessed in two ways. First, the participant was asked to report his/her possible exposure to any of 65 substances, as well as the form (liquid, gas, dust, smoke, solid) and route (inhalation, dermal, ingestion, clothing) of the exposure, the activities being performed during the exposure, the number of hours per week exposed, and the time frame during which the exposure occurred.

Second, these responses were then reviewed by a blinded industrial hygienist who reclassified any improbable exposures as nonexposed. The hygienist did not review the responses of participants who reported no exposure to any of the possible chemicals during their jobs; as a result, jobs that may have had exposure potential were not reclassified. The substances themselves were classified into five categories: halogenated hydrocarbons, a category which included tetrachloroethylene, nonvolatile hydrocarbons, volatile hydrocarbons, paints/inks/pigments, and metals/alloys/solders. Maternal exposure to halogenated hydrocarbons was reported by 15 (2.8%) cases and 19 (3.8%) controls. After the industrial hygienist's review, this decreased to 6 (1.1%) cases and 8 (1.6%) controls. Among the fathers, 8 (2.0%) cases and 11 (3.6%) controls reported exposure to tetrachloroethylene more specifically; the industrial hygienist's review subsequently decreased this to 4 (1.0%) cases and 6 (2.0%) controls.

Unconditional logistic regression was used to calculate exposure odds ratios and their corresponding 95% CIs for each of the five categories of substances as well as for each of the individual chemicals, adjusted for the child's age, maternal race, maternal age, and maternal education. Limitations to the study include possible misclassification of self-reported exposures, lack of adjustment for smoking, and recall bias. Additionally, the researchers' focus on correcting false positives means that the study may have included false negatives. No strengths were reported by the authors.

B.2.2.10. Pancreatic Cancer

B.2.2.10.1. Kernan et al. (1999)

Kernan, G. J.; Ji, B. T.; Dosemeci, M.; Silverman, D. T.; Balbus, J.; Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. States. Am J Ind Med, 36, 260-270. http://dx.doi.org/10.1002/(SICI)1097-0274(199908)36:2<260::AID-AJIM5>3.0.CO;2-P

Summary: This study used a case-control design to examine the risk of pancreatic cancer by occupation, industry, and exposure to solvents, including tetrachloroethylene. Cases were identified using International Classification of Disease Code 157 (pancreatic cancer) on death certificates in 24 states (Maine, New Hampshire, New Jersey, Rhode Island, Vermont, Indiana, Ohio, Wisconsin, Kansas, Oklahoma, Missouri, Nebraska, Kentucky, Georgia, North Carolina, South Carolina, Tennessee, West Virginia, Colorado, Idaho, Nevada, New Mexico, Utah, and Washington) that also included codes for occupation and industry, based on 1980 Census codes. Controls were chosen from among those who died of nonpancreatic, noncancer causes within the same time frame. Each case was matched to four controls based on state, race, gender, and 5-year age group. For the study period 1984−1993, 63,097 cases and 252,386 controls were selected. JEMs were developed by industrial hygienists for the solvents, including tetrachloroethylene. Indexes of probability and intensity of exposure to tetrachloroethylene were estimated and scored as "low," "medium," and "high." Overall, there were 5,344 participants exposed to "low" levels, 2,187 exposed to "medium" levels, and 903 exposed to "high" levels of tetrachloroethylene. Although not cited in the paper, the author's affiliation with the National Cancer Institute and the identified solvents make it likely that the JEM was that of Gomez et al. (1994) and Dosemeci et al. (1994).

Race and gender-specific mortality odds ratios and their corresponding 95% CIs were estimated for intensity and probability of exposure to solvents, including tetrachloroethylene, adjusted for age, marital status, metropolitan status, and region of residence. A strength of the study is its use of the JEM in exposure assessment. Limitations include the possibility of missing information related to occupation and potential confounders on death certificates, as well as the potential for misdiagnosis of pancreatic cancer.

B.2.2.10.2. Lin and Kessler (1981)

Lin, R. S. and Kessler, I. I. (1981). A multifactorial model for pancreatic cancer in man: epidemiologic evidence. JAMA, 245, 147-152.
http://www.ncbi.nlm.nih.gov/pubmed/7452829

Summary: This case-control study aimed to collate information of malignant neoplasms whose prevalence was so low as to render investigations in one institution—or even one city—largely impractical. The study was conducted in over 115 hospitals in Buffalo, Detroit, Miami, Minneapolis-St. Paul, and New York City and collected information on 13 (adrenal, gallbladder, kidney, liver, nasopharynx, pancreas, ureter, urethra, breast, penis, testis/scrotum, vagina, and vulva) cancers. Cases were identified through medical records and the pathology departments of each hospital and consisted of men and women aged 15 and over. Controls were randomly chosen from the admissions records of cancer-free patients of the same hospital as the case and matched to cases based on age, sex, race, and marital status. The authors do not report the

response rates for cases and controls, though they note that 22% of those eligible were not interviewed due to the extremity of their situation. Once these individuals were excluded, the male and female response rates were 86.2% and 86.3%, respectively. The final sample consisted of 109 case-control pairs (67 male pairs and 42 female pairs).

In-person interviews were conducted by blinded interviewers in the hospital or at the participant's home. The majority took place in the hospital and inquired about demographics, residential history, occupations, toxic exposures, animal contacts, smoking habits, diet, medical history, medications, and family history. The occupational history encompassed all jobs that were held full-time for at least 6 months or part-time for at least 1 year. Men were also asked about their sexual practices and urogenital conditions, and women were questioned about their marital, obstetric, and gynecologic histories. All medical conditions that were diagnosed within 1 year of the cancer diagnosis were excluded. Duration of exposure to dry cleaning and gasoline derivatives was categorized into 0 years, ≤2 years, 3−5 years, 6−10 years, and >10 years. Overall, there were 25 (37.3%) male cases and 23 (34.3%) male controls exposed to either dry-cleaning or gasoline derivatives.

Chi-squares and *t*-tests were used to examine the differences between cases and controls. Odds ratios were calculated to estimate the relative risk for pancreatic cancer among men and women who were exposed to a variety of risk factors, including occupational exposure to dry cleaning. A strength of this study is its detailed questionnaire, inquiring about part-time and full-time jobs, as well as a variety of possible confounders. A limitation is its failure to differentiate between occupational exposures to dry-cleaning and gasoline derivatives, as well as control group biases weighting for diabetics, which might have obscured the observed associations with pancreatic cancer.

B.2.2.11. Renal Cell Cancer

B.2.2.11.1. Asal et al. (1988)

Asal, N. R.; Geyer, J. R.; Risser, D. R.; Lee, E. T.; Kadamani, S.; Cherng, N. (1988). Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions. Cancer Detect Prev, 13, 263-279. http://www.ncbi.nlm.nih.gov/pubmed/3266567

Summary: This population-based case-control study examined risk factors of renal cell carcinoma. Cases were identified from 29 hospitals in Oklahoma that agreed to participate in the study. The authors do not report details regarding where the hospitals were located, but they do note that they included Tulsa and Oklahoma City. Cases consisted of men and women with renal cell cancer who had a tissue or radiological examination diagnosis between 1981 and 1984. Two sets of controls were used in this study. The first comprised hospital-based controls

matched to cases based on age, sex, race, hospital, and date of admission. The authors do not state how they identified the hospital-based controls, and it is not known whether controls were drawn from the same hospitals as cases, though they excluded anyone diagnosed with a kidney disease or a psychiatric illness. The second group consisted of population-based controls from the general Oklahoma population and were chosen through random digit dialing according to Waksberg (1978). These controls were matched to cases based on age and sex. Of 345 identified cases, 315 (91.3%) participated in the study. Those not included in the final sample either refused or were unable to participate or did not notify the study on time. The authors did not provide the response or participation rates for control groups. The final sample included 315 cases, 313 hospital-based controls, and 336 population-based controls.

Interviews were conducted in the hospital with cases and hospital controls and in the home or business with population-based controls, inquiring about medical history, medications, radiation exposure, occupational history for all jobs held at least 1 year, self-reported industrial exposure, tobacco smoking, beverage use, artificial sweeteners, family history of disease, height and weight at age 20, weight most recently, and highest weight. BMI was calculated from reported height and weights, and the occupational history was used to identify the predominant occupation or the job held the longest out of all reported occupations lasting 1 year or more. Employment in occupations and industries were assessed as a proxy for exposure; dry cleaning was examined as a high-risk industry and had 11 (3.5%) cases and 7 (1.1%) controls reporting at least 1 year of employment. Cox linear logistic regression modeling was employed to estimate odds ratios and 95% CIs for lifetime occupations and high-risk industries. All of the predominant lifetime occupations in men were adjusted for age, smoking, and weight. The authors do not report lifetime occupation calculations for women. The industry estimates varied in their adjustment of confounders. Painting and welding only adjusted for age, while chemical manufacturing, machining, petroleum refining, dry cleaning, and metal degreasing adjusted for age, smoking, and weight. All industry calculations were stratified by gender, though only petroleum refining and dry cleaning reported estimates for both men and women. Strengths of the study include its use of confirmed cases of renal cell carcinoma, its population-based design, its use of two control groups, and its adjustment for smoking. Limitations include its low-exposure prevalence and its inability to distinguish between jobs within the dry-cleaning industry.

B.2.2.11.2. Auperin et al. (1994)

Auperin, A.; Benhamou, S.; Ory-Paoletti, C.; Flamant, R. (1994). Occupational risk factors for renal cell carcinoma: A case-control study. Occup Environ Med, 51, 426-428. http://dx.doi.org/10.1136/oem.51.6.426

Summary: This hospital-based case-control study examined the relationship between occupation and renal cell carcinoma in France between 1987 and 1991. Cases consisted of 138 men and 58 women with histologically confirmed renal cell carcinoma in 1 of 10 hospitals. Two controls, one with a malignant disease and one with a nonmalignant disease (excluding tobacco related diseases), were matched for each case based on sex, age at interview, hospital, and interviewer. Patients with alcohol-related cirrhosis or diabetes were excluded from the study. Eligibility and matching criteria caused some recruitment difficulties, resulting in 151 cases being matched to 2 controls and 45 cases being matched to 1 control. In total, the study consisted of 161 controls with cancer (107 men and 54 women) and 186 controls with nonmalignant disease (128 men and 58 women). Only one of the eligible cases and two of the eligible controls refused to participate in the interview.

Trained interviewers used a standardized questionnaire to obtain information on education, height, weight, smoking habits, beverage consumption, and medication, as well as a complete occupational history. In the occupational history, participants provided their duration of employment for each job held (minimum 1 year). Although interviewers were not blinded to the individual's case or control status, the job history data were coded blindly, according to the International Standard Classification of Occupations. The authors did not report the code for launderers or dry cleaners. The numbers of exposed were not reported for launderers or dry cleaners, though the authors noted that the estimates for laundry workers could not be calculated due to the small numbers of exposed.

Conditional logistic regression was used to estimate odds ratios and their 95% CIs for occupations, including launderers and dry cleaners. Analyses looked at women and men separately, and matched odds ratios were adjusted for the matching criteria (age, hospital, interviewer). Covariates included educational level, cigarette smoking, and the Quetelet index. After similar results were obtained for each of the control groups, the groups were pooled into one control group. The authors do not report strengths of their study. A limitation is the small number of exposed laundry workers.

B.2.2.11.3. Delahunt et al. (1995)

Delahunt, B.; Bethwaite, P. B.; Nacey, J. N. (1995). Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry. Br J Urol, 75, 578-582. http://dx.doi.org/10.1111/j.1464-410X.1995.tb07410.x

Summary: This registry-based case-control study investigated the risk for renal cell carcinoma among various occupational groups. Cases consisted of men and women aged 20 years and older who were diagnosed with renal cell carcinoma and registered in the New Zealand Cancer Registry between 1978 and 1986. Controls were randomly selected from among

all other cancer cases during this same time frame, excluding those with a primary tumor outside of the urinary tract, and included men and women aged 20 years or older. Cases or controls without active occupational codes in their New Zealand Cancer Registry files were excluded from the analysis. Of the 1,060 identified cases, 914 (86.2%) were eligible for and included in the study. The proportion of female participants with occupational information was low (204 cases); as such, they were excluded from the analysis. The authors did not report any information regarding how many controls were identified for inclusion. The final sample consisted of 710 male cases and 12,756 male controls.

All information was obtained from the New Zealand Cancer Registry, which in 1978, began recording patients' current or most recent occupations and smoking habits. The registry coded all occupations according to the New Zealand Standard Classification of Occupations, and the authors did not delineate the codes used for each of the occupations they examined. All of the occupations included in this study were determined *a priori* due to their previously established or potential association with renal cell carcinoma. This included dry cleaning, which was classified within the occupational category of services. Overall, there were a total of 52 male cases (7.3%) and 737 male controls (5.8%) whose occupation was classified as a service, including catering/lodging, hairdressers, firefighters, and policemen, in addition to dry cleaners. The authors did not provide the numbers of case and control dry cleaners.

The Mantel-Haenszel method was used to estimate relative risks in stratified 10-year age groups for each occupation, including dry cleaning, and Miettinen's approximation method was used to calculate their associated 95% CIs. All were stratified by smoking history and 10-year age groups. A strength of this study is its use of other cancer patients in the registry for the selection of controls, which reduces information and selection bias. Limitations include selection bias if other cancers are associated with the selected occupations and/or their exposures, the assumption that current or most recent occupation represented lifetime occupation, and the lack of stratification of service jobs in terms of exposure prevalence.

B.2.2.11.4. Dosemeci et al. (1999)

Dosemeci, M.; Cocco, P.; Chow, W. H. (1999). Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons. Am J Ind Med, 36, 54-59. http://www.ncbi.nlm.nih.gov/pubmed/10361587

Summary: This case-control study evaluated the effects of organic solvents on renal cell carcinoma risk in Minnesota. Cases were identified through the Minnesota Cancer Surveillance System and consisted of Caucasian men and women aged 20 to 85 years who were diagnosed with histologically confirmed renal cell carcinoma between 1988 and 1990 (Chow et al., 1994). Of 796 eligible cases, 690 (87% response rate) were interviewed. Two groups of controls were

elicited: the first group included Caucasian men and women between 20 and 64 years of age who were identified through age- and gender-stratified random digit dialing; the second group consisted of Caucasian men and women aged 65 years and older who were identified through an age- and gender-stratified systematic sample of Health Care Financing Administration lists. Overall, 707 (86% response rate) controls were interviewed. The final sample for the occupational analyses consisted of 438 cases and 687 controls.

In-person interviews were conducted with blinded, trained interviewers about demographics, diet, smoking, and drug use, as well as medical, residential, and occupational histories. Of the 690 case interviews completed, 241 (34.9%) were proxy with next of kin. The occupational history inquired about recent and usual job and industry, activities performed, dates of employment, and part-time or full-time status. Duration of employment was also obtained for 13 occupations and industries, as well as 7 occupations with specific exposures. A job exposure matrix (Gomez et al., 1994) was used to estimate exposures based on reported occupations and industries. Occupations and industries were coded according to four digit U.S. SIC and SOC codes, respectively. All of the four digit codes were assigned exposure estimates of probability ("low," "medium," "high") and intensity (1, 2, 3) *a priori*. Intensity was defined as an average of the concentration and frequency of exposure. Occupations were also assigned a category. Jobs that fell within Category A, such as dry cleaner operators, had sufficient information to be assessed for exposure independent of their industry. For jobs that fell within Category B, the probability of exposure depended entirely on the industry, and the intensity was weighted by both the occupation and the industry. Those in Category C had their probability and intensity of exposure fully determined by the industry within which the job fell. Time of employment was accounted for in the matrix through a decade indicator. Overall, 48 (11%) cases and 76 (11%) controls were identified as potentially "ever" exposed to tetrachloroethylene. Logistic regression using the Breslow and Day (1980) method was employed to estimate relative risks and their corresponding 95% CIs, adjusted for age, smoking, BMI, and hypertension status and/or use of diuretics and/or antihypertension drugs. All analyses were stratified by gender and did not include subjects with proxy respondents. The authors did not examine duration of employment. The authors did not report any strengths of their methodology; limitations include the small number of exposed participants, potential survival bias, and the lack of a lifetime occupational history.

B.2.2.11.5. Harrington et al. (1989)

Harrington, J. M.; Whitby, H.; Gray, C. N.; Reid, F. J.; Aw, T. C.; Waterhouse, J. A. (1989). Renal disease and occupational exposure to organic solvents: A case

referent approach. Br J Ind Med, 46, 643-650. http://dx.doi.org/10.1136/oem.46.9.643

Summary: This case-control study conducted a detailed "blind" exposure assessment to identify occupational risk factors for renal cancer. Cases were identified through the West Midlands Regional Cancer Registry and consisted of living men and women in West Midlands with histologically confirmed renal adenocarcinoma that was diagnosed between May 1984 and April 1985. Controls were randomly selected from among the patient loads of each of the case's general practitioners and matched (one control per case) based on 5-year age group, sex, ethnicity, geographical location, and socioeconomic status. Of the 101 eligible renal cancer cases, 85 (84%) were allowed to be contacted, and of these, 59 (69%) cases agreed to be interviewed. Due to the fact that 5 of the cases were unable to have matched controls, the final sample decreased to 54 cases and 54 controls.

In-person interviews were conducted with each participant, inquiring about personal habits, such as smoking, coffee, and alcohol consumption; medical history; and occupational history. Exposure was assessed blindly by an experienced chemist/occupational hygienist using an independent checklist of exposures to solvents; exposure indices were calculated by a computer program that multiplied the exposure level by the duration of exposure. None of the cases or controls reported exposure to dry-cleaning fluids, but it appears that 9 (16.7%) cases and 12 (22.2%) controls reported exposure to degreasing agents. Paired analyses were conducted to calculate odds ratios and 95% CIs in two exposure categories using Schlesselman (1982)and three exposure categories using Pike et al. (1975). There were no strengths reported by the authors. Limitations to this study include its small sample size (low power), low prevalence of exposure to dry-cleaning fluids, low response rate, unaddressed renal cancer latency, and possible recall bias associated with self-reporting.

B.2.2.11.6. Mandel et al. (1995)

Mandel, J. S.; McLaughlin, J. K.; Schlehofer, B.; Mellemgaard, A.; Helmert, U.; Lindblad, P., . . . Adami, H.-O. (1995). International renal-cell cancer study. IV. Occupation. Int J Cancer, 61, 601-605. http://dx.doi.org/10.1002/ijc.2910610503

Summary: This international, multicenter case-control study evaluated factors possibly related etiologically to renal cell cancer (McLaughlin et al., 1995). Six centers in five countries (Australia, Denmark, Germany, Sweden, and United States;one center in each country, with the exception of Germany, which had two) participated in the study. Each center had different start dates, which were not provided. Cases were identified through population-based cancer registries in all locations except Germany, where they were obtained through a surveillance of all departments where renal cell cancer was diagnosed or treated. Cases consisted of men and

women aged 20 to 79 years (20−75 in Heidelberg) who were diagnosed with histologically or cytologically confirmed renal cell adenocarcinoma between 1989 and 1991. In all centers except in Australia and the United States, participants were required to have been born in their respective countries. Controls were ascertained through the following: population-based registers in Denmark and Sweden, electoral rolls in Australia, residential lists in Germany, and either random digit dialing for American controls <65 years of age or Health Care Finance Administration lists for American controls ≥65 years. All controls were matched to cases based on gender and 5-year age group. The final sample consisted of 1,732 cases (73.2% response rate) and 2,309 controls (74.7% response rate); cases and controls were comparable in terms of demographics: approximately 60% were men, and 62% were over the age of 60 years at the time of their diagnosis or interview.

In-person interviews were conducted by trained interviewers either in the hospital (German cases) or in the participant's home (German controls and all other countries) and inquired about tobacco, diuretics, analgesics, antihypertensive drugs, diet pills, hormones and alcohol, height and weight, physical activity, medical and reproductive histories, family history of cancer, demographics, and occupational history. The two centers in Germany obtained complete occupational histories, and the four other centers asked about industries, occupations, and exposures of interest. Occupations and industries were coded according to various standards, including the International Labour Office (1968, 1988), the UN Department of Economic and Social Affairs (1968, 1971, 1990), the U.S. Department of Commerce (1980), and the U.S. Office of Management and Budget (1987). Only those occupations, industries, or exposures that were commonly reported by all study centers were included in the analysis. The authors do not state if the codes were harmonized or if exposure was assessed blindly. Duration of exposure was assessed as the total number of years worked or exposed and was subsequently divided into tertiles based on the distribution among controls. Exposures to dry-cleaning solvents were stratified into duration categories of 1−7, 8−25, and 26−60 years. Participants were determined to be "exposed" if they had been employed in the occupation or industry or had been exposed to the chemical of interest for at least 1 year. There were 23 (1.3%) cases and 28 (1.2%) controls who reported "ever" working in the dry-cleaning industry and 302 (17.5%) cases and 265 (11.5%) controls who reported "ever" exposure to dry-cleaning solvents.

Logistic regression was used to estimate odds ratios and their corresponding 95% CIs stratified by gender and adjusted for age, smoking status, BMI, education, and study center. These estimations were performed for industry, occupation, exposure, and duration of exposure based on the categories stated above separately, though only the results for men were presented, as there were fewer cases among women were exposed. Tests of heterogeneity were used to assess differences between centers. Odds ratios and their corresponding 95% CIs were also

calculated to assess the effect of education, stratified by gender and adjusted for age, smoking, BMI and hypertension, and study center. A strength of this study is its large sample size and standardized methodology to collect information. Limitations are its failure to verify self-reported data and its inability to examine specific chemical agents, which was carried out by Dosemeci et al. (1999) for a subset of this study's cases from Minnesota.

B.2.2.11.7. McCredie and Stewart (1993)

McCredie, M. and Stewart, J. H. (1993). Risk factors for kidney cancer in New South Wales. IV. Occupation. Br J Ind Med, 50, 349-354. http://www.ncbi.nlm.nih.gov/pubmed/8494775

Summary: This case-control study sought to report the results of a New South Wales study examining the relationship between occupational exposure and renal cell cancer, as well as those pertaining to cancer of the renal pelvis. Cases were identified through urologists and the New South Wales Central Cancer Registry and consisted of men and women aged 20 to 79 years who were diagnosed with renal cell and renal pelvis cancer between 1989 and 1990. In order to be included in the study, cases needed to be registered in the current electoral roll, have a telephone number that could be found, and be able to speak English. Controls were selected through a proportional random sample of electoral rolls. Of the 744 eligible renal cell cancer cases and 200 eligible renal pelvis cancer cases, 503 (68%) renal cell and 149 (75%) renal pelvis cancer cases were interviewed. Of the 725 eligible controls, 535 (74%) participated in the interview. After excluding for those who completed self-administered questionnaires, the final sample included 489 renal cell cancer cases, 147 renal pelvis cancer cases, and 523 controls.

Interviews were conducted by a trained interviewer, and all but 10 case interviews took place within 1 year of diagnosis. Depending on the proximity of the participant to Sydney, interviews consisted of one of three formats: in-person (256 renal cell cases, 71 renal pelvic cases, and 232 controls), telephone (233 renal cell cases, 76 renal pelvic cases, and 291 controls), and self-administered (14 renal cell cases, 2 renal pelvic cases, and 12 controls). The questionnaire inquired about demographics, chemical exposures, and employment in various occupations and industries. Occupation was assessed as a proxy for exposure, and there were 16 (3.3%) renal cell cases, 8 (5.4%) renal pelvic cases, and 7 (1.3%) controls who reported employment in the dry-cleaning industry.

Logistic regression was used to estimate relative risks and their corresponding 95% CIs, adjusted for age, sex, method of interview, and smoking. Renal cell cancer estimates were also adjusted for BMI, and renal pelvic cancer estimates were further adjusted for education and phenacetin-containing analgesics. A strength of this study is its adjustment for smoking; limitations included the small exposure prevalence, potential recall bias due to self-reported

exposures, and the study's lack of detailed occupational information, which prevented any assessment of intensity of exposure.

B.2.2.11.8. Mellemgaard et al. (1994)

Mellemgaard, A.; Engholm, G.; McLaughlin, J. K.; Olsen, J. H. (1994). Occupational risk factors for renal-cell carcinoma in Denmark. Scand J Work Environ Health, 20, 160-165. http://www.ncbi.nlm.nih.gov/pubmed/7973487

Summary: This study used a population-based case-control design to examine the relationship between employment in specific occupations and risk of renal cell carcinoma. Cases were selected from among the Danish Cancer Registry and consisted of men and women aged 20 to 79 years who were born and living in Denmark. Controls were chosen from the Central Population Register and matched to cases based on gender and 5-year age group. After selecting the controls, the researchers found that they failed to account for the structure of the Central Population Register and had obtained an inaccurate representation of certain regions. To address this problem, the researchers randomly removed controls from the regions that had been overrepresented and randomly selected additional controls from the regions that had been underrepresented. Of the 482 eligible cases, 368 (76%) were interviewed. Of the 500 eligible controls, 396 (79%) were interviewed.

In-person interviews were conducted by trained interviewers who inquired about occupation and occupational exposure histories, as well as demographics, smoking, medical history, and diet. Jobs were coded according to the International Standard Classification of Occupation, and industries were coded according to the International Standard Industrial Classification. Although dry cleaning was among those identified *a priori* as a high risk industry, the authors did not provide the specific code used. Exposures were assessed for jobs held at least 1 year and occurred at least 10 years prior to the interview. A total of 4 (1.1%) cases and 2 (0.5%) controls were employed in the dry-cleaning industry. Unconditional logistic regression was used to estimate odds ratios and 95% CIs for men and women separately, adjusted for age, BMI, and smoking. Strengths of the study are its population-based design and its response rate of nearly 80% for both cases and controls. A limitation to the study is its low number of exposed participants.

B.2.2.11.9. Schlehofer et al. (1995)

Schlehofer, B.; Heuer, C.; Blettner, M.; Niehoff, D.; Wahrendorf, J. (1995). Occupation, smoking and demographic factors, and renal cell carcinoma in Germany. Int J Epidemiol, 24, 51-57. http://www.ncbi.nlm.nih.gov/pubmed/7797356

Summary: This population-based case-control study examined the demographic and occupational risk factors, as well as the risk of smoking on the development of renal cell cancer in the Rhein-Neckar-Odenwald area of Germany. Cases consisted of German men and women with histologically confirmed renal cell cancer between 1898 and 1991. Of the 328 cases identified, 277 (84.5%) participated in the study. Controls were randomly selected from the population register of the Rhein-Neckar-Odenwald area and matched to cases based on age and gender. Of the 381 controls identified, 286 (75%) participated in the study.

In-person interviews were conducted by trained interviewers with both cases and controls. The majority (92%) of cases was interviewed in the hospital; all of the control interviews took place at participants' homes. Efforts were made to interview matched cases and controls within 6 months of the case's diagnosis. A standardized questionnaire was used to collect information on demographics, smoking history, occupational history, medical history, family history, physical activity, weight, and diet. Occupational information was obtained on four levels: (1) all industries in which the subject was "ever" employed, (2) occupations in which the subject was trained, (3) activities performed during employment, and (4) exposure to specific substances. An individual was assessed as "exposed" to an industry, occupation, or substance if it occurred for 5 years or more. Industries were coded, and industries, occupations, and activities were grouped into different categories. Of the 51 substances examined for possible exposure, 22 were reported by at least 5% of male subjects and subsequently analyzed. This included chlorinated solvents, which consisted of tetrachloroethylene and tetrachlorocarbonate, and contained a total of 27 cases (14.6%) and 12 (13%) controls. Female exposures were not prevalent and, therefore, not examined in this study.

Unconditional logistic regression was used to calculate odds ratios and their corresponding 95% CIs for demographics, smoking, industry/occupation, and substance exposure separately. Demographic calculations were adjusted for age and smoking; smoking was adjusted for age; industry and occupational groups were adjusted for age, gender, and smoking; and substance groups were adjusted for age and smoking. Limitations to the study include its inability to independently evaluate the impact of tetrachloroethylene versus tetrachlorocarbonate within the chlorinated solvents category and possible misclassification due to self-reported exposure. The authors do not report any strengths of their methodology.

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
British Columbia					
Band et al. (1999); MacArthur et al. (2009)	Cases: from British Columbia Cancer Registry from 1983−1990, men, ≥20 yr, histologically confirmed cancer; Controls: from all other cancer sites examined, matched to cases on age, year of diagnosis Proxy—laundry and dry cleaner Site-specific cancer incidence (prostate, lung)	25,726 eligible cases contacted, 15,463 (60%) returned questionnaire	Self-administered questionnaire: demographics, lifetime smoking habits, alcohol consumption, occupational history (lifetime job descriptions, duration and period of employment, occupation/industry titles)	Occupations/industries coded according to Canadian SOC and the Canadian SIC; launderers and dry cleaners SIC Code 972, SOC code not reported; assessed "ever" and "usual" (longest employment) occupations/industries	Various (see below)
Band et al. (1999)	Cases: prostate cancer; Controls: excluded lung cancer, cancer of unknown primary site Prostate cancer incidence	Final sample: 1,516 cases and 4,994 controls	See above Proxy respondents for 19.9%, 19.3% controls	7 (0.5) cases ever, 2 (0.1%) cases usual employment in dry-cleaning industry; control exposures not reported	Conditional logistic regression for ORs, 95% CIs for occupations/industries, adjusted for education, alcohol consumption, smoking duration

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
MacArthur et al. (2009) Evaluate occupational risks for lung cancer Case-control	Cases: lung cancer; Controls: excluded unknown primary sites Proxy—launderers and dry cleaners Lung cancer (squamous cell carcinoma, adenocarcinoma, small cell, large cell)	5,528 eligible lung cancer cases, 2,998 (54.2%) returned questionnaire	See above	10 (0.3%) cases of lung cancer in SIC Code 972 (laundries and dry cleaners)	Matched case-control analyses for maximum likelihood estimates for ORs, 90% CIs; lung cancer subtypes separately evaluated Adjustments: all lung cancers—smoking, alcohol, education, questionnaire respondent; subtypes—varied

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Band et al. (2000)	Cases: from British Columbia Cancer Registry, women <75 yr, diagnosed with breast cancer from 1988−1989, Canadian citizens, residents of British Columbia, English speaking, no prior history of breast cancer; Controls : randomly selected from 1989 from British Columbia Provincial Voters List, no history of breast cancer before 1989, matched on age Proxy—dry cleaning Breast cancer incidence	1,489 eligible cases and 1,502 eligible controls, 1,018 (68%) cases and 1,025 controls returned questionnaire Final sample: 995 cases, 1,020 controls	Self-administered questionnaire: lifetime job descriptions, duration/period employment, occupation/industry titles, demographics, smoking, alcohol consumption, current body weight, weight in late teens, age at menarche, parity, age at first birth, history of breast biopsy before 1987, family history of breast cancer, breast feeding, birth control, estrogen replacement therapy	Occupations/industries coded according to Canadian SOC and Canadian SIC; dry cleaning: SOC Code 6162 and SIC Code 9721; assessed “usual” and “ever” occupation; 12 (1.2%) cases “ever” exposed, 9 (0.9%) cases “usual” exposure to laundry and dry cleaning occupation; 23 (2.3%) cases “ever” exposed, 10 (1.0%) cases “usual” exposure to power laundries and/or dry-cleaners industry; no information on control exposure	Conditional logistic regression for ORs and 90% CIs for each occupation for each estimate of exposure, stratified by menopausal status and “ever”/“usual” occupation; premenopausal adjustment: cigarette pack years groups, breast biopsy, family history of breast cancer in mother/sisters; Postmenopausal adjustment: weights in 1986, family history of breast cancer in first degree relative, history of breast biopsy for benign breast disease, cumulative alcohol scores; all women combined: both pre- and postmenopausal covariates

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Teschke et al. (1997)	Cases: from British Columbia Cancer Agency, men and women, 19+ yr, histologically confirmed nasal cavity/sinus/urinary bladder cancer from 1990−1992, exclusions: bladder cancer cases born before 1916 and carcinoma in situ; Controls: British Columbia residents, 19+ yr, randomly selected from provincial voter list, matched to cases based on age, sex; exclusions: in prison or mental health institution Proxy—laundry personnel Nasal cavity or sinus cancer, urinary bladder cancer	54 eligible nasal cancer cases and 195 eligible nasal cancer controls, 48 (88.9%) cases and 159 (81.5%) controls interviewed 119 eligible bladder cancer cases and 173 eligible bladder cancer controls, 105 (88.2%) cases and 139 (80.3%) controls interviewed Final sample: 153 cases and 298 controls	In-person or telephone interview by nonblinded RN; proxy interviews if not an English speaker, poor memory of life events, or deceased Structured questionnaire: occupational, residential, medical, smoking, exposure histories Blinded industrial hygienist evaluated interviews and asked follow-up questions when necessary	Occupations and industries coded according to standard classifications, blindly grouped; assignment based on whether occupation or industry more likely to determine exposure; if both, occupation used; all reviewed to verify accuracy; all groups with <20 reviewed for combination with others; In total, 57 occupational groups created No case/control laundry personnel for nasal cancer; 5 cases (3.3%), 4 (1.3%) controls of laundry personnel for bladder cancer	Exact methods for summary ORs and 95% CIs; if nonoccupational risk factors found positively associated, unconditional logistic regression for ORs and 95% CIs, adjusted for risk factors; all adjusted for sex, age, smoking Latency times: 5, 10, 15, 20 yr; only 20 yr reported

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Montreal					
Siemiatyki (1991); Aronson et al. (1996); Parent et al. (2000)	Cases: from hospitals in Montreal, male residents, 35−70 yr, diagnosed with histologically confirmed cancer from 1979−1985, 97% population based case ascertainment; Controls: (1) population controls from electoral lists/random digit dialing, (2) cancer controls from all other cases	4,576 cases identified, 3,370 (81.5%) participated; response rates varied from 78−85% for cancer sites; 740 population controls, 533 (72%) participated	In-person interviews by trained interviewers Structured questionnaire: demographics, residential history, lifetime consumption cigarettes, alcohol, coffee, tea, food with carotene, height, weight Semi-structured questionnaire: detailed occupational history	Occupations/industries coded according to Canadian Classification and Dictionary of Occupations/SIC; blinded chemists, evaluated for confidence exposure occurred, frequency, concentration, 294 substances + 98 occupations + 77 industries = 469 circumstances	See below

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Siemiatyki (1991)	See above PCE exposure and proxy—launderers and dry cleaners Site-specific cancer incidence	Cancer cases: 99 esophagus, 251 stomach, 497 colon, 257 rectum, 116 pancreas, 857 lung, 449 prostate, 484 bladder, 177 kidney, 103 melanoma, and 215 lymphoma; 533 controls	See above	6 (1.2%) colon, 7 (0.8%) lung, 9 (2.0%) prostate cases ever exposed to PCE; 4 (1.6%) stomach, 5 (1.0%) colon, 5 (2.0%) rectum, 12 (1.4%) lung, 9 (2.0%) prostate, 10 (5.6%) kidney, 3 (2.9%) skin melanoma, 3 (1.4%) non-Hodgkin lymphoma cases "ever" employed as launderers or dry cleaners	Mantel-Haenszel for ORs, 90% CIs for "ever"/"substantial" exposure; all adjusted for age, family income, cigarette index; stomach cancer also adjusted for birthplace; colon/rectum cancers also adjusted for ethnic origin, beer index; lung cancer also adjusted for ethnic origin, alcohol index, respondent; prostate cancer also adjusted for ethnic origin, Quetelet index, respondent;
Siemiatyki (1991) (continued)					kidney cancer and skin melanoma also adjusted for ethnic origin

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Aronson et al. (1996)	Cases: prostate cancer; Cancer controls: lung cancer excluded PCE exposure Prostate cancer incidence	557 prostate cancer cases, 449 (81%) participated Final sampled: 449 cases, 1,550 cancer controls, 533 population controls	See above	55 (27 substances, 11 industries and 17 occupations) of 469 occupational circumstances; PCE exposure classified as unexposed, nonsubstantial, or substantial (8 subjects with substantial exposure)	Unconditional logistic regress for ORs, 95% CIs for exposures; partially adjusted models controlled for age, ethnicity, socioeconomic status, Quetelet index, respondent status; fully adjusted models also controlled for core substances with ≥30 exposed cases; control groups pooled
Parent et al. (2000)	Cases: renal cell cancer; Controls: (1) population controls from electoral lists/random digit dialing, (2) cancer controls from all other cases Proxy—laundry and dry cleaners Renal cell cancer incidence	227 eligible cases, 177 (78%) participated, 142 renal cell carcinoma; 1,900 cancer controls with 78% participation rate Final sample: 142 cases, 1,900 cancer controls, 533 population controls	See above	4 cases (2.8%) ever employed in laundry/dry-cleaning industry, <4 cases exposed >10 yr and data not reported	Unconditional logistic regression for ORs, 95% CIs for each occupation/industry, stratified by exposure and duration exposure >10 yr, adjusted for respondent status, age, smoking, BMI

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Massachusetts (Cape Cod)					
Aschengrau et al. (1993) (1998); Paulu et al. (1999, 2002)	Cases: permanent residents of 5 Upper Cape Cod towns, diagnosed with cancer from 1983−1986, from Massachusetts Cancer Registry; Controls: (1) living <65 yr—random digit dialing, (2) living ≥65 yr—randomly from Health Care Finance Administration lists, (3) deceased—randomly from Massachusetts Department of Vital Statistics file; method: (1) cancer site stratified by age, vital status, year of death, gender (Aschengrau et al., 1993), (2) all controls in stratum with 1+ case chosen; exclusions: moved after index year, incomplete residential histories, no PCE data Proxy—residence near contaminated water	Controls: 2,236 controls <65 yr, 249 (11.1%) eligible/contacted, 184 (73.9%) interviewed; 611 controls ≥65 yr, 537 (87.9%) eligible/contacted, 464 (86.4%) interviewed; 918 deceased controls, 794 (86.5%) eligible/ ascertained, 723 (91.1%) interviewed via proxy respondent	In-person (14%) and telephone (86%) interviews by trained interviewers Questionnaire: 40-year residential history, demographics, smoking, medical and occupational histories and exposures, bottled water consumption, usual bathing habits	Various (see below)	Various (see below)

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Aschengrau et al. (1993)	Cases: men/women, all ages, diagnosed with bladder cancer, kidney cancer, or leukemia PCE in drinking water: Estimated quantity delivered to residence Site-specific cancer incidence: Bladder cancer, kidney cancer, leukemia	79 bladder cases, 72 (91.1%) eligible and contacted, 63 (87.5%) interviewed; 42 kidney cases, 36 (85.7%) eligible and contacted, 35 (97.2%) interviewed; 44 leukemia cases, 38 (90.5%) eligible and contacted, 35 (92.1%) interviewed Final sample: 61 bladder cancer cases, 852 bladder cancer controls, 35 kidney cancer cases, 777 kidney cancer controls, 34 leukemia cases, 737 leukemia controls	See above	Industries/job titles coded according to standard industrial (1987) occupational (1990) classifications; exposure based on industry, job titles, percentage reporting occupational exposure to solvents including PCE # (%) with any exposure to PCE in drinking water: 34.4% bladder cases, 26.2% bladder controls, 25.7% kidney cases, 25.2% kidney controls, 35.3% leukemia cases, 25.3% leukemia controls Water exposure (Relative Delivered Dose) via Webler and Brown (1993) algorithm, based on leaching model by Demond (1982); blinded assessments; 13 (21.3%) bladder cases, 127 (4.9%) bladder controls, 6 (17.1%) kidney cases, 112 (14.4%) kidney controls, 7 (20.6%) leukemia cases, 94 (12.8%) leukemia controls without latency period	Unadjusted OR for sites with 2+ exposed cases; Fisher exact test for 95% CIs. Analyses with and without latency periods (15 yr: bladder/kidney cancers, 5 yr: leukemia); stratified by bottled water, bathing habits; multiple logistic regression for ORs adjusted for sex, age at diagnosis/index year, vital status at interview, education, job exposures; other confounders if in 3+ cases; maximum likelihood estimates of standard errors for 95% CIs

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Aschengrau et al. (1998)	Cases: women of all ages, diagnosed with incident breast cancer PCE in drinking water: Estimated quantity delivered to residence Breast cancer incidence	334 cases, 295 (88.3%) eligible and contacted. Of these, 265 (89.8%) were interviewed. 2,236 population controls identified by random digit dialing, vital records for deceased controls, and HCFA records if >65 yr. There were 763 controls identified through the two-step control selection process After employing the additional exclusion criteria, the final sample consisted of 258 cases and 686 controls	See above	Water exposure (RDD) via Webler and Brown (1993) algorithm, based on a leaching model by Demond (1982); blinded assessments RDD categorized into low ($\leq 50^{th}$ percentile cumulative exposure), $>50^{th}$, $>75^{th}$, and $>90^{th}$ percentiles 36 (14%) exposed cases, 81 (11.8%) exposed controls without latency period	Unadjusted ORs, 95%CIs for crude associations/modifiers; multiple logistic regression for ORs adjusted for age at diagnosis or index year, vital status at interview, family history of breast cancer, age at first live birth or stillbirth, personal history of prior breast cancer and benign breast disease, occupational exposure to solvents; maximum likelihood estimates of the standard errors for 95% CIs; latency periods of 5, 7, 9, 11, 13, and 15 yr

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Paulu et al. (1999)	Cases: diagnosed with colon-rectum cancer, lung cancer, brain cancer, pancreatic cancer between 1983 and 1986 PCE in drinking water: Estimated quantity delivered to residence Site-specific cancer incidence	420 colon-rectum, 326 lung, 42 brain, and 43 pancreatic cancer cases selected; 366 (87.1%) colon-rectum, 272 (83.4%) lung, 40 (95.2%) brain, and 39 (90.7%) pancreatic cancer cases were contacted and eligible. Of these, 326 (89.1%) colon-rectum, 252 (92.6%) lung, 37 (88.1%) brain, and 37 (86.1%) pancreatic cancer cases were interviewed for an overall participation rate of 79% Final sample: 311 colon-rectum cancer cases, 1,158 colon-rectum cancer controls, 243 lung cancer cases, 1,206 lung cancer controls,	See above	# (%) with any exposure to PCE in drinking water: Excluding any latent periods: 44 (14.1%) colon-rectum cancer cases and 153 (13.2%) controls; 33 (13.6%) lung cancer cases and 158 (13.1%) controls; 3 (8.3%) brain cancer cases and 92 (13.1%) controls; 3 (8.3%) pancreatic cancer cases and 81 (13.0%) controls	Unadjusted ORs, 95% CIs for brain/pancreatic cancer. Multiple logistic regression for ORs, 95% CIs for colon-rectum/lung-cancer, adjusted for age at diagnosis or index year, vital status at interview, sex, occupational exposure to PCE and other solvents. Colon-rectum cancer further adjusted for history of polyps, inflammatory bowel disease, occupational history associated with colon-rectum cancer. Lung cancer further adjusted for usual number of cigarettes smoked and history of cigar/pipe use, living with a smoker, occupational history associated with lung cancer. Latency periods: 0, 5, 7, 9, 11, 13, and 15 yr

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Paulu et al. (1999)(continued)		36 brain cancer cases, 703 brain cancer controls, 36 pancreatic cancer cases, 622 pancreatic cancer controls; overall participation rate: 79%			
Paulu et al. (2002)	Cases: women diagnosed with breast cancer PCE in drinking water: GIS analysis Breast cancer incidence	334 cases, 295 (88.3%) eligible/contacted, 265 (89.8%) interviewed Final sample: 258 cases and 686 controls	40 year residential history during interview included full addresses and calendar years of residence; if complete address unknown, tax assessors' books used to identify	All participants blindly mapped onto U.S. Geological Survey map, later converted into digital format; Upper Cape Cod area divided into subregions in 2 ways: (1) fixed, multiscale grids, coding each participant as exposed or unexposed for each grid cell, (2) overlapping circles (adaptive k-smoothing) with sizes based on number of nearby cases/controls	Crude and adjusted ORs for both grid and k-smoothed methods, using map choropleths for visualization Multiple logistic regression for OR, adjusted for age, parity, vital status, family history of breast cancer in a first-degree female relative, age at first live birth or stillbirth, prior history of breast cancer or benign breast disease

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Aschengrau et al. (2003); Viera et al. (2005)	Follow-up to Aschengrau et al., 1998; permanent residents of 8 Cape Cod Towns from 1987−1993; Cases: women diagnosed with breast cancer from 1987−1993; identified via Massachusetts Cancer Registry; Controls: (1) random-digit dialing (≤64 yr); (2) random selection from a Medicare beneficiary roster (≥65 yr), (3) random selection from roster of deceased residents; Controls matched to cases based on age, vital status PCE in drinking water: Estimated quantity delivered to residence Breast cancer incidence	Various (see below)	Structured interviews: demographics, age at diagnosis, family history of breast cancer, personal history of prior breast cancer, age at first live birth/stillbirth, occupational exposure to PCE, etc., bathing habits, bottled water, and water filter use, 40-year residential history; proxy interviews with 211 (31.4%) cases, 192 (31.2%) controls	Various (see below)	Various (see below)

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Aschengrau et al. (2003)	See above	672 cases (81% selected and eligible cases) and 616 controls (157 [83%] random-digit dialed, 301 [76%] of Medicare roster, and 158 [79%] deceased) were included in the analysis	See above	RDD of PCE estimated using Webler and Brown's (1993) algorithm, which was based on PCE leaching model by Demond (1982); algorithm accounted for water flow, pipe characteristics for each home, inputs determined using maps; exposure assessed; estimates categorized as "never exposed" (private wells) and "ever exposed," with "ever" as low ($\leq 50^{th}$percentile) or high ($>50^{th}$, $>75^{th}$, and $>99^{th}$ percentiles)	EOR and 95% CIs for crude associations. Multiple logistic regression for ORs, adjusted for age at diagnosis or index year, vital status at interview, family history of breast cancer, personal history of breast cancer, age at first live birth or stillbirth, occupational exposure to PCE; maximum likelihood estimates of standard error were for 95% CIs Latent periods: 0, 5, 7, 9, 11, 13, 15, 17, 19 yr
Viera et al. (2005)	See above. Also, proxy interviews excluded from analyses, compared with results from total sample; Data not collected in interviews (inhalation rate, water flow rate, and air exchange rate) from literature	Full sample: 672 cases, 616 controls Nonproxy sample: 461 cases, 424 controls	Nonproxy information obtained via interviews: daily number of glasses of tap water or drinks with tap water, bottled water consumption, temperature, frequency, duration of showers/baths	Dose model estimated PDD (inhalation + dermal + ingestion for each exposed residence); inhalation: reported temperature, frequency, duration of baths/showers, and amount of PCE in bath/shower air; dermal: estimated according to Fick's first law, height and weight data to calculate surface area; ingestion: volume of tap water participant drank	Adjusted analyses limited to those with 3+ exposed cases and 3+ exposed controls Multiple logistic regression for ORs, adjusted for age at diagnosis/index year, family history of breast cancer, personal history of breast cancer, age at first live birth/stillbirth, occupational exposure to PCE;

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Viera et al, (2005)(continued)				RDD reestimated for nonproxy participants only, and both RDD and PDD were used to classify into nested exposure levels: $\leq 50^{th}$ percentile, $>50^{th}$, $>75^{th}$, and $>90^{th}$ percentiles. Without latency, full sample: 155 (23.1%) exposed cases, 136 (22.1%) exposed controls, nonproxy sample: 101 (21.9%) exposed cases, 88 (20.8%) exposed controls	Maximum likelihood estimates standard errors for 95% CIs; goodness-of-fit test compared RDD and PDD; nonparametric rank test evaluated whether RDD and PDD exposures differed significantly Latency periods: 0, 5, 7, 9, 11, 13, 15, 17, and 19 yr
New Zealand					
Corbin et al. (2011); Dryson et al. (2008); 't Mannetje et al, (2008); McLean et al. (2009)	Cases: From New Zealand Cancer Registry from 2003−2004 or 2007−2008 (Corbin et al., in press), men and women, 25−70 yr, diagnosed with bladder cancer or non-Hodgkin lymphoma; Controls: randomly chosen from 2003 electoral roll, matched to cases on age Proxy—occupation in textile bleaching, dyeing and cleaning machine operators (all four studies, and dry cleaners and launderers (Corbin et al., in press)	1,200 potential controls, 1,100 valid addresses, 660 contacted and eligible, 473 interviewed for response rate of 48% Final sample: 471 controls	In-person interviews with trained interviewer (occupational health nursing background) Questionnaire: demographics, smoking, occupational history, detailed information on all jobs lasting >1 year.	Jobs blindly coded according to 1999 New Zealand Standard Classification of Occupations and Australian/New Zealand SIC; textile bleaching, dyeing, cleaning machine operators: occupation Code 8264, *a priori* high risk	Unconditional logistic regression for ORs and 95% CIs for occupations/industries considered *a priori* and *a posteriori* to be high risk, adjusted for 5-year age group, sex, smoking, Maori ethnicity, occupational status; Semi-Bayes adjustments to minimize risk of false positives due to multiple comparisons

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Corbin et al. (2011) Identify occupations that may contribute to the risk of lung cancer in the New Zealand population Case-control	See above Lung cancer incidence	Of 1,057 cases, 744 eligible, 458 interviewed. Controls identified from 2003−2008; Of 2,000 potential controls, 1,878 with valid addresses, 1,134 replied, 796 interviewed. Excluding ineligible, case response rate: 53% control response rate 48% Final sample: 457 cases, 792 controls	See above	20 (0.2%) cases, 13 (1.6%) controls reported employment as bleaching, dyeing, cleaning machine operators; 3 cases (0.7%), 4 controls (0.5%) identified as dry cleaner; 9 cases (2.0%), 5 controls (0.6%) identified as launderer	See above

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Dryson et al. (2008)	See above Bladder cancer incidence	Of 358 cases, 232 eligible, 213 interviewed. Of 1,200 controls, 660 eligible, 473 interviewed. Excluding ineligible, case response rate: 64% Final sample: 213 cases, 471 controls	See above	3 (1.4%) cases, 10 (2.1%) controls reported employment as bleaching, dyeing, cleaning machine operators	See above
’t Mannetje et al. (2008)	See above Non-Hodgkin lymphoma incidence	533 cases, 335 contacted/eligible, 291 interviewed for response rate of 69% Final sample: 291 cases, 471 controls	See above	5 (1.7%) cases, 10 (2.1%) controls reported employment as bleaching, dyeing, cleaning machine operators	See above

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
McLean et al. (2009)	See above Leukemia incidence (chronic lymphocytic leukemia, AML, chronic myeloid leukemia, acute lymphoblastic leukemia, and other forms of leukemia)	391 eligible cases, 225 (57%) participated; 11 (3.7%) proxy with next of kin; 988 eligible controls, 660 contacted, 473 (48%) participated	In-person interviews by trained interviewers with background in occupational health nursing Questionnaire: demographics, smoking, detailed occupational history	All occupations coded according to New Zealand Standard Classification of Occupations; textile, bleaching, dyeing, cleaning machine: Code 8264 designated *a priori* as high risk 6 (2.7%) cases and 10 (1.0%) controls were in textile, bleaching, dyeing, cleaning machine occupation	Unconditional logistic regression for ORs and 95% CIs for "ever" vs. "never" occupation, adjusted for age, gender, smoking; Semi-Bayes adjustments to assess the impact of multiple comparisons
McCredie et al. (1993)	Cases: New South Wales residents, 20 to 79 yr, identified from hospitals and physicians, who were diagnosed with renal cell or renal pelvic cancer between 1989 and 1990, needed to be registered in the current electoral roll, have a telephone number, speak English; Controls: random sample of electoral rolls	744 eligible renal cell cancer cases and 200 eligible renal pelvic cancer cases, 503 (68%) and 149 (75%) interviewed, respectively; 725 eligible controls, 74% participated in interview	In-person (327 cases, 232 controls), telephone (309 cases, 291 controls), self-administered (16 cases, 12 controls) Questionnaire: occupations, industries, chemical exposures, demographics	Exposures quantified in textiles based on distribution in control group, though not provided for PCE or the dry-cleaning industry 16 (3.3%) renal cell cases, 8 (5.4%) renal pelvis cases, 7 (1.3%) controls reported employment in dry-cleaning industry	Logistic regression for RRs and 95% CIs; renal cell cancer adjusted for age, sex, method of interview, smoking, BMI; renal pelvis cancer adjusted for age, sex, method of interview, smoking, education, phenacetin-containing analgesics
McCredie et al. (1993) (continued)	Proxy—dry cleaning Renal cell carcinoma and renal pelvic carcinoma incidence	Final sample: 489 renal cell carcinoma, 147 renal pelvic cancer, 523 controls			
Germany					

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Pesch et al. (2000a; 2000b)	5 regions in Germany; Cases via hospitals, 1991−1995, German men/women with histologically confirmed urothelial or renal cell cancer within the 6 mo of study start; Controls: randomly selected via local residency registries, matched on age, sex, region; cases and controls required to be German nationals; no age limits JEM/JTEM for PCE Site-specific cancer incidence	Response rates: 84% cases, 71% controls Final sample: 1,970 cases (1,035 urothelial cancer, 935 renal cell cancer) and 4,298 controls	In-person with trained interviewers; cases: hospital within 6 mo diagnosis; controls: home Structured questionnaire: demographics, lifestyle, occupational exposures	Jobs held 1+ yr coded according to ISCO; based on self-reported occupational history, exposure to specific agents during tasks, average amount of time exposed daily (1) Lifetime exposure: total number of years spent at job title; weighted sum of years spent at task or exposed to specific agent; (2) JEM based on job title; (3) JTEM adjusted for region and time; JEM/JTEM evaluated probability, intensity of exposure	Conditional logistic regression for ORs and 95% CIs Adjusted for age, study center, smoking
Pesch et al. (2000a)	See above JEM/JTEM for PCE Urothelial cancer incidence	1,035 urothelial cancer cases, 4,298 controls	See above	PCE by JEM: 183 (17.7%) cases with “medium,” 188 (18.2%) cases with “high,” 74 (7.1%) cases with “substantial” exposure PCE by JTEM: 37 (3.6%) cases with “medium,” 47 (4.5%) cases with “high,” and 22 cases with “substantial” exposure	See above

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Pesch et al. (2000a; 2000b)	See above JEM/JTEM for PCE Renal cell cancer incidence	935 renal cell cancer cases, 4,298 controls	See above	PCE by JEM: 166 (17.8%) cases with "medium," 138 (14.8%) cases with "high," 54 (5.8%) cases with "substantial" exposure PCE by JTEM: 52 (5.6%) cases with "medium" 45 (4.8%) with "high," 18 (1.9%) with "substantial" exposure	See above

Table B-2. Summaries of characteristics of case-control studies: multiple cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Nordic Countries					
Lynge et al. (2006)	Nested case-control study Non-Hodgkin lymphoma, esophageal, gastric cardia, liver, pancreatic, cervix uteri, kidney, and bladder incident cancer cases in cohort of 46,768 individuals with occupational code "laundry and dry-cleaning worker" or industry code "laundry and dry cleaning" in 1970 Censuses in Denmark, Finland, Norway, Sweden. Cases: from 1970 (Denmark) or 1971 (Finland, Norway, Sweden) through 1997 to 2001; ascertained from mortality and cancer registries. Controls: randomly selected from cohort, matched based on country, sex, 5-year age group, 5-year calendar period at the time of diagnosis (1:3 matching except 1:6 for esophageal cancer cases) Proxy—dry cleaner	4,014 records—1,616 cases, 2,398 controls, 131 subjects were both cases and controls. Participation rates: 57% cases, 64% controls in Norway, 63% cases, 60% controls in Sweden	In Denmark and Finland, occupational task identified on the 1970 Census form. For subjects from Norway and Sweden, a blinded telephone interview was undertaken, as 1970 Census forms were unavailable. The questionnaire asked about occupational task for job title reported on the 1970 Census form, and if dry cleaning, questions sought answers on employment length, number of employees, solvents used, and personal habits of smoking and alcohol consumption. Proxy interviews: 76% cases (Norway, 72%; Sweden, 77%), 40% controls (Norway, 42%; Sweden, 39%)	Occupational classification: (1) dry-cleaners or other workers in dry-cleaning shops with <10 workers, assumed to have high-exposure potential as dry cleaners because of the shared work tasks and physical proximity in small dry-cleaning shops; (2) other workers in dry-cleaning shops; (3) unexposed laundry workers and other persons in dry cleaning, and (4) unclassifiable, a category for subjects with missing employment information 695 cases and controls were dry cleaners, 183 were exposed through other work in a dry-cleaning shop, 716 were unclassifiable	Logistic regression for RRs and corresponding 95% CIs, adjusted for matching criteria plus smoking and alcohol use for Swedish and Norwegian cohorts only All analyses were conducted at the level of the record rather than person because a subject may have appeared as a case or as a control in the study more than once

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Bladder cancer					
Burns and Swanson (1991); Swanson and Burns (1995)	Cases: Histologically confirmed urinary bladder cancer cases in men and women, aged 40−84 yr, identified from MDCSS, 1984−1991 Controls: Histologically confirmed colon and rectal cancer cases in men and women, 1984−1991, aged 40−84 yr, identified from MDCSS Proxy—dry cleaning Bladder cancer incidence	2,160 bladder cancer cases interviewed (94%); 3,979 cancer controls (95%)	Telephone interview Questionnaire for lifetime occupational history, lifetime smoking history, medical history, residential history, demographic information Proxy respondents: 25% of cases series; 27.6% of control series	1980 U.S. Census Bureau classification to Code 3-digit level job title and industry; dry-cleaning worker occupation and dry-cleaning and laundry industry 8 cases and 14 controls identified as dry-cleaning workers (0.4% prevalence cases, 0.4% prevalence controls) and 15 cases and 27 controls identified as working in dry cleaners and laundries (0.6% prevalence cases, 0.6% prevalence controls)	Unconditional logistic regression for ORs and 95% CI, adjusted for cigarette smoking, race, gender, and age at diagnosis
Colt et al. (2004)	Cases: Primary bladder cancer cases, diagnosed 1994−1998, in men and women, aged 25−74 yr, identified from New Hampshire Cancer Registry Controls: population controls identified with driver's licenses, if <65 yr age, or from state Medicare and Medicaid roles, if ≥65 yr. Controls series from previous melanoma study (1993−1995) with additional controls identified using same process for period 1995−1997	459 bladder cancer cases interviewed of 618 eligible cases (74%); 665 interviews among 990 eligible controls (67%)	In-person interview Questionnaire for sociodemographic information, tobacco use, medical history, work history since age 15 No proxy interviews	SOC Manual used to code to 2-, 3-, and 4-digit level job title; dry-cleaner and laundry workers, Codes 7657, 7658 5 cases and 5 controls identified as dry-cleaner/laundry worker. Exposure prevalence—cases (1%), controls (0.08%)	Unconditional logistic regression for ORs and 95% CIs, adjusted for 5-year age group and smoking

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Colt et al. (2004) (continued)	Proxy—dry-cleaner/laundry worker Bladder cancer incidence				
Colt et al. (2011)	Cases: Primary bladder cancer cases, diagnosed 2001−2004 (Maine, Vermont) or 2002−2004 (New Hampshire), in men and women, aged 30−79 yr, identified from rapid patient ascertainment systems; Controls: population controls identified with driver's licenses, if <65 yr age, or from state Medicare and Medicaid roles, if ≥65 yr. Controls: series from previous study, and frequency matched to cases by state, sex, and diagnosis age or control selection	1,170 cases (65% participation rate), 1,418 controls (65% participation rate). 1,158 cases and 1,402 controls completed interview	Mailed questionnaire with follow-up, in-person visit to administer a computer-assisted questionnaire for information on all jobs held since age 16 yr, demographic information, tobacco use, and other exposures. For certain occupations, a job-specific questionnaire used for information on exposures of interest	Proxy—ever employed as textile, apparel and furnishings machine operator, or tender (SOC Code, 765) for >6 mo (males, 46 exposed cases, 5%; females, 27 exposed cases, 10%), of which 6 cases were laundering and dry-cleaning machine operators and tenders (SOC Code, 7658) (0.5%) or in laundry, cleaning, and garment services (SIC Code, 721), 24 exposed cases (males, 14 cases, 13%; females, 10 cases, 3%) Each job coded blinded to case or control status to the 1980 SOC and the 1987 SIC scheme	Unconditional logistic regression for males and females separately, adjusted for age, race, Hispanic ethnicity, state, smoking status, and employment in high-risk occupation. Other analyses examined duration of employment, exposure-response using test of linear trend, year of first employment, and potential for interaction between occupation and smoking

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Gaertner et al. (2004)	Cases: from 7 Canadian province cancer registries, men and women, 20−74 yr, histologically confirmed, 1974−1997 Controls: population controls recruited through random digit dialing (2 provinces) or identified from provincial health insurance plan database (5 provinces) Proxy—dry cleaner Bladder cancer incidence	1,499 cases, 887 completed questionnaire (59% response rate); 4,604 controls, 2,847 completed questionnaire (62% response rate)	Mailed questionnaire with telephone follow-up when necessary; questionnaire sought socio-demographic information, occupation history (up to 12 occupations), smoking, specific agent exposures and dietary habits	Proxy—ever employed as dry cleaner for >1 year Up to 12 occupations categorized into SOC codes with employment duration calculated from time period reported for each occupational activity over subject's lifetime; dry cleaner was a suspect occupation Questionnaire sought information on individual agents, if >1 yr exposure 4 (0.7%) male and no female cases were reported with dry cleaner job title	Unconditional logistic regression for males and females, separately, adjusted for age, province, race, smoking, ex-smoking, consumption of fruit, fried food, and coffee, and ever employed in 8 other suspect occupations
Kogevinas et al. (2003)	Pooled data from 11 previous European case-control studies from 1976−1996; cases and controls aged 30−79 yr, cases excluded if interview occurred >2 yr after diagnosis; 3 studies used population controls; 1 used hospital/population controls; 7 used hospital controls; controls matched to cases on 5-year age group, geographic area. Proxy—launderers, dry cleaners, pressers Bladder cancer incidence	4,101 cases in pooled dataset, 3,346 (81.6%) met inclusion criteria; 7,365 controls in pooled dataset, 6,840 (92.9%) met inclusion criteria	None reported	All data coded according to ISCO-68 standards; launderers, dry cleaners, pressers: Code 56 19 (0.6%) cases and 30 (0.4%) controls were launderers, dry cleaners, or pressers	Unconditional logistic regression for ORs and 95% CIs, adjusted for 5-year age group, smoking, study center; interaction between age and study center found significant and included in models; attributable risk for occupations identified *a priori* as high risk calculated, did not include launderers, dry cleaners, pressers

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Reulen et al. (2007)	Cases: from Limburg Cancer Registry, men and women, 40−96 yr, diagnosed with histologically confirmed transitional cell carcinoma of the bladder from 1996−2004; Controls: Caucasian men and women, 50+ yr, no previous history of bladder cancer, randomly selected from general population of Limburg through simple random sampling Proxy—domestic helpers, cleaners, launderers Bladder cancer incidence	2,230 eligible cases, 202 (9.1%) participated in the study; 390 controls (response rate: 26%)	In-person interviews by 3 trained interviewers in homes Structured questionnaire: sociodemographics, lifetime smoking, lifetime occupational history of all jobs lasting 6+ mo	All occupations blindly coded according to ISCO; domestic helpers, cleaners, and launderers: Code 913 14 (6.9%) cases, 20 (5.1%) controls were domestic helpers, cleaners, launderers	Unconditional logistic regression for ORs and 95% CIs, adjusted for age, sex, current smoking status, years of cigarette smoking, number of cigarettes smoked per day, education; interaction term of sex and occupation also included in model; only occupations with 15+ participants reported
Schoenberg et al. (1984a)	Cases: men, 21−84 yr, diagnosed with histologically confirmed urinary bladder cancer from 1978−1979 in New Jersey, a rapid reporting location; Controls: (1) 21−64 yr random digit dialed, (2) ≥65 yr from stratified random sample of Health Care Finance Administration lists, matched to cases on age, sex Proxy—dry-cleaner/laundry worker Bladder cancer incidence	787 eligible cases, 706 (90%) participated in study; 1,608 eligible controls, 1,392 (87%) participated in study Analysis restricted to 658 Caucasian male cases and 1,258 Caucasian male controls	In-person interviews using structured questionnaire that sought information on demographic, personal and occupational history (all jobs held ≥6 mo and self-reported list of exposures)	All occupations coded to 1970 Census Index System with 19 *a priori* employment categories, including dry-cleaning and laundering (proxy exposure) 7 cases (1.1%) and 10 controls (0.8%) identified employment in dry cleaning or laundry	Logistic regression for ORs and 95% CIs, adjusted for age and cigarette smoking duration

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Smith et al. (1985); Silverman et al. (1989a; 1989b)	Data from National Bladder Cancer Study (Hartage et al., 1984), Cases: men, 21−84 yr, diagnosed with histologically confirmed urinary bladder cancer from 1977−1978 in 9 SEER reporting locations and 1 rapid reporting location; Controls: (1) 21−64 yr random digit dialed, (2) ≥65 yr from stratified random sample of Health Care Finance Administration lists, matched to cases on age, sex Proxy—laundry, dry cleaning occupation Bladder cancer incidence	Overall study response rates: 75% cases, 84% controls <65 yr, 83% controls 65+ yr	In-person interviews by trained interviewer within 3 mo of diagnosis Structured questionnaire: artificial sweeteners, smoking, coffee consumption, medical history, occupational history for all jobs ≥6 mo from age 12 yr onwards	Occupations/industries coded according to U.S. Census Bureau indices	Various (see below)
Smith et al. (1985)	Cases: transitional or squamous cell carcinoma of urinary bladder	Total: 7,748 # cases and controls not reported	See above	Exposure categories: (1) employed ≥6 mo as laundry or dry-cleaning operative; (2) chemicals in other occupations or industries; (3) unexposed; Duration of exposure: total number of years in profession; Exposed by category: 1: 103 subjects, 2: 5,776 subjects, 3: 1,869 subjects	Logistic regression for RRs of occupational exposure, adjusted for age, sex, and duration of exposure, adjusted for age, sex, smoking

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Silverman et al. (1989a; 1989b)	Cases and controls: non-Caucasian men	Final sample: 126 cases, 383 controls	See above	Occupations grouped by potential to have similar exposures; dry cleaners, ironers, pressers: 11 (8.7%) cases, 12 (3.1%) controls	Maximum likelihood method for OR; Gart's interval estimation procedure for 95% CIs; Mantel-Haenszel for tests of trend; Whittemore (1983) for PARs, 95% CIs All adjusted for smoking; dry cleaners adjusted for smoking, high risk occupation; PAR adjusted for age, geographic area, smoking
Steineck et al. (1990)	Cases: men, born 1911−1945 and residing in a county of Stockholm 1985−1987, source not identified in published paper Controls: population controls randomly sampled at 4 periods from population registers between 1985 and 1987 Proxy—dry-cleaning worker Bladder cancer incidence	254 cases, 287 controls Response rates: 80% cases, 79% controls	Interview method not identified in published paper. Structured questionnaire for information on occupational history and smoking	Self-reported occupational title 2 (0.8%) cases, 2 (0.7%) controls were dry cleaners or worked in dry-cleaning industry	

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Zheng et al. (2002)	Cases: histologically confirmed incident bladder cancer cases, 1986−1989, 40−85 yr, Iowa State Health Registry Controls: population controls frequency-matched (1.7:1) by sex and age and randomly selected from state driver's license records for subject <65 yr age or from HFCA records if ≥65 yr age Proxy—dry-cleaner/laundry worker Bladder cancer incidence	1,452 cases, 2,434 controls Response rates: 85% cases, 82% controls <65 yr, and 80% for controls ≥65 yr	Mailed and telephone interviews with structured questionnaire for information on each job held ≥5 yr, demographic factors, residence, smoking, past medical history, first-degree family history of bladder cancer, and other potential risk factors Proxy respondents for 156 cases (11%) and all controls	Self-reported occupation title and industry coded to SIC and SOC Proxy—laundering and dry cleaning occupation, SOC Code 7658 Employment duration: 10 yr, ≥10 yr	Unconditional logistic regression for ORs, 95% CIs and adjusted for age, lifetime pack-years of cigarette smoking, and having a first-degree relative with bladder cancer. Other variables such as education, frequency of strenuous or moderate exercise, duration of living in a residence served by chlorinated surface water, population size of places of residence, and other cancer in a first-degree relative did not result in material change in association and was not included in final statistical model

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Brain Cancer					
Heineman et al. (1994)	From death certificates in New Jersey, Pennsylvania; cases: Caucasian men, died from brain/other CNS tumors from 1978−1980, exclusions: no hospital diagnosis; Controls: Caucasian men, died from other causes, exclusions: death associated with occupation, epilepsy, suicide, homicide, cerebrovascular diseases, matched to cases based on age, year of death, location JEM for PCE Brain cancer mortality	741 cases, 654 (88%) contacted, 483 (74%) interviewed; 741 controls, 612 (83%) contacted, 386 (63%) interviewed Final sample: 300 cases, 320 controls	Blinded interviews with next of kin by trained interviewers Questionnaire: brain cancer risk factors, occupations held from age 15 yr onward (job title, tasks, company name and location, industry, products, employment dates, hours worked)	Occupations/industries coded according to U.S. standards; all codes assigned *a priori* estimates of probability and intensity of exposure; JEM by Gomez et al., 1994 to estimate exposures to PCE 111 (37%) cases, 106 (33.1%) controls “ever” exposed to PCE	Maximum likelihood estimates for ORs, 95% CIs using Gart (1970); Linear trends using Mantel (1963) Lag time of 10, 20 yr

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Breast cancer					
Peplonska et al. (2007)	Cases: hospital cases newly diagnosed histologically confirmed in situ or invasive breast cancers residents of Warsaw and Lódź, between 20−74 yr of age, 2000−2003; Controls: population controls identified from the Polish Electronic System of Population Evidence and matched to cases by city of residence and age within 5-year age groups. Proxy—laundry, cleaning, and garment services industry Breast cancer incidence	2,275 cases (79% response rate), 2,424 controls (66% response rate)	In-person interview with cases and controls by trained interviewer Questionnaire: known and suspected risk factors for breast cancer, reproductive history, occupations held ≥6 mo	Occupation/industry coded to SIC/SOC Manuals 28 (1%) cases and 32 (1%) controls worked in laundry, dry cleaning, and garment services industry	Unconditional logistic regression for ORs and 95% CIs adjusted for age, age at menarche, age at menopause, number of full-term births, breast cancer in first degree relative, education, and city of residence
Colon cancer					
Fredriksson et al. (1989)	All: alive at time of study, medically able to participate; Cases: from Swedish Cancer Registry, men and women, 30−75 yr, diagnosed with large bowel adenocarcinoma from 1980−1983; Controls: from National Population Register, matched to cases based on county of residence, sex, age Proxy—dry cleaning Colon cancer incidence	402 cases, 329 contacted/eligible, 312 (94.8%) participated; 717 controls, 658 contacted/eligible, 623 (94.6%) participated	Mailed questionnaire: occupational history, occupational exposures, food and drinking habits, previous diseases, drug intake	Occupational exposures assessed by 2 physicians and 1 hygienist as high grade, low grade 5 (1.6%) female cases, 5 (0.8%) female controls reported employment in dry cleaning	Mantel-Haenszel for ORs, Miettinen (1976) for 95% CIs for all occupations, stratified by age, physical activity

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Liver cancer					
Hernberg et al. (1988)	Cases: men and women, diagnosed with primary liver cancer reported to the Finnish Cancer Register in 1976−1978 and 1981; Controls: (1) randomly selected stomach cancer patients reported to Finnish Cancer Register in 1977; (2) patients whose hospital autopsy records noted death in 1977 due to coronary infarction; Coronary infarction controls matched to cases based on sex, age, and hospital of diagnosis; matching criteria for stomach cancer controls not reported in paper; cases excluded if no confirmed diagnosis Proxy—dry cleaning Liver cancer incidence	618 eligible cases, 526 contacted, 377 (71.7%) responded; 772 eligible stomach cancer controls, 654 contacted, 476 (72.8%) responded; 674 eligible coronary infarction controls, 558 contacted, 385 (69.0%) responded Final sample 344 cases, 861 controls	Mailed questionnaire: occupational history (employers, work sites, jobs held, and calendar years of work), alcohol, tobacco, coffee, tea, medicines, leisure activities, and for women, history of oral contraceptive use	2 occupational hygienists blindly assessed exposure, based on industries, workplaces, job titles; exposures not determined. Followed up with phone calls to workplace or proxy respondent; exposure classified as "heavy," "moderate," "light"; Dry-cleaning exposures based on 1950 records by Finnish Institute of Occupational Health, which noted PCE exposure ranged from 34−600 ppm during that time 2 cases (0.6%): possible chlorinated hydrocarbon exposures (laundry facility, dry-cleaning employment); 2 controls (0.5%): light exposure to PCE from dry-cleaning employment	Likelihood-based ORs and 90% CIs according to Cornfield (1956) for association between primary liver cancer and solvent exposure and for association between primary liver cancer and heavy/moderate alcohol use; both stratified by sex using Gart (1970) Latency period 10 yr
Houten et al. (1980)	Cases: men and women diagnosed with primary liver cancer from 1956−1965; Controls: all other cancer patients admitted to Roswell Park Memorial Institute from 1956−1965 Proxy—laundry and dry cleaners Liver cancer incidence	102 cases, number of controls not reported	None reported	Occupation assessed as a proxy for exposure 2 cases (2%) employed in laundry/dry-cleaning industry	Chi-square goodness-of-fit test, where distribution of cases compared to controls by each industry

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Stemhagen et al. (1983)	Cases: from NJ hospital records, NJ State Cancer Registry, death certificates, men and women living in NJ diagnosed with histologically confirmed primary liver cancer from 1975−1980; Controls: men and women admitted to same hospitals as cases and from death certificates, matched to cases based on age, race, sex, county of residence, vital status, excluded if history of liver cancer, hepatitis, liver disease; homicide, suicide Proxy—laundering, cleaning, and other garment services Liver cancer incidence and mortality	335 eligible cases, 296 contacted, 265 (79%) interviewed; 96% cases deceased, so proxy interview with next of kin; 825 eligible controls, 687 contacted, 530 (64.2%) interviewed	In-person interviews Questionnaire: lifetime residence, smoking, alcohol, medical history, and employment from age 12 yr onward	Occupations/industries coded according to Index of Industries and Occupations Standards developed by Bureau of Census; Occupations 6+ mo assessed as proxy for exposure; laundering, cleaning, other garment services industry: 10 (3.8%) male cases and 8 (1.5%) male controls Authors examined laundry/dry-cleaning industry by individual occupations but method not reported; no information for females not reported	Mantel-Haenszel methods for ORs and 95% CIs for men employed 6+ mo in selected industries and occupations; also looked at distribution of subjects by level of alcohol consumption, adjusted for age, smoking

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Suarez et al. (1989)	Death certificates from 1969−1980; Cases: men, 20+ yr, living in Texas, liver cancer cause of death; Controls: randomly selected from population-based group of 537,000 who died of all other causes, excluding neoplasms, liver and gallbladder diseases, infectious hepatitis, alcoholism; matched to cases on 5-year age group, race, ethnicity, year of death Proxy—dry cleaning occupation/industry Liver cancer mortality	1,771 potential cases, 1,742 (98.4%) eligible and included in study; did not report total number of controls	Not applicable	Occupations grouped according to U.S. Census Classified Index, groupings partially based on Hoar et al. (1980) 11 cases, 12 controls employed in dry-cleaning industry; 4 cases, 8 controls employed as dry-cleaning operators; unable to calculate exposure prevalence	Mantel-Haenszel for ORs; Miettinen's method for 95% CIs; adjusted for race, ethnicity Nonpetrochemical categories, occupations within categories with 10+ participants also analyzed
Lung and upper airway cancers					
Brownson et al. (1993)	Cases: from Missouri Cancer Registry and participating hospitals, Caucasian females, 30−84 yr, living in Missouri, diagnosed with primary lung cancer from 1986−1991, nonsmokers/selected ex-smokers; Controls: (1) <65 yr: state driver's licenses, (2) 65−84 yr: Medicare roster, matched to cases on age Proxy—dry cleaning Lung cancer incidence	650 eligible cases, 429 (66%) participated, 1,527 eligible controls, 1,021 (67%) participated Final sample: 429 cases, 1,021 controls	Telephone and in-person interviews by trained interviewers; Telephone: residential history, passive smoke, personal and family health histories, reproductive health history; In-person: diet, occupation	Occupational risk factors determined by 28 questions, based on review of literature, focused on job title and exposure; subjects reported years worked at each job/with each exposure; 30 (7.0%) cases, 39 (3.8%) controls employed in dry-cleaning industry	Multiple logistic regression for ORs and 95% CIs, adjusted for age, active smoking (for ex-smokers), history of previous lung disease

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Consonni et al. (2010)	Cases from 13 hospitals in Lombardy region of Italy, part of EAGLE study, 35−70 yr, 2002−2005; Controls: population controls identified through population databases, frequency matched by residence, sex, and age. Proxy—dry cleaning and laundry occupation Lung cancer incidence	2,100 eligible cases, 1,943 (92.5%) participated, 2,120 eligible controls, 2,116 (99.8%) participated	Computed-assisted questionnaire with in-person interview including lifetime history of jobs ≥6 mo	Occupations/industries blindly coded according to ISCO and ISIC; laundry and dry cleaners included in list of suspected occupations/industries 14 (0.7%) cases, 14 (0.7%) controls employed in laundry and dry cleaning occupation	Unconditional logistic regression for ORs and 95% CIs for "ever" worked in either known or suspected occupations associated with lung cancer, stratified by gender, adjusted for age, area, education, smoking pack-years, and number of jobs held
Pohlabeln et al. (2000)	Cases from 12 study centers in 7 countries, subjects ≤75 yr enrolled from 1988−1994; Controls: community and hospital-based; hospital-based controls had diseases not related to smoking Proxy—Launderers and dry cleaners Lung cancer incidence	650 nonsmoking cases, 1,542 nonsmoking controls; response rates ranged 55−95%, except 2 German centers, 1 Portuguese center (response rates <50%)	In-person interview: demographics, diet, smoking exposure, smoking history, and occupational history (6+ mo duration minimum)	Occupations industries blindly coded according to ISCO and ISIC; laundry and dry cleaners included in list of suspected occupations/industries 20 (3.1%) cases, 29 (1.9%) controls employed in laundry and dry cleaning occupation	Unconditional logistic regression for ORs and 95% CIs for ever worked in either known or suspected occupations associated with lung cancer, stratified by gender, adjusted for age, center; no effect of different sources of controls, so pooled results reported

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Richiardi et al. (2004)	Cases: histologically (74%) or cytologically (26%) confirmed lung cancers from hospitals in Turin and East Venice, Italy, men and women, residents ≤75 yr, 1990−1991 (Venice) and 1991−1992 (Turin) Controls: population control from local registries frequency matched on sex and age (≥1:1 frequency) Proxy—launderers and dry cleaners Lung cancer incidence	1,171 lung cancer cases, 1,569 controls; response rates for Turin and Venice regions, respectively, 86% and 72%, and 85% and 74% among cases and controls Final analyzed sample: 1,132 cases (956 men and 176 women) and 1,553 controls (1,253 men and 300 women)	In-person interview: demographics, diet, smoking exposure, smoking history, and lifetime occupational history for all jobs ≥6 mo	Occupations/industries blindly coded according to ISCO and ISIC; laundry and dry cleaners included in list of suspected occupations/industries 12 (1.1%) cases, 14 (0.9%) controls employed in laundry and dry cleaning occupation	Unconditional logistic regression for ORs and 95% CIs for "ever" worked in either known or suspected occupations associated with lung cancer, stratified by gender, adjusted for age, study center, cigarette smoking, consumption of other tobacco products, education, and total number of jobs

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Vaughan et al. (1997)	Cases from Fred Hutchinson Cancer Research Center (population-based registry), men and women, 20−74 yr, diagnosed with cancer of oral cavity/pharynx, larynx, esophagus/gastric cardia from 1983−1987, with adenocarcinoma of esophagus/gastric cardia from 1987−1990, residents of Washington state; exclusions: nonepithelial and nonspecified cancers, no telephones at diagnosis; Controls: random digit dialing, matched to cases on 5-year age group, sex PCE exposure for dry cleaning Upper aerodigestive tract cancer incidence	Case response rates: 85.2% oral cavity, 80.8% larynx, 82.9% esophagus/gastric cardia. Controls: 95.4% contacted were screened, 80.3% eligible were interviewed Final sample: 1,120 cases, 724 controls	In-person interviews Questionnaire: demographics, tobacco, alcohol consumption, occupational history (6+ mo duration, employer, business, job title, typical activities, dates, solvent exposures) Proxy interviews: 7.2% laryngeal cases, 18.7% oral/pharyngeal cases, 33.2% esophageal and gastric cardia cases	Blindly assessed by estimating probability PCE was used and 8-h time weighted average exposure in the job; Duration of employment and cumulative exposure assessed 16 (1.4%) cases, 8 (1.1%) controls “ever” employed in the dry-cleaning industry; 15 (1.3%) cases, 8 (1.1%) controls “possibly” exposed to PCE, 8 (0.7%) cases, 3 (0.4%) controls “probably” exposed to PCE	Conditional logistic regression for ORs and 95% CIs for those employed in dry-cleaning industry and those exposed to PCE, adjusted for age, sex, education, study period, alcohol consumption, cigarette smoking

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Lymphopoietic cancer					
Blair et al. (1993)	Cases: all pathology reviewed, Iowa: from Iowa State Health Registry, Caucasian men diagnosed with non-Hodgkin lymphoma from 1981−1983, Minnesota: from surveillance of hospitals, Caucasian men diagnosed from 1980−1982; Controls: Caucasian men without hematopoietic or lymphatic malignancies, matched on state, age, year of death, (1) <65 yr from random digit dialing, (2) 65+ yr from Medicare files, (3) deceased from state vital records; farmers excluded Proxy—laundry and garment workers Incidence of non-Hodgkin lymphoma	715 eligible cases, 622 (87.0%) participated; 1,245 controls participated (77% random digit dialing, 79% Medicare, 77% deceased) Final sample: 546 cases, 1,087 controls	In-person interviews with trained interviewers Structured questionnaire: sociodemographic characteristics, agricultural exposures, exposures to chemicals through hobbies, residential history, medical history, family history cancer, occupational history (all jobs held 1+ year from 18 yr onward, industry, employer, products produced, job titles, duties)	Blinded exposure assessment by an industrial hygienist; occupations/industries coded according to DOT and SIC standards; Job-exposure matrix used to evaluate probability (4-point scale) and intensity (3-point scale) exposure; laundry/garment workers: Code 721, 16 (2.9%) cases, 14 (1.3%) controls	*Polychotomous* unconditional logistic regression for ORs and 95% CIs, adjusted for age, state, direct or surrogate respondent, pesticides, tobacco, postsecondary education, hair dye use, first-degree family member with malignant lymphoproliferative diseases; exposure-response relationships for risk of non-Hodgkin lymphoma or subtypes by duration, intensity, probability exposure

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Clavel et al. (1998)	All from 18 hospitals in France; cases: patients diagnosed from 1980−1990, still alive at time of study; Controls: patients admitted to hospitals during same time for other reasons, exclusions: malignant disease, diseases related to occupations, work-related accidents, matched to cases based on birth date, sex, admission date, residence Proxy—launderers and dry cleaners Hairy cell leukemia incidence	278 eligible cases, 226 (81.3%) participated; 809 eligible controls, 465 (57.5%) participated Final sample: 226 cases, 425 controls	Self-administered questionnaires: socio-demographic characteristics, tobacco smoking, lifelong occupations, leisure activities; more sent to those with suspected occupational exposures; Semi-structured questionnaires: assess exposures to textile degreasing, among others	Occupations/industries coded according to ILO and ISIC; launderers/dry cleaners: ILO Code 5.6; (1) exposure blindly assessed by 2 researchers, based on responses, industry, job title, exposure; (2) job-exposure matrix for exposure to solvents based on ILO/ISIC codes for probability, intensity, frequency exposure; 1 (0.4%) case, 2 (0.5%) controls occupation as launderers and dry cleaner.	Conditional logistic regression for ORs and 95% CIs for job titles, occupational tasks, chemical families of organic solvents, adjusted for smoking, farming

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Fabbro-Peray et al. (2001)	All participants: French men and women, 18+ yr, living in Languedoc-Roussillon region of France; Cases: from 19 hospitals and 1 cancer research center, diagnosed with malignant lymphomas from 1992−1995, HIV-negative; Controls: randomly chosen from electoral lists in randomly selected municipalities based on size and population distribution and randomly selected individuals within each municipality; not matched to cases Proxy—dry-cleaning solvents Non-Hodgkin lymphoma incidence	627 eligible cases, 517 (82.5%) interviewed; 1,962 eligible controls, 1,025 (52.2%) interviewed Final sample: 445 NHL cases, 1,025 controls	Cases: in-person interviews at hospital; Controls: in-person at home or telephone Questionnaire: general characteristics, medical history, occupational history, environmental and occupational exposures, smoking	Age at first exposure, duration of exposure, and cumulative index of exposure calculated for each chemical for each participant; classified as either not exposed, lower than threshold, higher than threshold 35 (6.8%) cases, 77 (7.5%) controls exposed to dry-cleaning solvents	Mantel-Haenszel methods for ORs and 95% CIs for effect of sociodemographic characteristics, adjusted for age, gender; unconditional logistic regression using forward stepwise approach for ORs and 95% CIs for effect of chemical and other exposures on non-Hodgkin lymphoma, adjusted for age, gender, urban setting, education level Lag time 5 yr

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Gold et al. (2010a; 2010b)	Cases: Males and females, 35−74 yr, reported to Seattle-Puget Sound, 2000−2002, WA, and Detroit, MI SEER registry, alive at time of interview; Controls: population control identified previously for NHL study, random-digit dialing (for <65 yr) and Medicare roles (65+ yr) and frequency matched to NHL cases , resident of two areas, 1998−2004, 35−74 yr old, spoke English PCE exposure Proxy—dry cleaner or launderer Multiple myeloma incidence (ICO-O-2/3, 9731, 9732, plasmacytoma not otherwise specified or multiple myeloma)	255 eligible cases, 181 participated (71%) and 180 interviewed; 1,133 eligible controls, 481 participated and interviewed (52%)	Cases and controls: in-person interviews using a computer-assisted personal interview program Questionnaire: all jobs held for at least 1 year between 1941 (cases) or 1946 (controls) and enrollment date. Job-specific module for solvent exposures when participant held relevant job for ≥2 yr	Occupation, industry, ever exposed to 6 chlorinated solvents or to individual solvent (PCE, TCE, methylene chloride, 1,1,1-trichloroacetic acid, chloroform, carbon tetrachloride), exposure duration, cumulative exposure 9 (5%) cases, 4 (0.8%) controls with occupation as textile, apparel and furnishing machine operator and tender, of whom, 5 cases (3%) and 3 controls (0.7%) were dry cleaners; 29 cases (19%) and 63 controls (13%) "ever" exposed to PCE, of whom 17 (3%) cases and 15 (3%) controls with high cumulative PCE exposure (≥7,794 ppm-hours)	Unconditional logistic regression for ORs and 95% CIs adjusted for sex, age, race, education, and SEER site. Sensitivity analysis considered all occupations with confidence score ≥1 and repeated all analyses (Gold et al., 2010b) Lag time 10 yr (Gold et al., 2010b)

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Hardell et al. (1981)	Cases: men, 25−85 yr, histologically confirmed malignant lymphoma from 1974−1978. Controls: (1) living: from National Population Registry, exclusions: not in same municipality at case diagnosis, deceased, emigrated, (2) deceased: from National Registry for Causes of Death, exclusions: died in 1978, suicide, malignant tumor, date of last employment >5 yr from case; living matched on sex, age, municipality; deceased matched on sex, age, municipality, year of death Exposure to organic solvents, including PCE Hodgkin **lymphoma**, non-Hodgkin lymphoma incidence	Final sample: 169 cases (60 with Hodgkin lymphoma and 109 with non-Hodgkin lymphoma), 338 controls	Self-administered Questionnaire: leisure activities, smoking/drug use, chemical exposures, and occupational history (including time/place of employment) Blinded reviewer telephone interviews with participants when information unclear/incomplete	Exposure to organic solvents, including PCE, categorized into "high-grade" and "low-grade" 10 (5.9%) cases, 31 (9.2%) controls reported "low-grade" exposure to organic solvents, PCE-specific exposure not reported 40 (23.7%) cases, 47 (13.9%) controls reported "high-grade" exposure to organic solvents, only 1 case (0.6%) reported exposure to PCE	Chi-square tests based on Miettinen (1969, 1970) for chi-square estimates and ORs; Miettinen (1976) for 95% CIs

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Kato et al. (2005)	Cases: women, 20−79 yr, no prior history of hematologic cancer, living in upstate New York, diagnosed with non-Hodgkin lymphoma from 1995−1998; Controls: <65 yr from age-stratified random sample of driver's licenses, ≥65 yr from Health Care Finance Administration records Proxy—worker exposure to degreasers/cleaning solvents or dry-cleaning fluids Non-Hodgkin lymphoma incidence	722 eligible cases, 376 (56%) cases, 248 (30%) DMV controls, 215 (67%) HCFA controls	Blinded telephone interviews with cases and controls with structured questionnaire 21% case interviews and >3% of control interviews were conducted with proxy respondents Median time between the cancer diagnosis and the interview was 1.2 yr and ranged between 2 mo and 3.3 yr	Occupational: hours exposed, year of first and last exposure, and total number of years/months of exposure. Cumulative exposure hours based on hours per time unit and total exposure duration 50 (13.3%) cases, 48 (10.4%) controls reported exposure to degreasers/cleaning solvents, 7 (1.9%) cases, 8 (1.7%) controls reported exposure to dry-cleaning fluids	Unconditional logistic regression for ORs and 95% CIs, for occupational, household exposures to solvents, adjusted for age at index date, family history of hematologic cancer, college education, surrogate status, year of interview, BMI 10-yr preinterview, average frequency of use of pain-relieving drugs, total number of episodes of systemic antibiotic use, total number of household pesticides, duration of work involving pesticide exposures Lag period 1 yr

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Malone et al. (1989)	Cases: from SEER reporting sites in Washington state, Utah, Michigan, Georgia, men and women, <80 yr, diagnosed with chronic lymphocytic leukemia from 1977−1981; Controls: random digit dialing in Utah, Michigan, Georgia, random area sampling in Washington; controls matched to cases based on sex, race, and/or age, depending on location Chlorinated hydrocarbons (including, but not limited to dry-cleaning solvents) and proxy (dry-cleaning industry) Leukemia incidence	83% eligible cases responded, 430 interviewed (total eligible not stated and unclear if responded equals interviewed); Of 2,028 eligible controls, 83% interviewed Final sample: 427 cases, 1,683 controls	In-person or telephone interviews by trained interviewers Questionnaire: chemical exposures, other risk factors, employment in petroleum, dry cleaning, rubber, meat processing industries Cases: 76% in-person, 9% telephone, 16% next of kin; Controls: 81% in-person, 18% telephone, <1% next of kin	Chemical exposures assessed blindly by researchers and toxicologist into 20 categories; exposures with 10+ cases analyzed; chlorinated hydrocarbons (dry-cleaning solvents included) assessed; 1 case reported dry-cleaning solvent exposure 14 (3.3%) cases, 59 (3.5%) controls reported working for 6+ mo in dry-cleaning industry	Unconditional logistic regression for ORs and 95% CIs for all respondents and nonproxy respondents only; adjusted odds ratios controlled for race, 10-year age group, education, sex, study site
Mester et al. (2006) Siedler et al. (2007)	Part of EPILYMPH study; 6 regions in Germany; Cases: from physicians, diagnosed 1998−2003, German men and women, 18−80 yr, diagnosed with non-Hodgkin or Hodgkin lymphoma; Controls: from population registration office, matched to cases on sex, region, age; Exclusions: subjects who did not speak German . Lymphoma incidence	Participation rate among controls: 44.3%; participation rate among cases not reported Final sample: 710 cases, 710 controls	In-person with trained interviewers Questionnaire: lifestyle, medical history, occupational history (dates of employment, title, industry, tasks) for each job ≥1 year	Various (see below)	Conditional logistic regression for ORs and 95% CIs, adjusted for smoking, alcohol consumption Unconditional logistic regression for ORs and 95% CIs in unmatched analysis of most frequent lymphoma subentities, adjusted for age, sex, region, smoking, alcohol

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Mester et al. (2006)	Proxy—launderers, dry cleaners, pressers	See above	See above	Job titles/industries blindly coded according to ISCO-68 and Statistical Classification of Economic Activities in the European Community; launderers, dry cleaners, pressers: ISCO-68 Code 56 11 (1.5%) cases, 11 (1.5%) controls were launderers, dry cleaners, pressers	All estimates stratified by duration of employment (≤10 yr, >10 yr) Latency period of 10 yr, though data not reported
Seidler et al. (2007)	Chlorinated solvent exposure	See above	See above	Blinded, trained industrial physician Intensity: "low" (0.5−5 ppm), "medium" (>5−50 ppm), "high" (>50 ppm); frequency: percentage weekly working time exposed: "low" (1−5%), "medium" (>5−30%), or "high" (>30%); confidence in exposure: "possible," "probable," "certain"; cumulative exposure: ppm-years 36 (5.1%) cases, 31 (4.4%) controls exposed to PCE	Tests for trend used exposures as continuous variables in logistic regression

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Miligi et al. (1999) (2006); Costantini et al. (2008; 2001)	12 sites in Italy, 11 used for analysis; Cases: from hospitals, medical centers, local cancer registry, men and women, 20−74 yr, diagnosed with hematolymphopoietic malignancies from 1991−1993, Controls: randomly selected from general population in each site. Stratified by sex and age (5-year groups)	3,357 eligible cases, 3,118 contacted, 2,737 (88%) responded; 2,391 eligible controls, 2,196 contacted, 1,779 (81%) responded Final sample: 2,737 cases and 1,779 controls	In-person interviews and proxy with nextof kin (19% cases, 5% controls) Questionnaire: residential, medical, reproductive, and occupational histories, behaviors, education, solvent exposure	Industrial hygienists blindly assessed probability (“low,” “medium,” “high”) and intensity (“very low,” “low,” “medium,” “high”) of occupational exposures; job-exposure matrix created with consensus for jobs reported most frequently	Various (see below)
Costantini et al. (2001)	Information from 11 sites Proxy—launderers, dry cleaners, and pressers Incidence: NHL, HD, leukemia, MM stratified by sex, age	Final sample: 2,737 cases (1,450 NHL, 365 HD, 652 leukemia, 270 MM) and 1,779 controls	See above	Jobs coded according to International Standard Classification of Occupations; launderers, dry cleaners, pressers: Code 56: 3 (0.2%) NHL, 1 (0.3%) HD, 2 (0.3%) leukemia cases	Mantel-Haenszel method for ORs, 95% CIs, adjusted for age; reported results for men and compares with total sample; reported jobs with 5+ exposed cases

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Miligi et al. (2006)	Information from 8 sites PCE exposure NHL, HD incidence	1,719 eligible NHL cases, 1,428 (83%) responded; 347 eligible HD cases, 304 (88%) responded; 2,086 eligible controls, 1,530 (73%) responded Final sample: 1,732 cases (**285 small lymphocytic NHL, 100 follicular NHL, 308 diffuse NHL, 315 other NHL, 304 HD),** 1,530 controls	In-person interviews with 85% NHL cases, 93% HD cases, 97% controls; proxy interviews with remaining cases and controls	Intensity of exposure to PCE (NHL): 18 (1.3%) cases, 29 (1.9%) controls with "very low/low"; 14 (1.0%) cases, 15 (1.0%) controls with "medium/high"; duration of exposure to PCE (NHL): 10 (0.7%) cases, 10 (0.7%) controls with <15 yr; 3 (0.2%) cases, 5 (0.3%) controls with 15+ yr	ORs and 95% CIs calculated separately for non-Hodgkin lymphoma, non-Hodgkin lymphoma subtypes, and Hodgkin lymphoma; Adjusted for sex, age, education, area
Costantini et al. (2008)	Information from 6 sites PCE exposure Leukemia subtypes, MM	586 leukemia cases and 1,278 controls; 236 multiple myeloma cases and 1,100 controls Final sample: 822 cases and 2,378 controls	See above	Intensity of exposure to PCE: "Very low/low": leukemia—6 (1.0%) cases, 17 (1.3%) controls, MM—3 (1.3%), cases, 15 (1.4%) controls, "Medium/high": leukemia—7 (1.2%) cases, 12 (0.9%) controls, MM—2 (0.8%) cases, 12 (1.1%) controls	Individual point ORs, 95% CIs for leukemia, leukemia subtypes, and multiple myeloma, adjusted for gender, age, education, area; Linear test for trend using duration category midpoints

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Schenk et al. (2009)	Cases: men and women 20 to 74 yr and diagnosed with non-Hodgkin lymphoma between 1998 and 2000, living in Iowa, California, Michigan, or Washington state and in SEER registry; Controls: random digit dialing for <65 yr, Medicare files for ≥65 yr Matched based on 5-year age group, gender, and race within each study center Proxy—launderers and ironers Non-Hodgkin lymphoma incidence	2,248 eligible cases, 1,728 (77%) contacted, 1,321 (59%) interviewed; 2,409 eligible controls, 2,046 (85%) contacted and 1,057 (44%) interviewed Final sample: 1,189 cases (293 follicular, 366 diffuse large B-cell lymphoma, 487 other, 43 unknown), 982 controls	Mailed, self-administered questionnaire: family, medical history, diet; computer-assisted questionnaire in home: demographics, hair coloring, residential history since 1970, occupational history	Jobs blindly assigned occupation/industry codes according to standard conventions; launderers and ironers: occupation Code 503, 12 (1.0%) cases, 3 (0.3%) controls	Unconditional logistic regression for ORs, 95% CIs, adjusted for age, gender, ethnicity, study center; stratified by gender and histological subtype separately

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Scherr et al. (1992)	Cases: men and women, including children diagnosed with NHL between 1980 and 1982, histologically confirmed residents of Boston Standard Metropolitan Statistical Area, treated in one of nine participating hospitals; Controls: randomly selected from town and precinct population lists and, if over 17 yr of age, matched based on sex and age, or, if case ≤17 yr, one parent or guardian matched based on age and sex to adult resident (with interview to determine whether child was living in household of same age and sex as case) Proxy—occupation in laundry, dry cleaner, leather products fabrication industries; chlorinated solvents as a category NHL classified using Rapapport or Working Formulation classification system, diffuse or nodular tumors, or B- or T-cell	202 cases, 303 controls Response rates, 80% cases, 72% controls	In-person interview Questionnaire: current or most recent job, job held 15 yr prior, major and second major occupation, exposure to 10 specific agents or chemical classes (including chlorinated solvents) Proxy respondents: 33% cases, none for controls	Occupation and industries coded according to standard classification, or to any of 10 specific agents 3% of cases reported employment in laundering, dry cleaning, leather products fabrication industries; 24% reported exposure to chlorinated solvents	Hierarchal approach that aggregated histological subtypes into groups with similar histological characteristics and exposure defined as a function of calendar time (1901−1949, 1950−1959, 1960−1969, 1970 and later) or exposure duration (10 yr, 20 yr). All exposure that showed consistent patterns within histological categories over calendar time or over duration were considered as candidate variables for conditional logistic models with covariates for age and sex

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Childhood lymphopoietic cancer					
Costas et al. (2002)	Follow-up to a study (Cutler et al., 1986) that found a cluster of leukemia cases in Woburn, MA. Cases: pre-1982 cases from pediatric health professionals/pediatric oncology centers; post-1982 cases from Massachusetts Cancer Registry, children, diagnosed with leukemia ≤19-yr-old from 1969−1989; Controls: randomly selected from Woburn Public School records, matched on race, sex, and date of birth; excluded if not Woburn resident at case diagnosis Proxy—drink contaminated water Leukemia incidence	21 eligible cases, 19 (90.5%) participated; 38 controls selected, 1 excluded; no control response rates reported Final sample: 19 cases, 37 controls	In-person interviews with parents of cases and controls, except 2 fathers via telephone Questionnaires: Maternal—lifestyle, demographics, medical history, environmental/ occupational exposures, public drinking water at home; (2) Paternal—occupational history/exposures; Residential history for each mother/child for 2 yr preconception to case diagnosis	Based on well water contaminant levels from before 1979 closure; determined by potential for residence to receive water from contaminated wells using distribution model by Murphy (1991); 2 exposures assessed (cumulative and average); 16 (84.2%) cases, 24 (64.9%) controls “ever” exposed; 7 cases (36.8%), 13 controls (35.1%) “most” exposure, 9 cases (47.4%), 11 controls (29.8%) “least” exposure	Conditional logistic regression with proportional hazards model for ORs, 95% CIs; unadjusted ORs for effect of possible confounders; adjusted ORs for “ever” and “most”/“least”/“never” exposure, adjusted with composite covariate controlling for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, breastfeeding; trends evaluated with chi-square method

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Infante-Rivard et al. (2005)	Cases: children 0−14 yr, diagnosed with acute lymphoblastic leukemia, treated in tertiary care centers in Quebec Province, 1980−2000; Controls: (1) 1980−1993 from family stipend records; (2) 1994−2000 from health insurance records; Exclusions: adopted/foster, French/English not spoken at home, not in Canada, parents unavailable; matched to cases on sex, age Proxy—occupational exposure to PCE Leukemia incidence	848 eligible cases, 790 (93.1%) parents interviewed; 916 eligible controls, 790 (86.2%) parents interviewed Final sample: 790 cases, 790 controls	Telephone interviews Questionnaires: (1) structured: risk factors and confounders, maternal job history from 18 yr to child's birth; (2) semi-structured: company activities, raw materials or machines, goods, responsibilities, working conditions, coworker activities, solvents/ chemical presence, etc; (3) detailed tasks: time, exposures, environment	Blind classification by chemists and industrial hygienists; Jobs coded according to Canadian industrial titles (3-digit) and job titles (7-digit); assessed exposure to chemicals through interview responses, geographical information, previous knowledge industry exposures; then chemicals assigned codes based on Siemiatycki (1991), PCE Code 243; jobs 2 yr before birth, coded separately based on confidence that exposure occurred, frequency and concentration of exposure Not enough detail to calculate exposure prevalence	Conditional logistic regression for ORs and 95% CIs for each chemical, stratified by time period, adjusted for maternal age, education

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Lowengart et al. (1987)	Cases: from Los Angeles County Cancer Surveillance Program, ≤10 yr at diagnosis from 1980−1984, biological mothers required availability for interview; controls: (1) friends of cases identified by case mothers, (2) population-based controls via random digit dialing, matched to cases on age, sex, race, Hispanic origin (if "white"); additional exclusions if incomplete occupational history PCE exposure Leukemia incidence	216 eligible cases, 202 (94%) contacted, 159 (79%) case mother interviews; 154 case father interviews; 136 control mother interviews, 130 control father interviews; 30 case and 43 control paternal interviews proxy with mothers; control response rates not reported Final sample: 123 case-control pairs	Telephone interviews by 2 nonblinded, trained interviewers Structured questionnaire: family and personal medical histories, alcohol and tobacco use, household and personal products, X-ray exposure, occupational history (job title, industry, time period worked); maternal questionnaire also asked about use of drugs, medical complications, diet during index pregnancy, child's medical history, child's exposure to ionizing radiation	Industries/occupations coded according to 1970 U.S. Census classifications, grouped based on hydrocarbon exposure; occupations/exposures within 1 year conception excluded; 4 case fathers reported exposure to PCE 1 year before pregnancy (1 case), during pregnancy (1 case), or after delivery (2 cases); no control fathers reported exposure to PCE; maternal exposure to PCE not reported	Conditional logistic regression for ORs and 95% CIs

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Shu et al. (1999)	Cases: children ≤15 yr, diagnosed with acute lymphocytic leukemia from 1989−1993 by Children's Cancer Group member or institution, exclusions: no matched control; Controls: random digit dialing, matched to cases on age, race, telephone area code and exchange; Excluded if no telephone residence; no biological, English-speaking mother available PCE exposure Leukemia incidence	2,081 eligible cases and 2,597 eligible controls; Mothers: 1,914 (92%) case mothers and 1,987 (76.5%) control mothers interviewed Final sample: 1,842 cases and 1,986 controls Fathers: 1,801 (86.5%) case fathers and 1,183 (69.8%) control fathers interviewed; 16.6% cases and 32.3% control interviews were proxy with mothers Final sample: 1,842 cases, 1,986 controls	Telephone interviews with parents Structured questionnaire: (1) Maternal—demographics, personal habits, household exposures before/during pregnancy, environmental hazards exposure, medical/family/reproductive/job histories; (2) Paternal—personal habits, household exposures, medical/family/job histories; occupational history: job titles, industries, duties, employment dates, exposures	Maternal—all jobs 6+ mo from 2 yr prepregnancy through cancer diagnosis; Paternal—all jobs 6+ mo from age 18 yr onwards; Self-reported exposures not on exposure list blindly assessed by industrial hygienist; timing of exposure (preconception, pregnancy, postnatal): dates of employment; duration of exposure: control group's median time as cut-off; Maternal exposures to PCE: anytime: 4 (0.2%) cases, 9 (0.5%) controls; preconception: 3 (0.2%) cases, 2 (0.1%) controls; pregnancy: 3 (0.2%) cases, 2 (0.1%) controls; postnatal: 4 (0.2%) cases, 8 (0.4%) controls; Paternal exposures to PCE: anytime: 25 (1.4%) cases, 23 (1.9%) controls; preconception: 21 (1.2%) cases, 22 (1.9%) controls; pregnancy: 8 (0.4%) cases, 14 (1.2%) controls, postnatal: 10 (0.6%) cases, 15 (1.3%) controls	Maternal exposures: Conditional logistic regression for ORs, 95% CIs, adjusted for maternal education, race, family income; Paternal exposures: Unconditional logistic regression for ORs, 95% CIs, adjusted for paternal education, race, family income, age, sex of case; Tests for trend: add categorical variables of exposure as continuous variables in the models

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
DeRoos et al. (2001)	Cases: male and female children, ≤18 yr, diagnosed with neuroblastoma from 1992−1994, registered in participating hospital in United States or English-speaking Canada; Controls: random digit dialing, matched to cases on birth date; all proxy interviews excluded Halogenated hydrocarbons, including PCE Neuroblastoma incidence	741 eligible cases, 538 (73%) enrolled; 71% recruited; 74% screened households participated Final sample: 538 neuroblastoma cases, 504 controls	Telephone interviews with mothers/fathers; proxy interview with mothers if father unavailable Questionnaire: demographics, occupational history, occupational exposure history of all jobs within 2 yr of child's birth Interviews with 537 case mothers, 472 case fathers (14.2% proxy), 503 control mothers, 445 control fathers (31.7% proxy)	Blinded industrial hygienist reclassified improbable exposures; did not review participants who failed to report any exposures; classified substances into 5 categories, included halogenated hydrocarbons, which included PCE Maternal exposure to halogenated hydrocarbons: 15 (2.8%) cases, 19 (3.8%) controls, after review, decreased to 6 (1.1%) cases, 8 (1.6%) controls. Paternal exposure: 8 (2%) cases, 11 (3.6%) controls, after review, decreased to 4 (1.0%) cases, 6 (2.0%) controls	Unconditional logistic regression for ORs and 95% CIs for each category and individual chemicals, adjusted for child's age, maternal race, maternal age, maternal education

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Pancreatic cancer					
Lin and Kessler (1981)	>115 hospitals in Buffalo, Detroit, Miami, Minneapolis-St. Paul, New York City; Cases: from medical records and hospital pathology departments, men and women ≥15 yr; Controls: randomly chosen from admissions records of cancer-free patients of same hospital as case, matched to cases based on age, sex, race, marital status Proxy—unspecified occupational exposure to PCE and gasoline derivatives combined Pancreatic cancer incidence	Response rates not reported but 22% eligible not interviewed due to extreme illness; once excluded, response rates: 86.2% men and 86.3% women Final sample: 109 case-control pairs (67 male pairs and 42 female pairs)	Blinded, in-person interviews in hospital (most) or at home Questionnaire: demographics, residential history, occupations (all jobs held full-time 6+ mo or part-time for 1+ year), toxic exposures, animal contacts, smoking habits, diet, medical history, medicines, family history; sexual practices (men), urogenital conditions; marital, obstetric, gynecologic histories (women)	Duration of exposure to dry-cleaning and gasoline derivatives categorized into 0, ≤2, 3−5, 6−10, >10 yr; 25 (37.3%) male cases, 23 (34.3%) male controls exposed to either dry-cleaning or gasoline derivatives	Chi-squares and *t*-tests to examine differences between cases and controls; ORs for relative risk for pancreatic cancer among men and women exposed to a variety of risk factors, including occupational exposure to dry cleaning
Kernan et al. (1999)	1984−1993; Cases: from death certificates, all International Classification of Disease Code 157 in 24 states, included occupation/industry codes based on 1980 Census. Controls: from death certificates, nonpancreatic, noncancer causes, matched to cases based on state, race, gender, 5-year age group PCE Pancreatic cancer mortality	63,097 cases and 252,386 controls were selected	Not applicable	JEM developed by industrial hygienists for solvents, probability and intensity of exposure estimated and scored as "low," "medium," or "high"; 5,344 exposed to "low" levels, 2,187 exposed to "medium" levels, and 903 exposed to "high" levels of PCE	Race and gender-specific mortality odds ratios for intensity and probability of exposure to PCE, adjusted for age, marital status, metropolitan status, region of residence

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Renal cancer					
Asal et al. (1988)	Cases: from 29 hospitals in Oklahoma; men and women with renal cell cancer diagnosed from 1981−1984; Controls: (1) hospital-based: excluded kidney disease/psychiatric illness, matched to cases based on age, sex, race, hospital, date of admission, (2) population-based: random digit dialing, matched to cases based on sex, age Proxy—dry cleaning Renal cell cancer incidence	345 identified cases, 315 (91.3%) participated; control response/participation rates not reported Final sample: 315 cases, 313 hospital-based controls, 336 population-based controls	In-person interviews in hospital with cases and hospital-based controls, home with population-based controls Questionnaire: medical history, medications, radiation exposure, occupational history for all jobs held ≥1 year, industrial exposures, tobacco smoking, beverage use, artificial sweeteners, family history disease, height, weight	Dry cleaning examined as high-risk industry: 11 cases (3.5%), 7 controls (1.1%)	Cox linear logistic regression for ORs, 95% CIs for lifetime occupations and high-risk industries, adjusted for age, smoking, weight
Auperin et al. (1994)	Cases: men and women with histologically confirmed renal cell carcinoma identified at 10 selected hospitals; Controls: (1) with a malignant disease, (2) with a nonmalignant disease, excluded tobacco-related diseases, matched for each case based on sex, age at interview, hospital, and interview. Patients with alcohol-related cirrhosis or diabetes excluded from study. Proxy—laundry workers Renal cell carcinoma incidence	151 cases matched to two controls, 45 cases matched to 1 control; 161 controls with cancer and 186 with nonmalignant disease	Unblinded, trained interviewers Questionnaire: education, height, weight, smoking habits, beverage consumption, and medication, complete occupational history, including duration of employment for each job held. Interviewers were not blinded to the case or control status	Blinded exposure assessment; coded according to International Standard Classification of Occupations; minimum of 1 year employment for each job held; numbers of exposed laundry workers not reported	Conditional logistic regression for ORs, 95% CIs, stratified by gender; pooled control group; adjusted for age, hospital, interview, educational level, cigarette smoking, and the Quetelet index

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Delahunt et al. (1995)	Cases and controls: men and women in New Zealand Cancer Registry from 1978−1986; Cases: men and women, 20 yr and older, diagnosed with malignant neoplasm of kidney; Controls: men and women, 20 yr or older, diagnosed with primary tumor outside of urinary tract; women subsequently excluded Proxy—dry cleaning Renal cell carcinoma incidence	1,060 eligible cases, 914 (86.2%) information on occupations Final sample: 710 cases, 12,756 controls	New Zealand Cancer Registry for current/most recent occupations, smoking habits	Occupations coded according to New Zealand Standard Classification of Occupations, selected *a priori* 52 (7.3%) cases and 737 (5.8%) controls in service occupation, including but not limited to dry cleaners	Mantel-Haenszel method for RRs for each occupation; Miettinen's approximation method for 95% CIs; all stratified by smoking history, 10-year age groups
Dosemeci et al. (1999)	Cases: from Minnesota Cancer Surveillance System, Caucasian men and women, 20−85 yr, diagnosed with histologically confirmed renal cell carcinoma from 1988−1990; Controls: Caucasian men and women, (1) 20−64 yr from random digit dialing, (2) ≥65 yr from systematic sample of Health Care Financing Administration lists PCE Renal cell carcinoma incidence	796 eligible cases, 690 (87% response rate) interviewed, 241 (34.9%) proxy with next of kin; 707 (86% response rate) controls interviewed Final sample: 438 cases, 687 controls	In-person interviews with blinded, trained interviewers Questionnaire: demographics, diet, smoking, drug use, medical/residential histories, occupational histories recent and usual job and industry, activities, employment dates, part-time/full-time status. Duration of employment for specific industries, occupations, exposures	Occupations/industries coded according to SOC and SIC; linked with JEM by Gomez et al., 1994; 11% cases, 11% controls exposed to PCE	Logistic regression using Breslow and Day (1980) method for RRs and 95% CIs Adjusted for age, smoking, BMI, and hypertension status, and/or use of diuretics and/or antihypertension drugs All stratified by gender

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Harrington et al. (1989)	Cases: from West Midlands Regional Cancer Registry, men and women, living in West Midlands, diagnosed with renal adenocarcinoma from 1984−1985; Controls: randomly selected from patients of general practitioners, matched based on 5-year age group, sex, ethnicity, geographical location, socioeconomic status; excluded if no matching controls Proxy—dry-cleaning fluids, degreasing agents Renal cancer incidence	101 eligible renal cancer cases, 85 (84%) contacted, 59 (69%) interviewed Final sample:54 cases, 54 controls	In-person interviews Questionnaire: personal habits (smoking, coffee, and alcohol consumption), medical history, occupational history	Exposure assessed blindly by chemist/occupational hygienist using checklist of exposures; exposure indices calculated by computer program (exposure level × duration exposure) No cases or controls reported exposure to dry-cleaning fluids; 9 (16.7%) cases, 12 (22.2%) controls reported exposure to degreasing agents	Paired analyses for ORs and 95% CIs for 2 exposure categories using Schlesselman (1982) and 3 exposure categories using Pike et al. (1975)

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Mandel et al. (1995)	6 centers: Australia, Denmark, Germany (2 centers), Sweden, United States; Cases: from population-based cancer registries except Germany (surveillance of diagnosis/treatment departments), men and women, 20−79 yr, diagnosed with histologically or cytologically confirmed renal cell adenocarcinoma from 1989−1991; required in-country birth (except Australia/United States); Controls: Denmark/Sweden: population-based registers, Australia: electoral rolls, Germany: residential lists, United States: Health Care Finance Administration lists and random digit dialing, matched on gender, 5-year age group Proxy—dry-cleaning industry, dry-cleaning solvents Renal cell cancer incidence	Final sample: 1,732 cases (73.2% response rate) and 2,309 controls (74.7% response rate)	In-person interviews by trained interviewers in hospital (German cases) and homes (German controls/all others) Questionnaire: tobacco, diuretics, analgesics, antihypertensive drugs, diet pills, hormones, and alcohol, height and weight, physical activity, medical/reproductive histories, family history cancer, demographics, occupational history	Industries/occupations coded according to International Labour Office (1968, 1988), UN Department of Economic/Social Affairs (1968, 1971, 1990), U.S. Department of Commerce (1980), U.S. Office of Management Budget (1987); Duration: total number years worked/exposed; tertiles based on control distribution; dry-cleaning solvents duration: 1−7, 8−25, 26−60 yr; 23 (1.3%) cases, 28 (1.2%) controls in dry-cleaning industry; 302 (17.5%) cases and 265 (11.5%) controls exposed to dry-cleaning solvents	Logistic regression for ORs and 95% CIs for industry, occupation, exposure, stratified by gender, adjusted for age, smoking status, BMI, education, study center; only men reported Only industries, occupations, exposures reported by all centers analyzed; tests of heterogeneity to assess differences between centers

Table B-3. Summaries of characteristics of case-control studies: single cancer site studies (continued)

Reference, objective/hypothesis, study type	Study design	Sample size	Data collection	Exposure assessment	Statistical approach
Mellemgaard et al. (1994)	Cases: from Danish Cancer Registry, women and men 20−79 yr, born and living in Denmark; Controls: from Central Population Register; matched to cases on gender, 5-year age group Proxy—dry cleaning Renal cell carcinoma incidence	482 eligible cases, 368 (76%) interviewed; 500 eligible controls, 396 (79%) interviewed	In-person interviews with trained interviewers Questionnaire asked about occupation, occupational exposures, medical history, diet, smoking, demographics	Occupations and industries coded according to ISCO and ISIC; dry cleaning identified *a priori* as high risk (code not provided); exposures assessed for jobs held 1+ year and occurred 10+ yr prior to interview	Odds ratios and 95% CIs were calculated for men and women separately Adjusted for age, BMI, and smoking
Schlehofer et al. (1995)	Cases: German men and women, histologically confirmed renal cell cancer, from 1988−1991; Controls: randomly selected from population register of the Rhein-Neckar-Odenwald area Matched on age, gender Chlorinated solvents Renal cell cancer incidence	Of the 328 cases identified, 277 (84.5%) participated in the study Of the 381 controls identified, 286 (75%) participated in the study	In-person interviews by trained interviewers; 92% case interviews in hospital; 100% control interviews at home Questionnaire: medical, smoking family, weight, diet, demographics, physical activity, occupational history (industry, occupation, activities, chemical exposures)	Industries coded; industries, occupations, activities grouped into different categories; 51 possible substances, 22 reported by ≥5% male subjects and analyzed, including chlorinated solvents (PCE and tetrachlorocarbonate); exposed if 5+ yr duration 27 (14.6%) male cases, 12 (13%) male controls exposed to chlorinated solvents; female exposures not examined	Unconditional logistic regression for ORs and 95% CIs for smoking, age, and sex.

HD = Hodgkin lymphoma.

B.3. GEOGRAPHICALLY BASED AND OTHER STUDIES

The following papers examined tetrachloroethylene using geographically based (ecological) and other study designs. Summaries of the study characteristics of each paper are provided in Table B-4.

B.3.1. Cohn et al. (1994)

Cohn, P.; Klotz, J.; Bove, F.; Berkowitz, M.; Fagliano, J. (1994). Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphoma. Environ Health Perspect, 102, 556-561.
http://www.ncbi.nlm.nih.gov/pubmed/9679115

Summary: This ecological incidence rate study examined the following four hypotheses: (1) the incidence of leukemia is associated with exposure to trichloroethylene and/or tetrachloroethylene; (2) childhood leukemia is associated with trichloroethylene and/or tetrachloroethylene; (3) non-Hodgkin lymphoma is associated with trichloroethylene and/or tetrachloroethylene; and (4) gender may be an effect modifier. Cases were identified through the New Jersey State Cancer Registry and consisted of men and women residing in 1 of 75 municipalities diagnosed with primary leukemia (acute lymphocytic, chronic lymphocytic, acute myelogenous, chronic myelogenous, other specified, and unspecified) or non-Hodgkin lymphoma (low-grade, intermediate-grade, intermediate-grade/diffuse large cell/reticulosarcoma, high-grade, and high-grade NHL/non-Burkitt's) between 1979 and 1987. Information was supplemented with death certificates; any cases that were determined exclusively through death certificates were excluded. Municipalities were chosen on the basis of their water supply. Only those where at least 80% of the population received their water from a public water supply were selected. In total, 1,190 cases of leukemia (118 acute lymphocytic, 354 chronic lymphocytic, 276 acute myelogenous, 146 chronic myelogenous, 61 other specified, 235 unspecified) and 1,658 cases of non-Hodgkin lymphoma (434 low-grade, 708 intermediate-grade, 402 intermediate-grade/diffuse large cell/reticulosarcoma, 69 high-grade, 51 high-grade/non-Burkitt's) were included in the study.

Tetrachloroethylene exposure potential was based on water monitoring data—averages from 1984−1985 by the New Jersey Department of Environmental Protection and Energy. Although the authors do not explicitly state these were the same municipalities, due to the mandatory nature of the monitoring data, this may be assumed. Samples were taken from water treatment plants as well as tap sites within the distribution system. Tetrachloroethylene exposures were categorized as <0.1, 0.1−5, and >5 ppb, based on EPA standards. Surveys conducted by the New Jersey Department of Environmental Protection and Energy and the

Department of Health between 1978 and 1983 were used to provide corroborating evidence for use of the 1984−1985 estimates. The authors do not state if these were the same municipalities. The latter data were used as the primary source of exposure estimation because the earlier surveys were conducted primarily in response to known contamination, and the quality assurance and quality control of the latter mandatory monitoring were reported to be better. The 1978−1983 data are further described elsewhere (Cohen et al., 1993).

There were 440 cases of leukemia (37%) and 662 cases of non-Hodgkin lymphoma (39.9%) that were assessed as exposed due to their residence in a municipality with tetrachloroethylene levels between 0.1 and over 5 ppb. The remainder were determined to have <0.1-ppb exposure. Log-linear regression models with the Poisson distribution were used to estimate incidence rate ratios and their corresponding 95% CIs, adjusted for age and stratified by sex with subjects, identified <0.1 ppb as referents. The rate ratios were also stratified by sex and type of leukemia or non-Hodgkin lymphoma. The authors do not report strengths of their methodology. Limitations included the lack of adjustment for possible confounders, potential misclassification of exposure that biases the result away from the null, and the ecological study design, which measured exposure and disease at the same time, assigned exposure and leukemia incidence at the municipal level, and lacked information on individual exposure potential.

B.3.2. **Lee et al. (2003)**

Lee, L.; Chung, C.; Ma, Y.; Wang, G.; Chen, P.; Hwang, Y.; Wang, J. (2003). Increased mortality odds ratio of male liver cancer in a community contaminated by chlorinated hydrocarbons in groundwater. Occup Environ Med, 60, 364-369. http://dx.doi.org/10.1136/oem.60.5.364

Summary: Exposure potential to chlorinated hydrocarbons was assigned in this community case-control study of liver cancer in males >30 years of age using residency as coded on death certificates obtained from local household registration offices. No information is available to assess the completeness of death reporting to the local registration office. Of the 1,333 deaths between 1966 and 1997 in two villages surrounding a hazardous waste site, an electronics factory operating between 1970 and 1992 in Taoyuan, Taiwan, 1,266 cancer deaths were identified; 53 liver cancer deaths, 39 stomach cancer deaths, 26 colorectal deaths, and 41 lung cancer deaths. Controls were identified from 344 deaths due to cardiovascular and cerebrovascular diseases, without arrhythmia; 286 were included in the statistical analysis. Residents from a village north and northeast of the plant were considered exposed and residents living south considered unexposed to chlorinated hydrocarbons. Additionally, death certificates were obtained from the registration offices in two villages near the factory. These records

contained information on gender, age, date of birth and death, address, and cause of death. The underlying cause of death was then blindly assessed by a team of nosologists. Cases consisted of any individual whose cancer was coded by the nosologists as either an underlying cause of death or as a significant condition. All individuals were also linked to the Taiwan National Cancer Registry to verify the accuracy of coded cancer cases.

Residence was assessed as a proxy for exposure, with exposed cases considered exposed if living downstream of the factory and unexposed if living upstream of the factory. Geographical exposure was confirmed through well water sampling. Between 1999 and 2000, 74 groundwater samples were collected from off-site residential wells near a factory whose soil and groundwater had been previously found to be contaminated with chlorinated hydrocarbons, including tetrachloroethylene. Overall, 20 (45.5%) of the wells downstream had concentrations above the maximum contaminant level for tetrachloroethylene. No upstream wells were found to be contaminated with tetrachloroethylene. Death certificates were also linked to the Labour Insurance Bureau to ascertain those who had previously worked in the factory.

The Mantel-Haenszel method was used to estimate mortality odds ratios and their corresponding 95% CIs, adjusted for age. Multiple logistic regression was also conducted, adjusted for age and time period. The Cochran-Armitage test for trend calculated the effect of time period for downstream and upstream villages. A latency period of 10 years was also included.

One strength of this study is its linkage with the National Cancer Registry, which located an additional 12 cancer cases that had not been recorded in the death certificates. Limitations to the study include possible selection bias due to the use of only cardiovascular and cerebrovascular deaths as controls, possible misclassification due to the use of residence as a proxy for exposure status, and the lack of control for potential confounders such as Hepatitis C virus, which was of high prevalence in this area.

B.3.3. **Ma et al. (2009)**

Ma, J.; Lessner, L.; Schreiber, J.; Carpenter, D. O. (2009). Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York City. J Environ Public Health, 2009, 183920. http://dx.doi.org/10.1155/2009/183920

Summary: The hypothesis tested in this study was living in an area with a high density of tetrachloroethylene dry cleaners increases tetrachloroethylene exposure and the risk of kidney cancer. Subjects were individuals 45 years of age or older with a principal or other diagnosis of kidney cancer and identified from a New York State register of hospital discharges between 1993

and 2004. The database used to identify subjects did not include personal identifiers leading to an inability to distinguish multiple hospital discharges by a single individual. A subject had the potential for multiple entries for this reason. The inclusion criteria were restricted to subjects whose residence at the time of discharge was in a New York City zip code having a median household income from $17,864 to $142,926. No information is provided in the paper on how temporal a change as zip code's median income may have affected the inclusion criteria. Of the total of 181 zip codes in New York City, 164 zip codes met the inclusion criteria; six zip codes were not considered because population or income information was unavailable, and 10 zip codes had median household incomes either below or above the inclusion criteria. A total of 674,519 discharges with a diagnosis of cancer, of which 10,916 were of kidney cancer, were identified with a residence at the time of discharge within the 164 eligible zip codes. Population estimates, year not identified by authorsm, by zip code were derived from U.S. Census data and stratified by age, race, and sex.

Dry-cleaning establishments were identified from a listing maintained by the New York State Department of Environmental Conservation. This listing included dry-cleaning establishments who were required under state statutes to report their usage of tetrachloroethylene. The authors do not provide information as to whether the statute identified a minimal usage level that would lead to an underreporting of the number of dry-cleaning establishments. The density of dry cleaners by zip code (number of dry cleaners per km^2) was estimated for each zip code from the number of dry-cleaning establishment and the population density, based upon a zip code's population estimate and area. The authors do not provide information in the paper for the source for estimating area of individual zip codes.

A negative binomial model was fit to the data to examine the rate of discharge rate for a principal or other diagnosis for kidney cancer as functions of the densities of dry-cleaning businesses. For each of the exposure strata, the authors examined different variables as possible effect modifiers, and these included median household, age, and sex, with a finding that effect modifiers differed for each exposure strata. The authors also used a Poisson regression model but did not report findings because of an inadequate fit to the observed data.

This study is ecological in design, with associated limitations known as "ecological fallacy" because variables of exposure and outcome measured on an aggregate level do not represent association at the individual level. A significant shortcoming of this study is the potential for a subject to have multiple discharges, inflating the numerator, but not the denominator, for estimating the discharge rate, and its use of a crude exposure surrogate. The authors did not validate how well the density of dry-cleaning businesses predicted atmospheric concentrations of tetrachloroethylene for individual zip codes or potential exposure to individual subjects. The authors noted New York City zip code densities varied by boroughs, particularly

Staten Island, which had large areas but lower population densities and lead to large variation in the exposure surrogate. Furthermore, risk ratios from the negative binomial model are difficult to interpret because each exposure strata's rate ratio was based upon a different set of covariates. On the other hand, the study was able to characterize disease distribution geographically, as well as dry-cleaning business location.

B.3.4. Mallin (1990)

Mallin, K. (1990). Investigation of a bladder cancer cluster in northwestern Illinois. Am J Epidemiol, 132, S96-106. http://www.ncbi.nlm.nih.gov/pubmed/2356842

Summary: This ecological study examined the incidence of bladder cancer to determine if the high mortality rates also reflect high incidence rates, and if high incidence rates were found in areas of known groundwater contamination. Incident cancer cases were identified through medical records in 8 of the 9 counties within a region of northwestern Illinois. Resident cases diagnosed or treated in the bordering states of Iowa or Wisconsin were also ascertained through the Iowa State Health Registry and the Wisconsin Cancer Reporting System. Cases consisted of men and women who were diagnosed with histologically confirmed bladder cancer between 1978 and 1985. Deaths due to bladder cancer during this time period were also ascertained. Incidence data were stratified by county and zip code. After significantly higher risks of bladder cancer incidence and mortality were found only in Winnebago County, the researchers searched Illinois EPA and Department of Energy and Natural Resources documents and found well water in this county was contaminated with tetrachloroethylene and other compounds.

Indirect standardization was used for the estimation of standardized incidence ratios and SMRs, both adjusted for age. Expected numbers of cases were derived from age-specific rates for 1978−1991 and 1982−1985. Their corresponding 95% CIs were calculated according to Miettinen's exact limits; significance was evaluated using a chi-square distribution. Where the expected counts were less than 5, Fisher exact test limits were used for the estimation of 95% CIs, and a Poisson distribution was assumed for the significance tests. The authors did not report any strengths of their study. Limitations include the lack of control for potential confounders, ecological design causing chance associations, lack of survival data, lack of medical treatment data, and no data on water consumption among Winnebago inhabitants.

B.3.5. Morton and Marjanovic (1984)

Morton, W. and Marjanovic, D. (1984). Leukemia incidence by occupation in the Portland-Vancouver metropolitan area. Am J Ind Med, 6, 185-205. http://www.ncbi.nlm.nih.gov/pubmed/6475965

Summary: An examination of occupational risks using incident leukemia cases identified over a 15-year period, 1963−1977, was carried out in the Portland-Vancouver Metropolitan area, Oregon. Cases [*n* = 1,622] were identified through a search of 24 hospitals in the four-county area of Portland-Vancouver and included a Veteran's Administration hospital and two closed hospitals (whose records were accessible in storage). In addition, death certificates that mentioned leukemia from the same period were searched, adding 244 cases, for a total of 1,866 leukemia cases. The finding of additional cases using death certificates suggests hospital records may have been incomplete. Associations with job title as coded to usual occupation and leukemia cases aged 16−74 years were carried out, examining age-standardized rates based on the direct method of age standardization using the 1970 U.S. population census (midpoint of case ascertainment period). Given census records group population estimates for individuals aged 65 or older, occupation-specific analyses truncated case inclusion at age 67. The determination of significance of a deviation of an occupational leukemia rate from its respective area-wide rate for all women or all men was based on the assumption that a rate is a mean for a distribution of binomial events, and the distribution of such means was regarded as approximately normal. Age-adjusted incidence rates for separate occupations were calculated for all leukemia, all lymphatic leukemia, and all nonlymphatic leukemia. Lymphatic leukemia cases, including chronic lymphatic leukemia, are now classified as subtypes of non-Hodgkin lymphoma (Morton et al., 2005). One female dry cleaner and launderer was identified with both lymphatic and nonlymphatic leukemia subtypes and was counted twice in the statistical analyses.

Occupations were broadly grouped into over 20 categories and included dry cleaners and launderers, a grouping that contained 313 males and 1,298 females with associated exposure prevalences (based on the 1970 population) of 0.1% and 0.3%, respectively. Morton and Marjanovic (Morton and Marjanovic, 1984) do not identify the source for job title information and stated the trained coder could identify "usual occupation," but little else. The lack of information on full job history, in addition to possible misclassification of occupation on death certificates, suggests an incomplete occupation history.

This study is less sensitive for identifying cancer hazard because case ascertainment may be incomplete and because of possible selection bias associated with hospital records, inability to identify specific exposures, and use of age-adjusted incidence rates, rather than a relative risk estimate.

B.3.6. **Vartiainen et al. (1993)**

Vartiainen, T.; Pukkala, E.; Rienoja, T.; Strandman, T.; Kaksonen, K. (1993). Population exposure to tri- and tetrachloroethene and cancer risk: Two cases of

drinking water pollution. Chemosphere, 27, 1171-1181.
http://dx.doi.org/10.1016/0045-6535(93)90165-2

Summary: This parallel standardized incidence ratio study had three aims: (1) to find out whether inhabitants in the villages of Oitti and Hattula had been exposed to tetrachloroethylene by analyzing urinary excretion; (2) to examine which compound(s) would provide the best index of exposure to low levels of tetrachloroethylene; and (3) to determine whether the cancer incidence was increased in the municipalities in question. The first part of this parallel study consisted of residents of two villages (Oitti and Hattula) in Finland who consumed contaminated drinking water. Of the 116 possible participants, 8 were excluded because they had not drunk any contaminated water. The reference population was divided into two groups: (1) ground water controls included volunteers residing in a nearby town whose drinking water came from ground water, and (2) surface water controls included volunteers whose drinking water came from bank-filtrated surface water. The final sample consisted of 108 exposed (87 from Oitti and 21 from Hattula) and 60 unexposed (45 ground water and 15 surface water). All participants were interviewed about their source of drinking water and the approximate amount of water they consumed each day. Gas chromatography was used to detect tetrachloroethylene in the urine samples. These results were then compared among all four locations (2 exposed villages and 2 unexposed villages), though the authors do not report the methods they used to conduct the comparison. The second part of the parallel study used the Finnish Cancer Registry to identify the number of all cancers, liver cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia in Hausjarvi (municipality where Oitti is located) and Hattula. Overall, there were 1,931 cancer cases identified (972 from Hausjarvi and 959 from Hattula). Standardized incidence ratios, along with their corresponding 95% CIs, were calculated assuming a Poisson distribution. Expected numbers of cancer cases were estimated based on annual age- and sex-specific numbers for the whole of Finland for each year between 1953 and 1991. A strength of the latter part of this parallel study was use of the Finnish Cancer Registry, which contained all cancer cases since 1953 and increased the confidence in calculated estimates. Limitations overall included the extended latency time between exposure to tetrachloroethylene and cancer diagnosis, as well as the ambiguity related to the time period within which cases were exposed. Exposure misclassification bias is likely, given the ecologic design of this study, and exposure assignment to both cases and controls is not validated, given the lack of monitoring data for the examined time period. Furthermore, the presentation of incidence rates for a presumed unexposed population provide little insight on site-specific cancer incidence in the two presumed exposed towns, given direct comparison of SIRs has methodological limitations due to differences in population age structure.

Table B-4. Summaries of characteristics of geographically based and other studies

Reference	Study design[b]	Sample size	Data collection	Exposure assessment[c]	Statistical approach[d]
Cohn et al. (1994)	Cases: identified from New Jersey State Cancer Registry, men and women, diagnosed with primary leukemia or non-Hodgkin lymphoma from 1979−1987, living in 1 of 75 municipalities, information supplemented with death certificates; only municipalities where ≥80% population received public water supply selected Proxy exposure surrogate—PCE Leukemia incidence (acute lymphocytic, chronic lymphocytic, acute myelogenous, other specified, unspecified), NHL (low-grade, intermediate-grade, high-grade)	1,190 cases leukemia (118 acute lymphocytic, 354 chronic lymphocytic, 276 acute myelogenous, 146 chronic myelogenous, 61 other specified, 235 unspecified), 1,658 cases of NHL (434 low-grade, 708 intermediate-grade, 402 intermediate-grade/diffuse large cell/ reticulosarcoma, 69 high-grade, 51 high-grade/non-Burkitt's)	Records based—cancer registry data and summary data from state of average drinking water concentration in each municipality	PCE exposure based on water monitoring data (average from 1984−1985 by NJ Department of Environmental Protection and Energy), calculated for each municipality based on water measurements and proportion of water purchased elsewhere; samples from treatment plants and tap sites within distribution system; PCE exposures categorized as <0.1, 0.1−5, and >5 ppb, based on EPA standards; surveys from 1978−1983 used to corroborate 1984−1985 estimates; 440 (37%) cases of leukemia, 662 (39.9%) cases of NHL exposed due to residences in a municipality with PCE levels from 0.1 through >5 ppb	Log-linear regression models assuming Poisson distribution for incidence rate ratios, 95% CIs, adjusted for age, stratified by sex and type of leukemia or non-Hodgkin lymphoma

Lee et al. (2003)	Death certificates from 2 villages near factory from 1966−1997; nosologists blindly assessed cause of death; Cases: cancer cause of death, linked to Taiwan National Cancer Registry; Controls: cardiovascular or cerebrovascular disease cause of death; Exclusions: arrhythmia, all noncancer diseases also used as controls Cancer mortality (liver, stomach, colorectal, lung, all cancers)	1,333 decedents: 266 cancer cases; 344 cardiovascular-cerebrovascular controls	Not applicable	Proxy—residence near factory. Exposed lived downstream of factory; unexposed: lived upstream Death certificates linked to Labour Insurance Bureau to find previously employed in factory	Mantel-Haenszel for mortality ORs, 95% CIs, adjusted for age Multiple logistic regression for exposure effect, adjusted for age, time period Cochran-Armitage test for trend for effect of time period Latency period of 10 yr

Table B-4. Summaries of characteristics of geographically based and other studies (continued)

Reference	Study design[b]	Sample size	Data collection	Exposure assessment[c]	Statistical approach[d]
Ma et al. (2009)	Cases discharged from hospital with diagnosis of kidney cancer, 1993−2004, for New York City zip codes with median household income of $17,864−$142,926. Population estimate by zip code from U.S. Department of Census. Proxy exposure surrogate: density of dry-cleaning businesses (number of dry cleaners/zip code area in square kilometers) Renal cell cancer prevalence	10,916 discharges, 1,458 discharges in lowest exposure category (referent group) Unit of analysis is discharge, and a subject could be counted as many times as discharged from hospital	Discharge information obtained from New York Statewide Planning and Research Cooperative System	Density of dry cleaners per zip code (number of dry cleaners/zip code area) proxy surrogate for PCE exposure. Proxy exposure surrogate not validated with ambient monitoring data	Negative binomial regression for prevalence rate ratios, 95% CIs, adjusted for population density, age, race, and interactions specific to individual exposure level
Mallin (1990)	Cases: identified from medical records in 8 counties of northwest Illinois, men and women, diagnosed with histologically confirmed bladder cancer from 1978−1985, those diagnosed or treated in Iowa or Wisconsin also identified from Iowa State Health Registry, Wisconsin Cancer Reporting System; deaths from bladder cancer obtained Proxy—residence near contaminated well water Bladder cancer incidence and mortality	Cases and residence from medical records and cancer registries 712 bladder cancer cases among Caucasian men and women	Not applicable	Incidence data stratified by county and zip code; Winnebago county later found to have well water contaminated with PCE and other compounds	Indirect standardization for SIRs and SMRs, each adjusted for age; 95% CIs using Miettinen's exact limits; chi-square tests for significance except when expected counts <5: Fisher exact test for 95% CIs, significance assumed Poisson distribution

Table B-4. Summaries of characteristics of geographically based and other studies (continued)

Reference	Study design[b]	Sample size	Data collection	Exposure assessment[c]	Statistical approach[d]
Morton and Marjanovic (1984)	Cases: Men and women leukemia cases, diagnosed 1963−1977, residing in Portland-Vancouver Metropolitan Area, 16−74 yr old, Referents: 1970 age-specific leukemia rates for U.S. population, direct method of age standardization Proxy—occupational title on hospital record or on death certificate Leukemia incidence and mortality, including subtype (lymphatic, nonlymphatic)	975 leukemia cases among males, 336,850 population 703 leukemia cases among females, 102,310 population	Record-based information—Cases ascertained from hospital records and death certificates. Record source for usual occupational title not reported	Occupations grouped into 20 categories, 313 males and 1,298 females identified as dry cleaner or launderer (0.1% and 0.3%, respectively)	Comparison of directly standardized age-adjusted incidence rates
Vartiainen et al. (1993)	(1) Cases: 2 villages who consumed contaminated water, 2 reference groups: drank ground water, drank surface water (2) Identified from Finnish Cancer Registry, all cancers, liver cancer, non-Hodgkin lymphoma, multiple myeloma, leukemia in 1 exposed village and 1 exposed municipality Proxy—residence in exposed village Cancer incidence (liver, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, leukemia, all cancers combined)	(1) 116 identified cases, 108 exposed; 60 unexposed references (2) 1,931 cases in exposed villages	(1) Interviewed about drinking water source and daily water consumption, urine samples collected (2) Not applicable	(1) Exposed: drank contaminated water; gas chromatography to detect PCE in urine samples (2) Residence in exposed village or municipality	(1) Compare urine levels in villages; methodology not reported (2) SIR, 95% CIs, assuming Poisson distribution; expected numbers based on age- and sex-specific number of cancer cases for Finland each year 1953−1991

Table B-4. Summaries of characteristics of geographically based and other studies (continued)

[a]A study's hypothesis is included here if explicitly stated; otherwise, only the objective is included.
[b]Study design includes the overall approach, study population, relevant dates, type of exposure, and endpoint measured. For type of exposure, when a proxy is not explicitly stated for PCE, an attempt was made to identify proxies based on relevant industries and occupations, including laundry/dry cleaners and textile industry, and to some extent, metal industry, aerospace industry, appliance industry, automotive industry, and manufacturing of chloroflourocarbons (though not used).
[c]Exposure assessment includes exposure assignment (e.g., was coding conducted and by whom), exposure approach (e.g., what kind of coding was used), and exposure-assessment metrics (e.g., length of exposure).
[d]Statistical approach includes adjustment for covariates, latency, or lag period, and documentation of statistical analysis and observations.

C. CONSISTENCY OF TETRACHLOROETHYLENE AND TRICHLOROACETIC ACID HEPATOCARCINOGENICITY

Trichloroacetic acid (TCA), a metabolite of tetrachloroethylene, is associated with hepatocarcinogenicity in male and female mice (Bull et al., 2002; Bull et al., 1990; Daniel et al., 1993; DeAngelo et al., 2008; Ferreira-Gonzalez et al., 1995; Herren-Freund et al., 1987; Pereira, 1996), as is NCI (1977), NTP (1986) and JIRA (1993).

There has been some suggestion that TCA does not account for all of the toxicity observed with tetrachloroethylene exposure (Buben and O'Flaherty, 1985; Clewell, 2005), while others have suggested that TCA can account for liver tumors induced by tetrachloroethylene (Sweeney et al., 2009). The purpose of this investigation is to examine quantitatively what fraction of tetrachloroethylene hepatocarcinogenicity may be associated with TCA, using tetrachloroethylene and TCA bioassay data along with updated physiologically based pharmacokinetic (PBPK) model-based predictions.

C.1. METHODS

C.1.1. Response Data

Because of the more robust liver tumor response in males, and because the PBPK modeling was calibrated exclusively to data in male mice, only response data in male mice were considered. Table C-1 provides the hepatocellular adenoma or carcinoma incidence data from the two tetrachloroethylene inhalation bioassays considered in this assessment, National Toxicology Program (NTP, 1986) and Japan Industrial Safety Association (JISA, 1993) (for convenience, the studies will be referred to in the remainder of this appendix as the NTP and JISA studies). These were previously described in Section 5, and so are not discussed further here.

EPA generally emphasizes combining hepatocellular adenomas and carcinomas in developing cancer risk values, for three reasons: (1) Hepatocellular adenomas develop from the same cell lines as carcinomas and can progress to carcinomas; (2) Adenomas are often distinguished from carcinomas only on the basis of size; and (3) histopathologic decision criteria may vary between laboratories or over time.

Table C-2 summarizes data from the available TCA studies considered for carrying out dose-response modeling. A number of these TCA studies lack information for a complete comparison of hepatocarcinogenicity between tetrachloroethylene and TCA, either in terms of exposure (i.e., drinking water intake not reported so total intake of TCA cannot be calculated) or

in terms of responses. In particular, most of the TCA studies either did not consider adenomas or did not report combined incidence of adenomas and carcinomas. Lacking data on adenomas, the

Table C-1. Incidence of hepatocellular adenomas and carcinomas in male $B6C3F_1$ mice exposed to tetrachloroethylene in two inhalation bioassays

Sex	Bioassay	Administered exposures (ppm)	Cumulative liver tumor incidence at Week 104			Total at risk[a]
			Adenomas	Carcinomas	Adenomas or carcinomas	
Male	NTP (1986)	0	12	7	17	49
		100	8	25	31	47
		200	19	26	41	50
	JISA (1993)	0	7	7	13	46
		10	13	8	21	49
		50	8	12	19	48
		250	26	25	40	49

[a] Animals dying before the first appearance of a hepatocellular tumor, but no later than Week 52, were omitted from the totals because these animals were presumed not to have adequate time on study to develop tumors.

Table C-2. TCA drinking water studies in male mice: incidence of hepatocellular adenomas and carcinomas

Source	Weeks of exposure	TCA exposure, (g/L)	Average TCA intake (mg/kg-day)	*N*	Incidence of adenomas	Incidence of carcinomas	Incidence of adenomas or carcinomas	Proportion responding with carcinomas
Bull et al. (1990)[a]	37	2	330	11	0	3	3	0.27
	52	0 1 2	0 170 330	35 11 24	0 2 1	0 2 4	0 NR NR	0.0 0.18 0.17
Bull et al. (2002)	52	0 0.5 2	0 NR NR	20 20 20	0 5 6	0 3 3	0 6 8	0.0 0.15 0.15
Herren-Freund et al. (1987)	61	0 5	0 NR	22 22	2 8	0 7	2 NR	0.0 0.32
Ferreira-Gonzalez et al. (1995)	104	0 4.5	0 NR	16[b] 11	NR NR	3[b] 8	NR NR	0.19 0.73
DeAngelo et al. (2008)	104	0 0.06[c] 0.7[c]	0 6.7[d] 81.2[d]	56 48 51	10 10 20	26 14 32	31 21 36	0.55 0.44 0.71

[a] Cumulative TCA exposures were provided in g/kg for the mice evaluated at 52 wk. Those exposures were converted to mg/kg-day by multiplying by (1,000 mg/g)/(7 d/wk * 52 wk).
[b] Estimated from the reported proportion responding by selecting the smallest group size and incidence value consistent with the precision of the reported proportion.
[c] Measured concentrations—nominal concentrations were 0.05 and 0.5 mg/L.
[d] Calculated based on measured concentrations (different than those reported in the manuscript, which were based on nominal concentrations).

NR = not reported.

studies that only provided carcinoma incidence may under-represent hepatocellular tumor incidence. For studies not reporting combined incidence of adenomas and carcinomas, there could be some double-counting of animals when the separate totals of adenomas and carcinomas are added together. Only the chronic (104-week) study of DeAngelo et al. (2008) reported data on both total TCA intake as well as combined incidences of adenomas and carcinomas, and only this study was considered further for comparing with the tetrachloroethylene bioassays in male mice. However, one significant limitation of the DeAngelo et al. (2008) study is the high incidence of liver tumors in control animals as compared to other TCA studies and as compared to the historical background rates of these tumors in $B6C3F_1$ mice. This raises concerns about the representativeness of the DeAngelo et al. (2008) study for comparison to other studies. Nonetheless, because this is the only available chronic-duration study that reports all the data needed, it was used for this analysis.

C.1.2. **Exposure-Level Conversions**

TCA bioassay exposures were generally reported in terms of water concentration, in mg/L or mmol/L. Table C-2 provides the exposure levels as reported by each set of authors. Some reports provided mg/kg-day equivalents. To account for TCA bioavailability, the best estimates of bioavailability from Chiu were used. These are modeled as an "effective" concentration C_{eff} that changes as a function of actual concentration C: $C_{eff} = C_{max} \times C/(C_{½} + C)$, where C_{max} is a "maximal" effective concentration, and $C_{½}$ is the actual concentration where the effective concentration is half the maximal value. Thus, the rate of TCA absorption will be given by C_{eff} × Drinking water intake rate = (C_{eff}/C) × TCA intake. The best fit values of the parameters are C_{max} = 1.34 mg/L and $C_{½}$ = 1.82 mg/L. The area under the curve (AUC) of TCA in the liver is also calculated using the Chiu PBPK model for TCA. This model is based on a model previously calibrated to TCA kinetic data from trichloroethylene exposure and TCA oral gavage and i.v. exposures, and subsequently updated by Chiu with TCA kinetic data from drinking water exposures (the same data used by Sweeney et al., 2009). The Chiu and Ginsberg PBPK model was used to estimate the AUC of TCA in the liver corresponding to the bioassay exposures in the NTP and JISA studies. As shown in Table C-3, accounting for reduced TCA bioavailability, the exposures in the DeAngelo et al. (2008) study lead to internal doses that are within the range of the internal doses predicted for the tetrachloroethylene inhalation bioassays.

Table C-3. PBPK model-estimated TCA internal dose measures for tetrachloroethylene and TCA bioassays used in analysis

Study	*N*	Exposure group	Proportion with adenomas or carcinomas	TCA absorbed[a] (mg/kg-day)	TCA produced from PCE[b] (mg/kg-day)	AUC of free TCA in plasma[a,b] (mg-hr/L-day)	AUC of TCA in liver[a,b] (mg-hr/L-day)
NTP (1986)	49	0 ppm PCE	0.35	–	0	0	0
	47	100 ppm PCE	0.66	–	29	454	487
	50	200 ppm PCE	0.82	–	53	834	895
JISA (1993)	46	0 ppm PCE	0.28	–	0	0	0
	49	10 ppm PCE	0.43	–	4.5	73	78
	48	50 ppm PCE	0.40	–	16	260	280
	49	250 ppm PCE	0.82	–	64	1,043	1,121
DeAngelo et al. (2008)	56	0 g/L TCA	0.55	0	–	0	0
	48	0.06 g/L TCA	0.44	5.9	–	74	58
	51	0.7 g/L TCA	0.71	53	–	666	526

[a] Calculated using PBPK model of Chiu , using posterior mean parameter estimates and best-fit estimate of the fractional absorption from drinking water (88% at 0.6 g/L and 66% at 0.7 g/L).
[b] Calculated using PBPK model of Chiu and Ginsberg , using highest posterior mode parameter estimates.

C.1.3. **Dose-Response Modeling and Statistical Analysis**

Due to significantly different tumor incidences in control groups across the TCA and tetrachloroethylene data sets, combined analysis using standardized software such as BMDS is not feasible. Therefore, to test the consistency of the dose-response relationships, a standard statistical approach for binomial data is used. In particular, logistic regression was applied to the various data sets, with potential independent variables of dose, chemical, study, and their interactions (products). For a *k*-length vector of independent variable $\boldsymbol{x}$, and a probability of effect $p(\boldsymbol{x})$, the logistic model is defined by

$$p(\boldsymbol{x}) = 1/(1 + \exp[-z(\boldsymbol{x})]) \quad \text{(C-1)}$$

$$z(\boldsymbol{x}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k \quad \text{(C-2)}$$

with parameters β_j, $j = 1 \ldots k$. This is equivalent to linear regression with binomial variance of the variable *z*, which is the natural log of the odds of a effect $\ln(p/(1-p))$.

For the purposes of this analysis, β_0 is called the "intercept," β_1 is called the "slope" with respect to the dose metric x_1, $x_2 = 0$ or 1 is either the study (NTP = 0, JISA = 1, for tetrachloroethylene data) or the chemical (tetrachloroethylene = 0, TCA = 1) with β_2 the

corresponding regression coefficient (i.e., "different intercepts"), and $x_3 = x_1 \times x_2$ is the interaction term (i.e., "different slopes"). In this analysis, all β coefficients are unconstrained.

This model was implemented using the "glm" function in the R statistical package (version 12.2.1), which reports optimized estimates, standard errors, and *p*-values for each regression parameter. In addition, analysis of variance (ANOVA) using the "anova" function in R (with a chi-squared test statistic) can also be used to determine whether additional regression parameters produce significant improvement in model fit.

Of particular interest is the "interaction term" with regression coefficient β_2. In the event that this parameter is statistically significant (p-value < 0.05, confirmed by ANOVA), then this would be evidence that tetrachloroethylene and TCA have different dose-responses as a function of internal TCA dose (after accounting for possible differences in control incidences). In the event that this parameter is not statistically significant, it is well known that failure to reject a null hypothesis of no effect may simply be the result of low statistical power. While there is a large literature on "postexperiment power calculations," Hoenig and Heisey (2001) show that such an approach is fundamentally flawed and yield no further insights than confidence intervals (CIs). Therefore, the CI of the β_2 parameter is used as an indication of the range of possible contributions of TCA to tetrachloroethylene hepatocarcinogenesis.

C.2. RESULTS

C.2.1. Logistic Model Fits to Individual Data Sets

Each bioassay was first individually (using an intercept β_0 and a slope β_1) and goodness-of-fit evaluated using the chi-squared test on the residuals (see Table C-4, Figures C-1A and C-2A). All p-values were ≥0.15, suggesting the logistic model is an adequate description of the data for the purposes of this comparison.

C.2.2. Consistency of NTP and JISA Data

Analysis was conducted on the NTP and JISA studies to see if they are consistent, which would increase statistical power in the subsequent analysis of the contribution of TCA. Three logistic models were fit (see Table C-4, Figures C-1B, C-1C, and C-1D). Neither the study intercept β_2 nor the study-dose interaction term β_3 was statistically significant (CIs overlapped with 0, p-values from ANOVA were 0.17 and 0.14, respectively). Thus, the null hypothesis that the two bioassays for tetrachloroethylene have a common slope and intercept cannot be rejected.

As suggested by Hoenig and Heisey (2001), looking at the CIs gives insight into the power to reject this null hypothesis. The difference in intercepts (β_2) has a 95% confidence

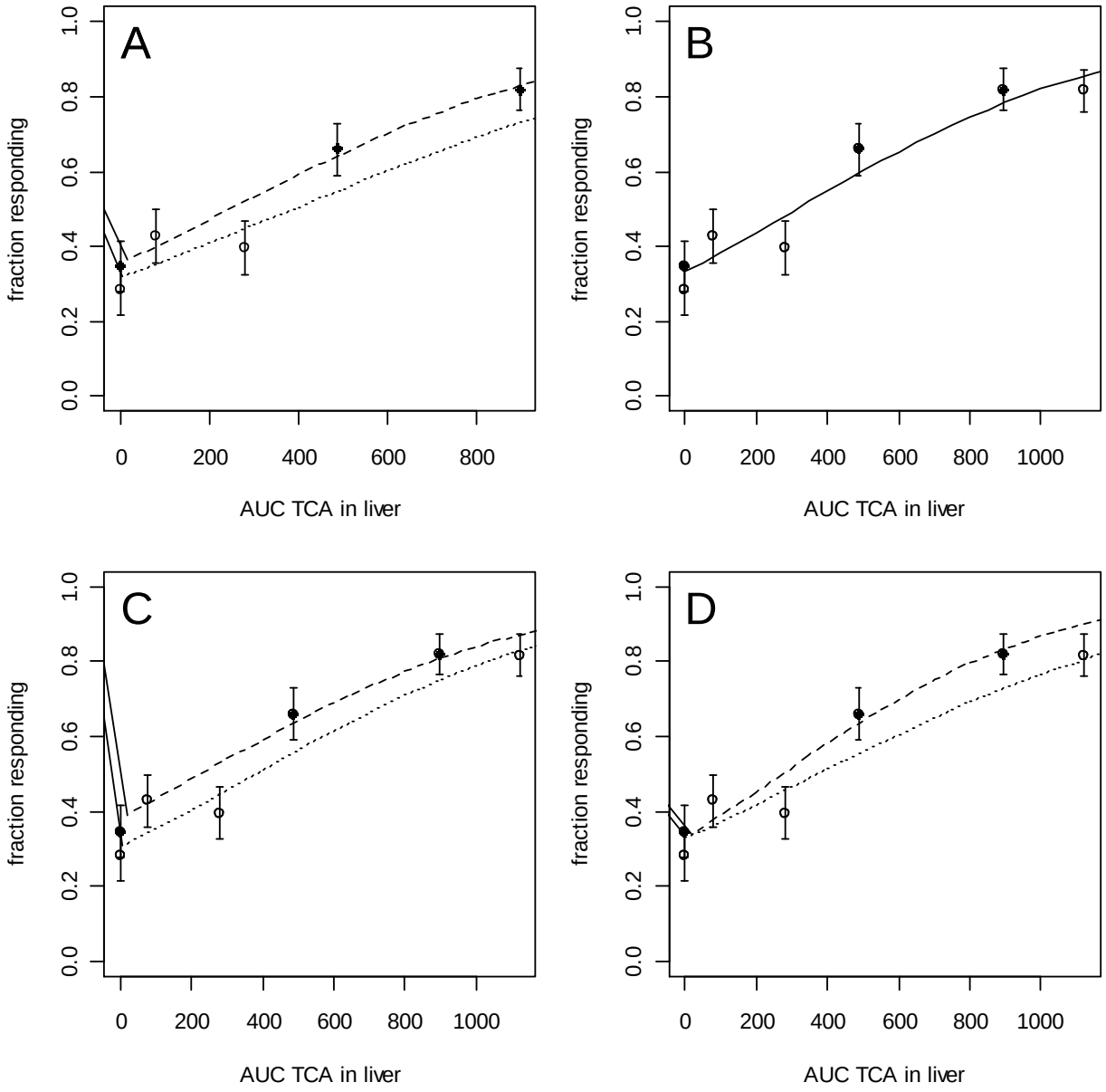
Table C-4. Logistic regression model fits—beta coefficients and standard errors[a]

Data analyzed	β_0 (Intercept)	1,000 × β_1 (Dose coefficient)	β_2 (Study or chemical intercept)	1,000 × β_3 (Dose × [study or chemical])	Chi-squared goodness-of-fit p-value[b]	Figure
NTP (1986)	–0.599 ± 0.280	2.43 ± 0.53	Not included	Not included	0.75	C-1A
JISA (1993)	–0.763 ± 0.199	1.97 ± 0.39	Not included	Not included	0.37	C-1A
DeAngelo et al. (2008)	–0.028 ± 0.207	1.64 ± 0.72	Not included	Not included	0.15	C-2A
NTP (1986) + JISA (1993)	–0.696 ± 0.162	2.21 ± 0.32	Not included	Not included	0.47	C-1B
	–0.482 ± 0.223	2.14 ± 0.32	*–0.334 ± 0.244*[c]	Not included	0.77	C-1C
	–0.709 ± 0.162	2.59 ± 0.42	Not included	*–0.683 ± 0.467*[c]	0.80	C-1D
NTP (1986) + JISA (1993) + DeAngelo et al. (2008)	–0.428 ± 0.125	1.95 ± 0.28	Not included	Not included	0.068	C-2B
	–0.665 ± 0.155	2.12 ± 0.29	0.556 ± 0.211	Not included	0.40	C-2C
	–0.696 ± 0.162	2.21 ± 0.32	0.668 ± 0.262	*–0.572 ± 0.790*[c]	0.36	C-2D

[a] Logistic model: proportion responding = $p(\mathbf{x}) = 1/(1 + \exp[-z(\mathbf{x})])$, $z(\mathbf{x}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$,.
where
x_1 = dose
x_2 = study (NTP = 0, JISA = 1) for analysis of NTP (1986) + JISA (1993)
= chemical (PCE [NTP or JISA] = 0, TCA [DeAngelo] = 1) for analysis of NTP (1986) + JISA (1993) + DeAngelo et al. (2008).

[b] Chi-squared percentage point at the sum-squared residuals (weighted by inverse binomial variance), with degrees of freedom equal to the number of data points minus the number of parameters.

[c] Parameters in *italics* are not significant ($p > 0.05$) either by regression CI or by ANOVA.



1

Figure C-1. Logistic regression dose-response fits to tetrachloroethylene data (open circle: JISA, 1993; filled circle: NTP, 1986). A: separate model fits to each dataset; B: single model fit to both data sets; C: model with separate intercepts and common slope; D: model with common intercept and separate slopes. See Table C-4 for parameter values, standard errors, and goodness-of-fit *p*-values.

2

region (based on ± 1.96 × standard error) of (−0.81, 0.14), implying that the odds of a tumor in JISA control animals is between 0.44- and 1.16-fold that of NTP control animals. The difference in slopes (β3) has a 95% confidence region of (−1.60, 0.23), implying that the odds ratio for JISA-exposed animals is between 0.20- and 1.26-fold that of NTP animals with equivalent AUCs of TCA in the liver. These ranges are quite large—up to twofold difference in background odds, and up to a fivefold difference in exposed/unexposed odds ratios cannot be ruled out by the available data. Nonetheless, for the purposes of further analysis, the NTP and JISA studies are combined, as these provide greater statistical power for determining the extent to which the TCA bioassay is consistent with the tetrachloroethylene bioassays on the basis of TCA internal dose.

C.2.3. **Consistency of Tetrachloroethylene and TCA Data**

Analysis was conducted on the combined NTP and JISA studies and the DeAngelo et al. (2008) TCA study to see if they are consistent. Three logistic models were fit (see Table C-4, Figures C-2B, C-2C, and C-2D). The chemical intercept term β_2 was statistically significant (parameter CI did not overlap with 0, *p*-value from ANOVA was 0.009). Thus, the null hypothesis that the two bioassays for tetrachloroethylene have a common intercept is rejected. The chemical slope term β_3 was not statistically significant (parameter CI overlapped with 0, *p*-value from ANOVA was 0.46). Thus, the null hypothesis that the TCA and tetrachloroethylene bioassays have a common slope (after accounting for different background rates) cannot be rejected.

As suggested by Hoenig and Heisey (2001), looking at the CIs gives insight into the power to reject this null hypothesis. The difference in slopes (β_3) has a 95% confidence region of −2.12, 0.98, implying that the odds ratio for TCA exposed/unexposed animals is between 0.12- and 2.65-fold that of tetrachloroethylene-exposed/unexposed animals with equivalent AUCs of TCA in the liver. These ranges are quite large—up to an eightfold difference in exposed/unexposed odds ratios cannot be ruled out by the available data. Moreover, these CIs are under the assumption that the tetrachloroethylene data reflect a common dose-response—relaxing this assumption would lead to wider CIs for the relative odds ratios between TCA and tetrachloroethylene bioassays.

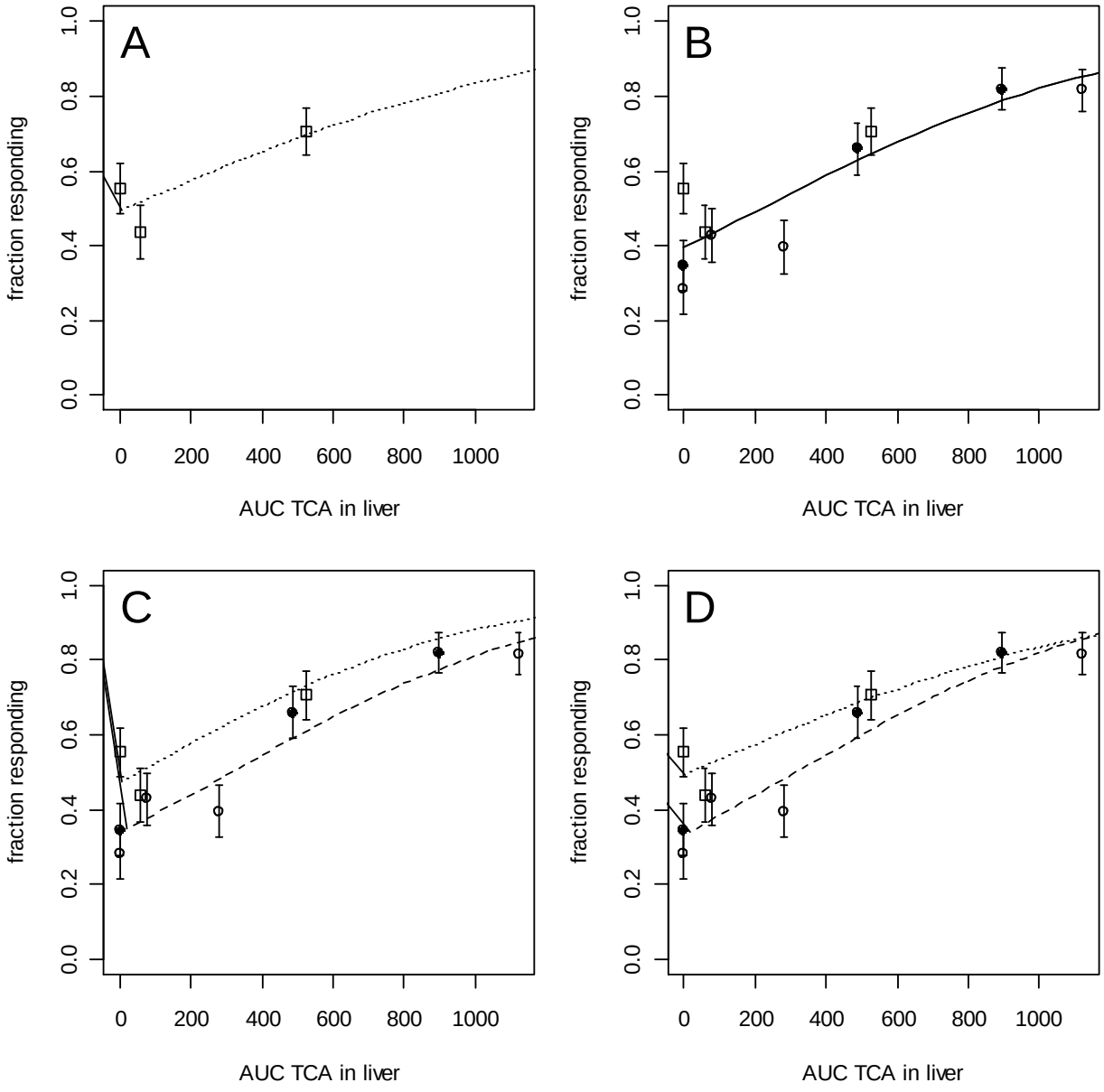


Figure C-2. Logistic regression dose-response fits to TCA (open square: DeAngelo et al., 2008) and combined TCA and tetrachloroethylene data (open circle: JISA, 1993; filled circle: NTP, 1986). A: model fit to TCA data only; B: single model fit to all data sets; C: model with chemical-specific intercepts and common slope; D: model with chemical-specific intercepts and chemical-specific slopes. See Table C-4 for parameter values, standard errors, and goodness-of-fit *p*-values.

C.3. CONCLUSIONS

This analysis suggests that TCA might explain the incidence of carcinomas observed in the available tetrachloroethylene bioassays but that a wide range of possible contributions cannot be ruled out by the available data. Specifically, a contribution of TCA from as little as 12 up to 100% cannot be ruled out, under the assumptions that the tetrachloroethylene NTP and JISA bioassay data can be combined, and using the Chiu and Ginsberg PBPK model for tetrachloroethylene and the Chiu PBPK model for TCA and TCA bioavailability. If either of these assumptions is relaxed—i.e., given that residual uncertainties of about twofold exist in the PBPK model predictions for TCA internal dose and that there may be some underlying differences between the NTP and JISA bioassays—then the CIs will be greater. Furthermore, the high control tumor incidence reported in the TCA bioassay of DeAngelo et al. (2008) raise questions as to the representativeness of that bioassay for comparison to tetrachloroethylene bioassays. Overall, as discussed in Chiu with regards to the contribution of TCA to TCE-induced hepatomegaly, factors such as study-to-study experimental variability in kinetics (e.g., metabolism, bioavailability) or in dynamics (e.g., background tumor rates), different analytical methods used to quantify TCA in blood and tissues and uncertainty in TCA dosing patterns in drinking water studies further limit the ability to discern the quantitative contribution of TCA. A more precise quantitative measure of the relative contribution of TCA to tetrachloroethylene-induced liver tumors requires an appropriately designed experiment to better control for these factors.

D. CANCER DOSE-RESPONSE MODELING

D.1. Model Selection Details For Tumor Sites from JISA (1993)

1

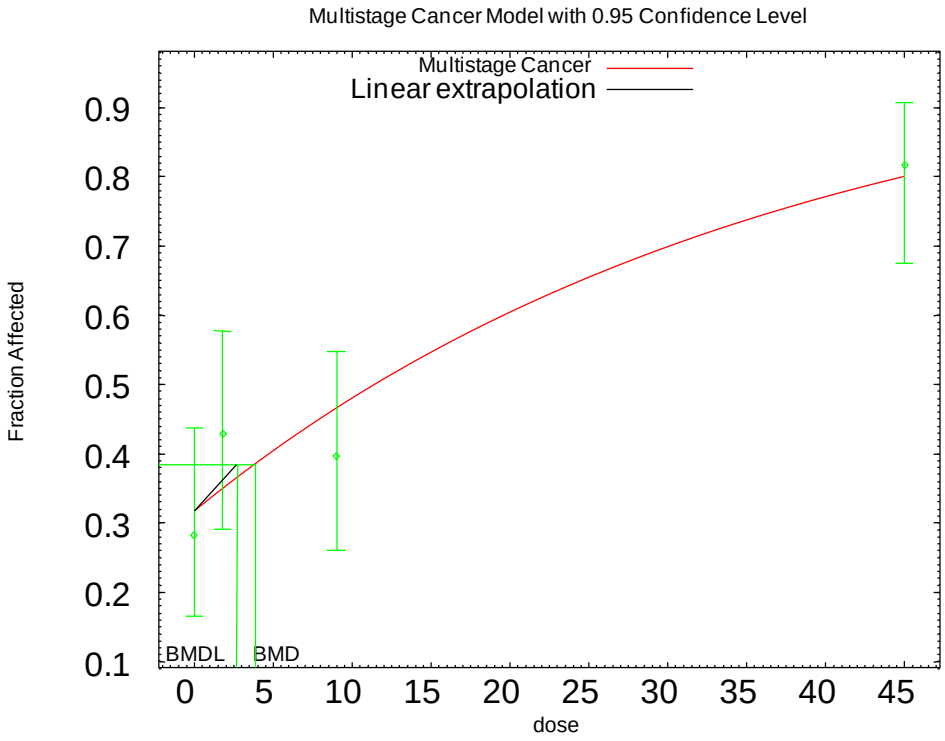
Table D-1. Model predictions for hepatocellular tumors in male mice (JISA, 1993)[a], using several dose metrics and multistage cancer model

Model stages	Goodness of fit			BMD_{10}	$BMDL_{10}$	Conclusion
	p-value[b]	Largest standardized residual(s)	AIC			
Total liver oxidative metabolism (mg/kg$^{0.75}$-day)						
One	**0.24**	**1.1, low-dose −1.2, mid-dose**	**239.7**	**2.9**	**2.1**	All three fits were adequate by conventional criteria.[b] There was no statistical improvement in adding higher-order coefficients (using likelihood ratio test); one-stage fit was selected.
Two	0.16	−0.7, control 1.1, low-dose	240.8	6.4	2.2	
Three	0.18	−0.7, control 1.0, low-dose	240.6	6.5	2.2	
TCA AUC in liver (mg-hr/L-day)						
One	**0.25**	**1.0, low-dose −1.2, mid-dose**	**239.7**	**97.1**	**68.8**	All three fits were adequate by conventional criteria.[b] There was no statistical improvement in adding higher-order coefficients (using likelihood ratio test); one-stage fit was selected.
Two	0.17	−0.7, control 1.1, low-dose	240.8	209.9	72.8	
Three	0.19	−0.7, control 1.0, low-dose	240.6	213.9	73.8	
Administered tetrachloroethylene concentration (ppm)						
One	**0.27**	**1.2, low-dose −1.0, mid-dose**	**239.5**	**3.9**	**2.7**	All three fits were adequate by conventional criteria.[b] There was no statistical improvement in adding higher-order coefficients (using likelihood ratio test); one-stage fit was selected.
Two	0.16	−0.8, control 1.1, low-dose	240.9	9.0	2.8	
Three	0.17	−0.8, control 1.1, low-dose	240.8	8.2	2.9	

[a] Incidence data and human equivalent continuous exposure estimates provided in Table 5-5.
[b] Goodness-of-fit *p*-values <0.05 for a preferred model, or <0.10 when considering many models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered. Best fit model is highlighted in bold; output for best fit models provided in following pages.
AIC = Akaike's Information Criteria, BMD = benchmark dose, BMDL = lower bound benchmark dose.

2

D.1.1. Modeling Output for Male Mice, Hepatocellular Tumors (JISA, 1993)



D.1.1.1. With total oxidative metabolism in liver as dose metric

Figure D-1 One-degree multistage model fit to hepatocellular tumors in male mice (JISA, 1993), with BMD and BMDL at 10% extra risk, using total oxidative metabolism in liver (mg/kg$^{0.75}$-day).

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=============================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)

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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0.285739
Beta(1) = 0.0395068

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.53
Beta(1)	-0.53	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.301268	*	*	*
Beta(1)	0.0361674	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-116.442	4			
Fitted model	-117.844	2	2.80477	2	0.246
Reduced model	-132.99	1	33.0977	3	<.0001

AIC: 239.688

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3013	13.858	13.000	46	-0.276
2.2500	0.3559	17.438	21.000	49	1.063
8.3000	0.4825	23.158	19.000	48	-1.201
33.6000	0.7927	38.844	40.000	49	0.408

Chi^2 = 2.81 d.f. = 2 P-value = 0.2448

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.91314

BMDL = 2.06187

BMDU = 4.49484

Taken together, (2.06187, 4.49484) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0484996

D.1.1.2. With TCA AUC in liver as dose metric

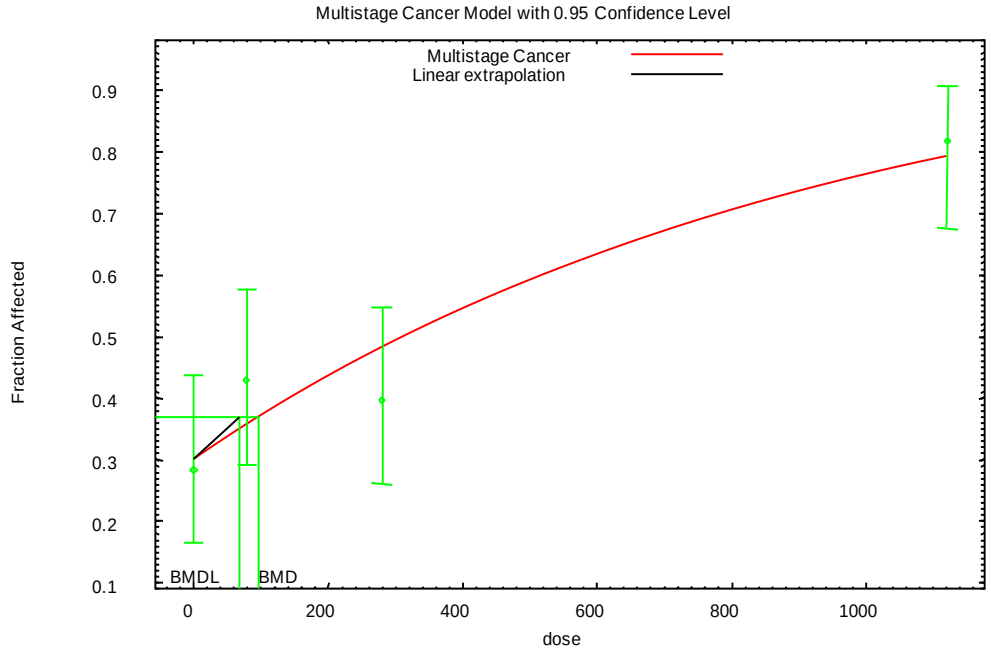


Figure D-2 One-degree multistage model fit to hepatocellular tumors in male mice (JISA, 1993), with BMD and BMDL at 10% extra risk, using

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)

=================================================================

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
               -beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Response
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                   Background =     0.283935
                      Beta(1) =   0.00118591


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)
```

```
Background            1        -0.53

   Beta(1)        -0.53            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.299803            *               *                   *
        Beta(1)        0.0010848            *               *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -116.442         4
    Fitted model        -117.833         2       2.78303      2          0.2487
  Reduced model          -132.99         1       33.0977      3         <.0001

           AIC:         239.666


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.2998        13.791    13.000          46       -0.255
   78.4900     0.3570        17.491    21.000          49        1.046
  279.7000     0.4831        23.186    19.000          48       -1.209
 1121.1000     0.7925        38.832    40.000          49        0.411

 Chi^2 = 2.79      d.f. = 2        P-value = 0.2477


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        97.1242

             BMDL =        68.7915

             BMDU =         149.76

Taken together, (68.7915, 149.76 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00145367
```

D.1.1.3. With administered tetrachloroethylene concentration (ppm) as dose metric

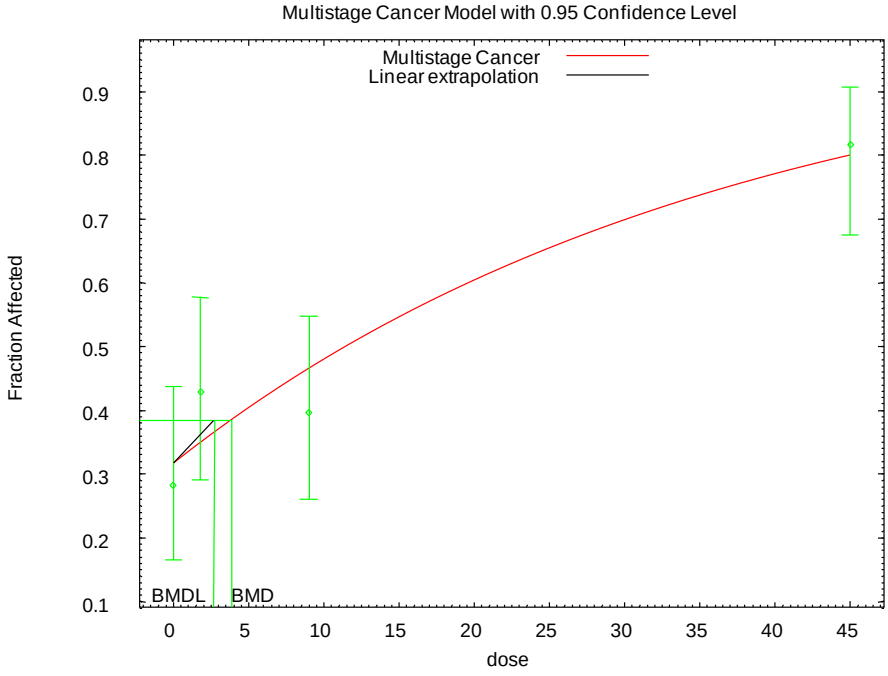


Figure D-3. One-degree multistage model fit to hepatocellular tumors in male mice (JISA, 1993), with BMD and BMDL at 10% extra risk, using administered tetrachloroethylene concentration (ppm).

```
 ================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
 ================================================================

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =     0.307193
                        Beta(1) =    0.0290723
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.48
Beta(1)	-0.48	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.316506	*	*	*
Beta(1)	0.0273229	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-116.442	4			
Fitted model	-117.738	2	2.59226	2	0.2736
Reduced model	-132.99	1	33.0977	3	<.0001
AIC:	239.476				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.3165	14.559	13.000	46	-0.494
1.8000	0.3493	17.116	21.000	49	1.164
9.0000	0.4655	22.344	19.000	48	-0.968
45.0000	0.8001	39.206	40.000	49	0.284

Chi^2 = 2.62 d.f. = 2 P-value = 0.2704

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 3.85613

BMDL = 2.70709

BMDU = 5.98909

Taken together, (2.70709, 5.98909) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.03694

1

Table D-2. Model predictions for hepatocellular tumors in female mice (JISA, 1993), using several dose metrics[a] and multistage cancer model

Model stage	Goodness of fit			BMD_{10}	$BMDL_{10}$	Comments	Conclusions
	p-value[b]	Largest standardized residual(s)	AIC				
Total liver oxidative metabolism (mg/kg$^{0.75}$-day)							
One-stage	0.14	-1.4, mid-dose	154.9	3.7	2.8	Adequate fit	Selected two-degree multistage, based on likelihood ratio test.
Two-stage	**0.82**	**-0.18, low-dose**	**152.8**	**8.4**	**4.0**	Adequate fit	
Three-stage	0.82	-0.18, low-dose	152.8	8.4	3.9	Adequate fit	
TCA AUC in liver (mg-hr/L-day)							
One-stage	0.13	-1.4, mid-dose	155.1	129	98	Adequate fit	Selected two-degree multistage, based on likelihood ratio test.
Two-stage	**0.82**	**-0.18, low-dose**	**152.9**	**292**	**141**	Adequate fit	
Three-stage	0.82	-0.18, low-dose	152.9	292	139	Adequate fit	
Administered tetrachloroethylene concentration (ppm)							
One-stage	**0.36**	**−1.1, mid-dose**	**153.0**	**5.0**	**3.8**	Adequate fit	Selected one-degree multistage; no statistical improvement in adding higher order parameters.
Two-, three-stage	0.83	−0.1, low-dose	152.8	9.7	4.3	Identical fits resulted from both models	

[a] Incidence data provided in Table 5-5, and dose metrics provided in Table 5-9; both are included in following output.

[b] Values <0.05 for a preferred model, or <0.10 when considering a suite of models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered. Best fit model is highlighted in bold; output for best fit models provided in following pages.

D.1.2. Modeling Output for Female Mice, Hepatocellular Tumors (JISA, 1993)

D.1.2.1. With total oxidative metabolism in liver as dose metric

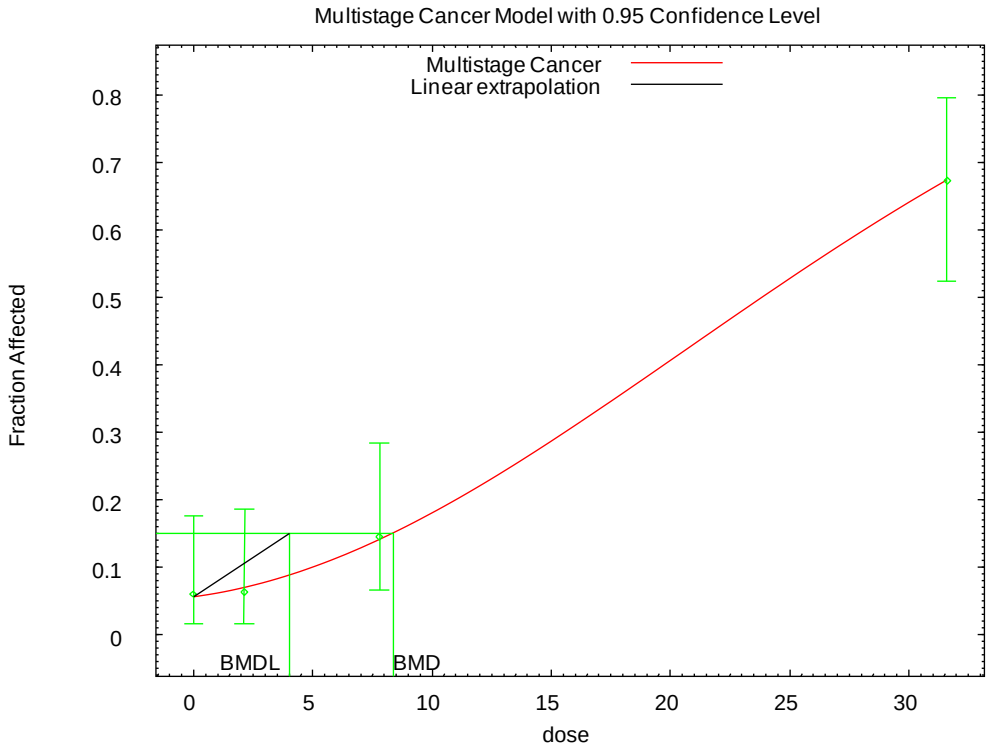


Figure D-4. Two-degree multistage model fit to hepatocellular tumors in female mice (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
 ========================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Usepa\BMDS21\msc_JISA1993_MF_HepAC_oxmet_Perc3_MultiCanc2_0.1.(d)
========================================================================

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0.0554081
Beta(1) = 0.00569729
Beta(2) = 0.000883583

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.69	0.59
Beta(1)	-0.69	1	-0.97
Beta(2)	0.59	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0566119	*	*	*
Beta(1)	0.00500318	*	*	*
Beta(2)	0.000907152	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-73.398	4			
Fitted model	-73.4233	3	0.050713	1	0.8218
Reduced model	-106.26	1	65.7232	3	<.0001

AIC: 152.847

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0566	2.831	3.000	50	0.104
2.1300	0.0704	3.311	3.000	47	-0.177
7.8000	0.1414	6.789	7.000	48	0.087
31.6000	0.6744	33.048	33.000	49	-0.015

Chi^2 = 0.05 d.f. = 1 P-value = 0.8230

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 8.36661

BMDL = 4.02336

BMDU = 11.6726

Taken together, (4.02336, 11.6726) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0248549

D.1.2.2. With TCA AUC in liver as dose metric

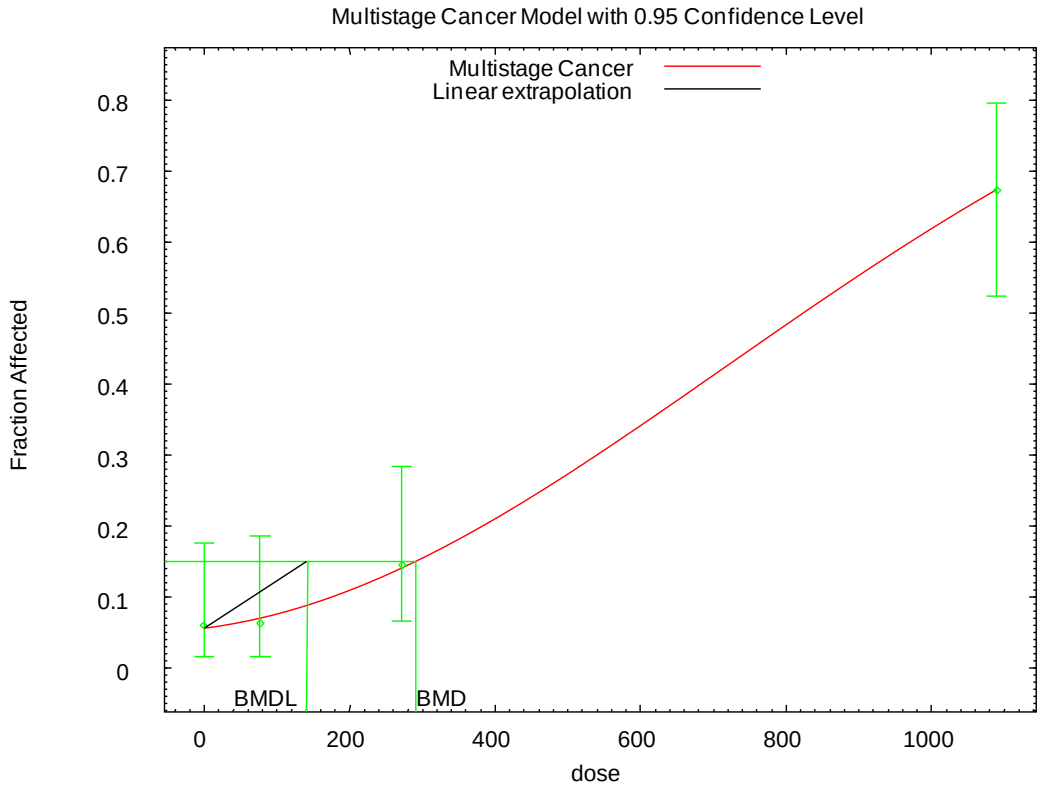


Figure D-2 Two-degree multistage model fit to hepatocellular tumors in female mice (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
=================================================================
          Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
          Input Data File: C:\Usepa\BMDS21\msc_JISA1993_MF_HepAC_tcaAUC_Perc3_MultiCanc2_0.1.(d)
=================================================================

    The form of the probability function is:

    P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1-beta2*dose^2)]

    The parameter betas are restricted to be positive


    Dependent variable = Response
    Independent variable = Dose

  Total number of observations = 4
  Total number of records with missing values = 0
  Total number of parameters in model = 3
  Total number of specified parameters = 0
  Degree of polynomial = 2


  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008



                    Default Initial Parameter Values
                       Background =     0.0553149
                          Beta(1) =   0.000156854
                          Beta(2) = 7.50947e-007
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)	Beta(2)
Background	1	-0.69	0.6
Beta(1)	-0.69	1	-0.97
Beta(2)	0.6	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0565811	*	*	*
Beta(1)	0.000135812	*	*	*
Beta(2)	7.71737e-007	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-73.398	4			
Fitted model	-73.4249	3	0.0538645	1	0.8165
Reduced model	-106.26	1	65.7232	3	<.0001

AIC: 152.85

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0566	2.829	3.000	50	0.105
76.9500	0.0706	3.320	3.000	47	-0.182
271.8000	0.1412	6.776	7.000	48	0.093
1089.6000	0.6745	33.051	33.000	49	-0.016

Chi^2 = 0.05 d.f. = 1 P-value = 0.8177

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 291.833

BMDL = 141.409

BMDU = 402.749

Taken together, (141.409, 402.749) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000707168

D.1.2.3. With administered tetrachloroethylene concentration (ppm) as dose metric

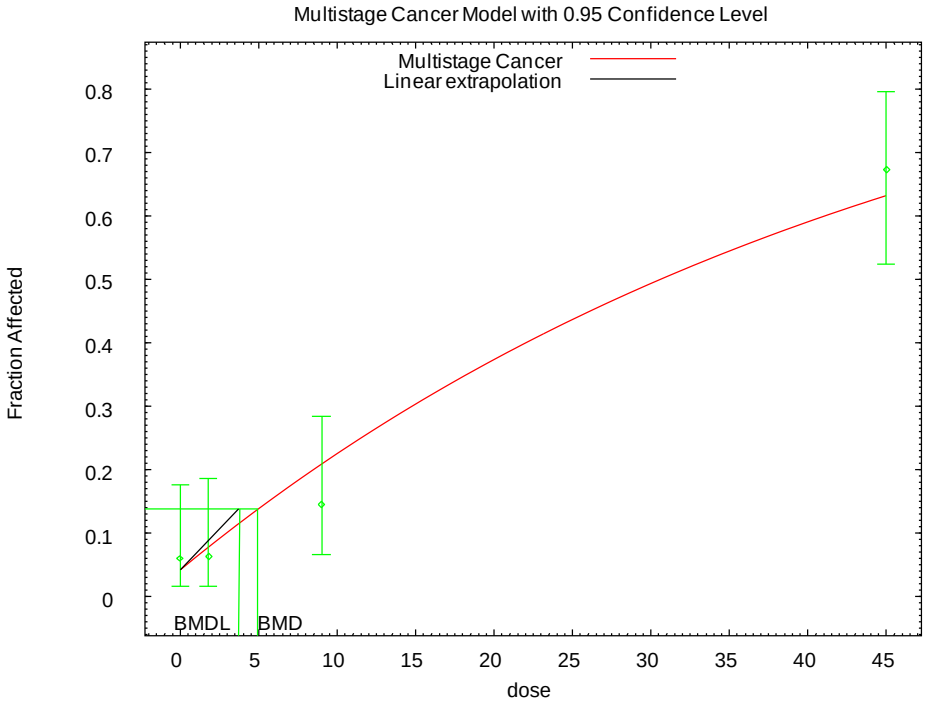


Figure D-3. One-degree multistage model fit to hepatocellular tumors in female mice (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
=================================================================
          Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)

=================================================================

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0124442
```

Beta(1) = 0.0242761

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.47
Beta(1)	-0.47	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0427836	*	*	*
Beta(1)	0.0212108	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-73.398	4			
Fitted model	-74.4575	2	2.11904	2	0.3466
Reduced model	-106.26	1	65.7232	3	<.0001

AIC: 152.915

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0428	2.139	3.000	50	0.602
1.8000	0.0786	3.696	3.000	47	-0.377
9.0000	0.2091	10.038	7.000	48	-1.078
45.0000	0.6315	30.942	33.000	49	0.610

Chi^2 = 2.04 d.f. = 2 P-value = 0.3609

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.96731

BMDL = 3.75394

BMDU = 6.8242

Taken together, (3.75394, 6.8242) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0266387

1

Table D-3. Model predictions for hemangiomas or hemangiosarcomas in male mice (JISA, 1993), using tetrachloroethylene AUC in blood and administered tetrachloroethylene concentration as dose metrics[a] and multistage cancer model

Model stage	Goodness of fit			BMD_{10}	$BMDL_{10}$	Conclusions
	p-value[b]	Largest standardized residual(s)	AIC			
Tetrachloroethylene AUC in blood (mg-hr/L-day)						
One-, two-, three-stage	**0.38**	**−1.0, low-dose, 0.9, mid-dose**	**142.0**	**63.0**	**34.3**	Fits for all three models were the same; only the first order term was >0.
Administered tetrachloroethylene concentration (ppm)						
One-, two-, three-stage	**0.38**	**−1.0, low-dose, 0.9, mid-dose**	**142.0**	**24.4**	**13.3**	Fits for all three models were the same; only the first order term was >0.

[a] Incidence data and human equivalent continuous exposures provided in Table 5-5 and in the output below.
[b] Values <0.05 for a preferred model, or <0.10 when considering suite of models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered. Best fit model is highlighted in bold; output for best fit models provided in following pages.

1
2
3

D.1.3. Modeling Output for Male Mice, Hemangiomas or Hemangiosarcomas (JISA, 1993)

D.1.3.1. With tetrachloroethylene AUC in blood as dose metric

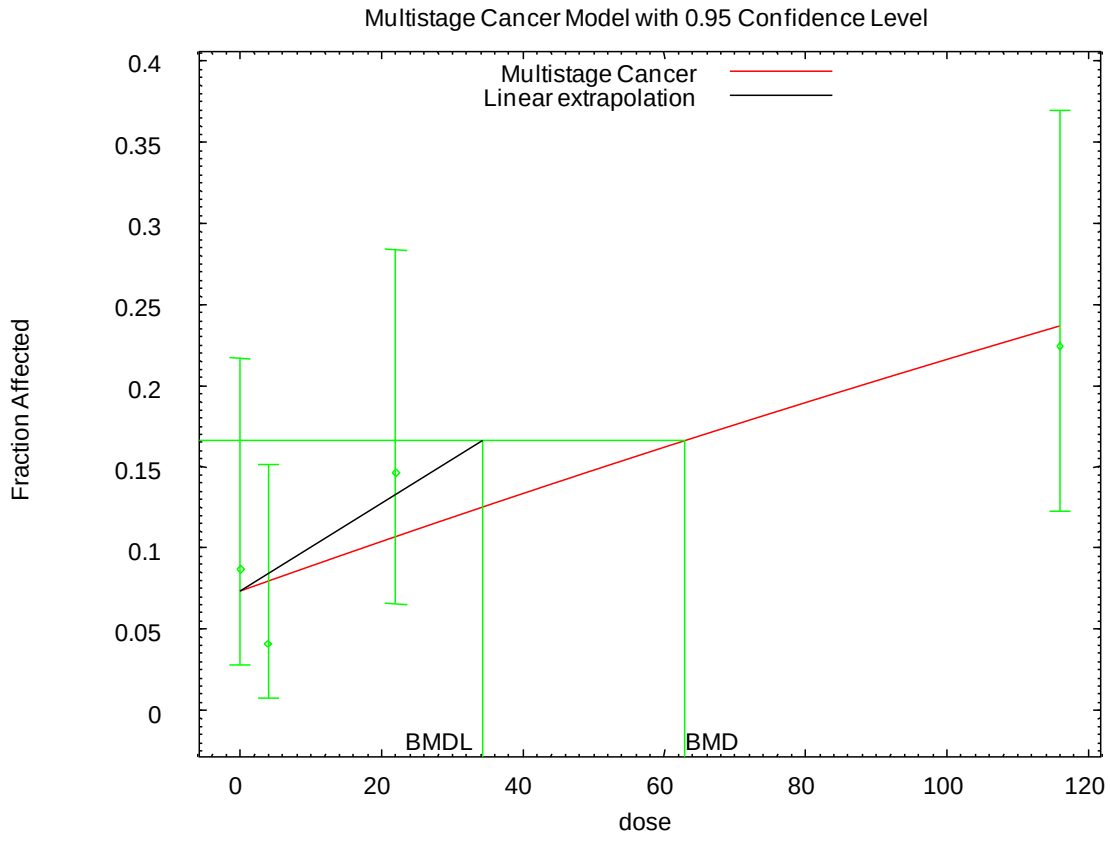


Figure D-7. One-degree multistage model fit to hemangioma or hemangiosarcoma incidence in male mice (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)

======================================================================


   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1
```

```
 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =    0.0779832
                        Beta(1) =   0.00154747


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1         -0.6

   Beta(1)         -0.6            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background        0.0731517            *                *                   *
        Beta(1)       0.00167339            *                *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -67.9801         4
   Fitted model         -69.0102         2       2.06035      2          0.3569
  Reduced model         -72.3399         1       8.71962      3         0.03326

           AIC:          142.02


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0732         3.365     4.000          46        0.360
    4.0000     0.0793         3.887     2.000          49       -0.998
   22.0000     0.1067         5.119     7.000          48        0.879
  116.0000     0.2367        11.597    11.000          49       -0.201

 Chi^2 = 1.94      d.f. = 2        P-value = 0.3794


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        62.9622

             BMDL =        34.3348

             BMDU =          191.7

Taken together, (34.3348, 191.7  ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =     0.0029125
```

D.1.3.2. With administered tetrachloroethylene concentration (ppm) as dose metric

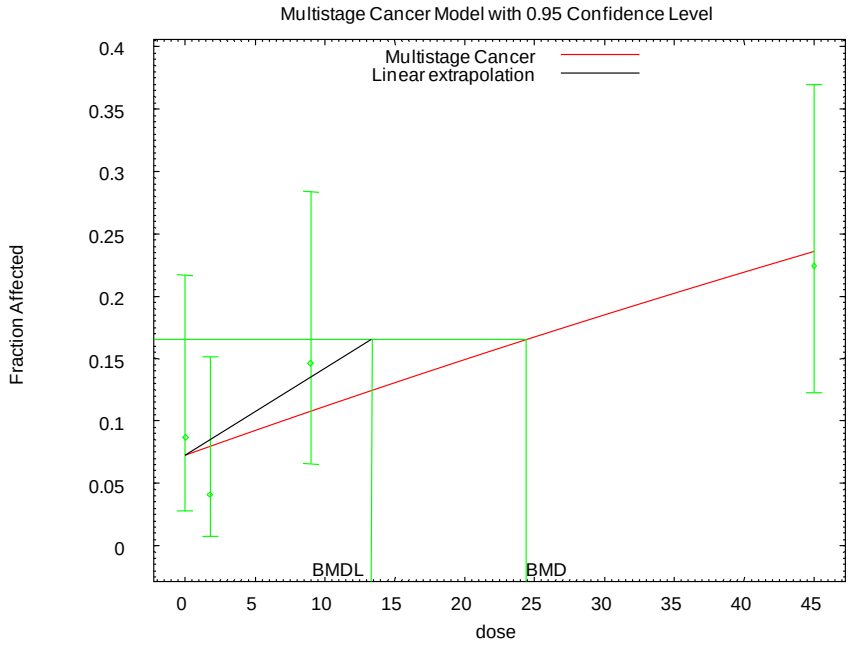


Figure D-8. One-degree multistage model fit to hemangioma or hemangiosarcoma incidence in male mice (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
=================================================================
        Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)

=================================================================

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = Response
  Independent variable = Dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values
Background = 0.0770402
Beta(1) = 0.00401128

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.6
Beta(1)	-0.6	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0723269	*	*	*
Beta(1)	0.00432149	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-67.9801	4			
Fitted model	-69.001	2	2.04183	2	0.3603
Reduced model	-72.3399	1	8.71962	3	0.03326

AIC: 142.002

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0723	3.327	4.000	46	0.383
1.8000	0.0795	3.896	2.000	49	-1.001
9.0000	0.1077	5.170	7.000	48	0.852
45.0000	0.2363	11.577	11.000	49	-0.194

Chi^2 = 1.91 d.f. = 2 P-value = 0.3843

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 24.3806

BMDL = 13.3404

BMDU = 73.8608

Taken together, (13.3404, 73.8608) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.00749601

1

D.1.3.3. Modeling Output For Male Mice (*JISA, 1993*), Combined Risk of Hepatocellular Tumors or Hemangiomas/Hemangiosarcomas, at 10% Extra Risk, using Administered Concentration and Multistage Modeling (Discussed in Section 5.4.4.1)

```
================================================================
        MS_COMBO. (Version: 1.5 Beta;  Date: 01/25/2011)
        Input Data File: C:\Usepa\BMDS220\Data\SessionFiles\New.(d)

 ================================================================

[For separate model fits of hepatocellular tumors and hemangiomas/hemangiosarcomas
using administered concentration, see Sections D.1.1.3 and D.1.3.2, respectively.
Duplicate output from MS_COMBO was omitted here.]


**** Start of combined BMD and BMDL Calculations.****

  Combined Log-Likelihood                    -186.73874141530868

  Combined Log-likelihood Constant            169.44438524661712


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        3.32952

            BMDL =         2.4128
```

1

2

Table D-4. Model predictions for male rat mononuclear cell leukemia (MCL) (JISA, 1993), using tetrachloroethylene AUC in blood and administered tetrachloroethylene concentration as dose metrics[a] and multistage model

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Conclusions
	p-value[b]	Largest standardized residual(s)	AIC			
Tetrachloroethylene AUC in blood (mg-hr/L-day)						
One-, two-, three-s**tage**	**0.52**	**1.0, mid-dose**	**254.9**	**46.1**	**29.7**	Fits for all three models were the same; only the first order term was >0
Administered tetrachloroethylene concentration (ppm)						
One-, two-, three-**stage**	**0.52**	**1.0, mid-dose**	**254.9**	**20.5**	**13.2**	Fits for all three models were the same; only the first order term was >0

[a] Incidence data and human equivalent continuous exposures provided in Table 5-7 and in the output below.
[b] Values <0.05 for a preferred model, or <0.10 when considering suite of models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within $\pm$2 units) are considered. Best fit model is highlighted in bold; output for best fit models provided in following pages.

1
2

D.1.4. **Modeling Output for Male Rats, MCL (JISA, 1993)**

D.1.4.1. With tetrachloroethylene AUC in blood as dose metric

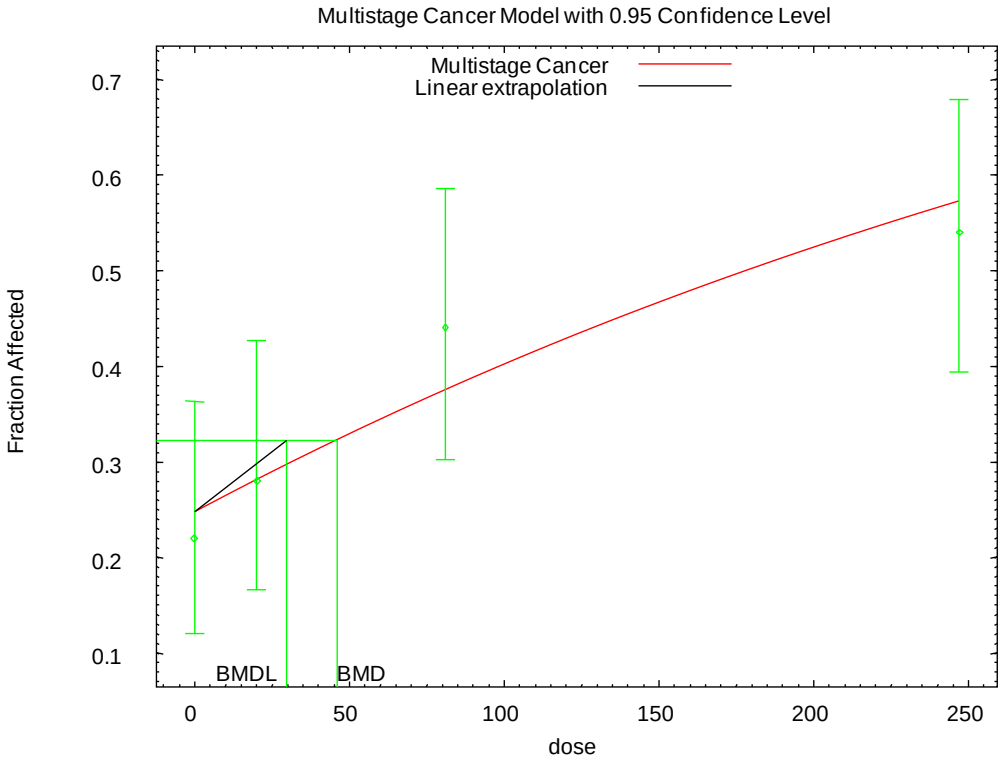


Figure D-9. One-stage model fit to MCL incidence in male rats (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
 ======================================================================
         Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
         Input Data File: C:\Usepa\BMDS21\msc_JISA1993_RM_MCL_percAUC_Perc3_MultiCanc1_0.1.(d)
======================================================================

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = Response
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1
```

```
 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                     Background =     0.263087
                        Beta(1) =   0.00204647


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.63

   Beta(1)        -0.63            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background          0.24777            *               *                   *
        Beta(1)        0.0022863            *               *                   *

* - Indicates that this value is not calculated.


                         Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -124.787         4
   Fitted model         -125.442         2       1.31081      2          0.5192
  Reduced model         -131.791         1       14.0088      3        0.002893

           AIC:          254.884


                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.2478        12.388    11.000          50       -0.455
   20.0000     0.2814        14.070    14.000          50       -0.022
   81.0000     0.3749        18.747    22.000          50        0.950
  247.0000     0.5723        28.617    27.000          50       -0.462

 Chi^2 = 1.32      d.f. = 2        P-value = 0.5158


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        46.0834

            BMDL =        29.6814

            BMDU =        90.5076

Taken together, (29.6814, 90.5076) is a 90     % two-sided confidence
interval for the BMD
```

```
Multistage Cancer Slope Factor =    0.00336911
```

D.1.4.2. With administered tetrachloroethylene concentration (ppm) as dose metric

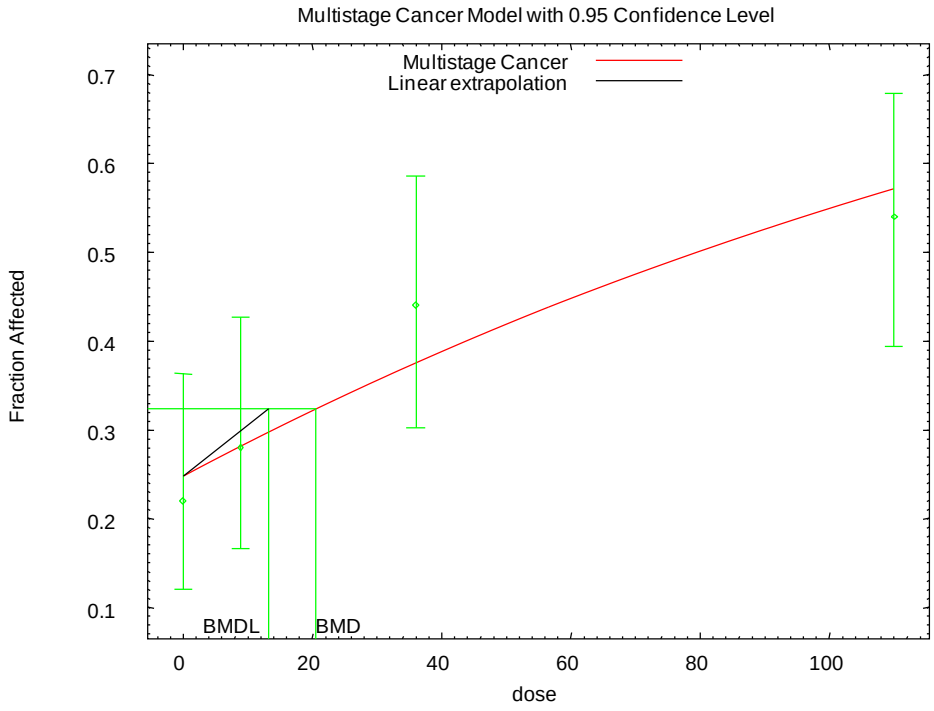


Figure D-10. One-stage model fit to MCL incidence in male rats (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
=================================================================

          Multistage Cancer Model. (Version: 1.5;  Date: 02/20/2007)
=================================================================

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

   The parameter betas are restricted to be positive


   Dependent variable = mcl
   Independent variable = hecdose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3

 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                 Default Initial Parameter Values
```

```
                    Background =     0.263191
                       Beta(1) =   0.00459397
                       Beta(2) =            0
                       Beta(3) =            0


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(2)    -Beta(3)
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)

Background            1        -0.63

   Beta(1)        -0.63            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    Background         0.247855            *                 *                   *
       Beta(1)       0.00513336            *                 *                   *
       Beta(2)                0            *                 *                   *
       Beta(3)                0            *                 *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -124.787         4
   Fitted model        -125.445         2        1.3173      2          0.5175
  Reduced model        -131.791         1       14.0088      3        0.002893

           AIC:         254.891


                                Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.2479        12.393        11          50       -0.456
    8.9000     0.2814        14.072        14          50       -0.023
   36.0000     0.3748        18.738        22          50        0.953
  110.0000     0.5724        28.618        27          50       -0.463

 Chi^2 = 1.33      d.f. = 2        P-value = 0.5141


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        20.5247

             BMDL =        13.2172

             BMDU =        55.2398

Taken together, (13.2172, 55.2398) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =    0.00756592
```

1

Table D-5. Model predictions for female rat MCL (JISA, 1993),[a] using administered tetrachloroethylene concentration (ppm)[c] and multistage model

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Conclusion
	p-value[b]	Largest standardized residual(s)	AIC			
Tetrachloroethylene AUC in blood (mg-hr/L-day)						All three models provided identical fits, with only the first-order parameter >0. However, model did not adequately estimate responses at control and low-dose. **Multistage model not selected** (output shown for administered concentration only)**.**
One-, two-, three-stage	0.34	−1.0, control 1.0, low-dose	249.4	136	61	
Administered tetrachloroethylene concentration (ppm)						
One-, two-, three-stage	0.34	−1.0, control 1.0, low-dose	249.4	60.4	26.8	

[a] Incidence data and human equivalent continuous exposure estimates provided in Table 5-7.
[b] When there is no preferred model, values <0.10 fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered.
[c] Due to the proportionality of tetrachloroethylene AUC in blood, the preferred dose metric, to administered concentration, only administered concentration was used as the dose metric until the final model selection was made.

2

Table D-6. Comparison of model predictions for female rat MCL (JISA, 1993),[a] using administered tetrachloroethylene concentration as dose metric[d]

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Comments	Conclusion
	p-value[b]	Largest standardized residual(s)	AIC				
All dose groups							
Michaelis-Menten	0.55	(0.0, control) −0.5, mid-dose	249.6	5.3	NA	Best visual fit (see output)	
LogLogistic	0.34	−1.0, control 1.0, low-dose	249.4	56.2	NA	Slope parameter unrestricted[c]	Poor fit to control and low-dose responses.
Gamma, Weibull	0.34	−1.0, control 1.0, low-dose	249.4	60.4	NA	Power parameters unrestricted[c]	
Probit	0.33	−1.1, control 1.0, low-dose	249.5	67.6	35.5	—	
Logistic	0.33	−1.1, control 1.0, low-dose	249.5	68.4	36.5	—	
LogProbit	0.26	−1.0, control 1.0, low-dose	250.0	88.0	NA	—	
Highest dose group dropped							
Weibull	0.83	(0.0, control) 0.2, low-dose	181.0	NA	NA	Power parameter unrestricted[c]; step-function	Implausible fit
LogLogistic	0.17	−0.7, control 1.1, low-dose	182.7	26.5	NA	Slope parameter unrestricted[c]	Poor fit to control and low-dose responses
Multistage (one-degree)	0.17	−0.8, control 1.1, low-dose	182.7	28.3	10.3	No statistical improvement with higher order models	
Probit	0.16	−0.8, control 1.1, low-dose	182.8	31.5	13.7	—	
Logistic	0.16	−0.9, control 1.1, low-dose	182.8	31.9	14.1	—	
LogProbit	0.09	Inadequate					
Gamma, Michaelis-Menten	Insufficient degrees of freedom						
Highest two dose groups dropped							
Multistage	Fit statistics not relevant			4.9	2.3	Adequate fit to control data	
Other models	Insufficient degrees of freedom						

[a] Incidence data and human equivalent continuous exposures provided in Table 5-7.
[b] When there is no preferred model, values <0.10 fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered. Best fit model is highlighted in bold; output for best fit models provided in following pages.
[c] Slope or power parameters were initially limited to be ≥1 to avoid infinite slopes at zero dose. However, fits with restricted parameters may not provide BMDLs with correct statistical coverage. Fits to these data with unrestricted power or slope parameters did not provide BMDLs, effectively 0.
[d] Due to the proportionality of tetrachloroethylene AUC in blood, the preferred dose metric, to administered concentration, only administered concentration was used as the dose metric until the final model selection was made.

D.1.5. Modeling Output for Female Rats, MCL (JISA, 1993), with administered tetrachloroethylene concentration as dose metric

D.1.5.1. Multistage model fit

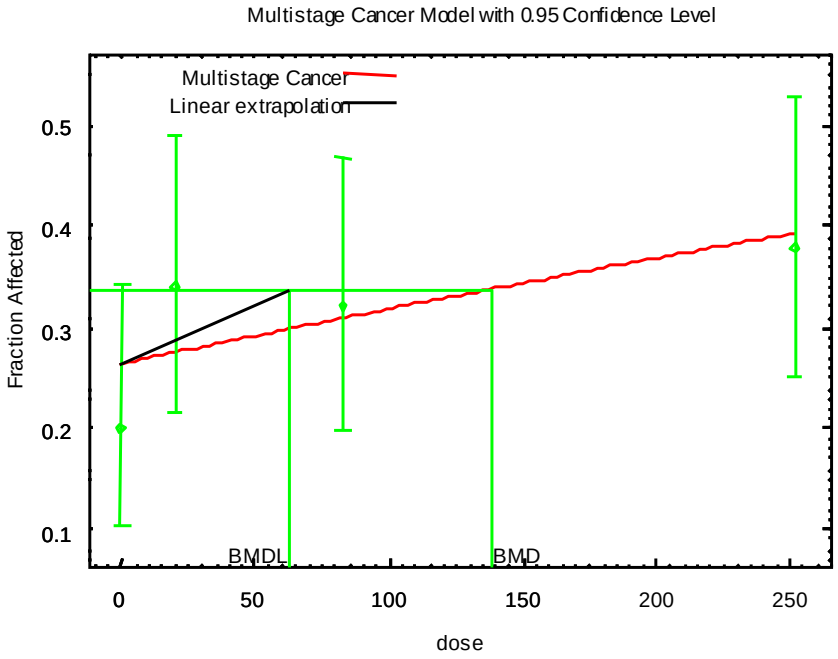


Figure D-11. One-stage multistage model fit to MCL incidence in female rats (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
 ======================================================================
          Multistage Cancer Model. (Version: 1.7;  Date: 05/16/2008)
          Input Data File: C:\Usepa\BMDS21\msc_JISA1993_RF_MCL_admc_Perc3_MultiCanc1_0.1.(d)
======================================================================

    The form of the probability function is:

    P[response] = background + (1-background)*[1-EXP(
                  -beta1*dose^1)]

    The parameter betas are restricted to be positive


    Dependent variable = Response
    Independent variable = Dose

  Total number of observations = 4
  Total number of records with missing values = 0
  Total number of parameters in model = 2
  Total number of specified parameters = 0
  Degree of polynomial = 1


  Maximum number of iterations = 250
```

```
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.269118
                        Beta(1) =   0.00160326


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.66

   Beta(1)        -0.66            1



                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
     Background         0.263768            *               *                   *
        Beta(1)       0.00174342            *               *                   *

* - Indicates that this value is not calculated.



                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -121.619         4
   Fitted model         -122.71         2       2.18339      2          0.3356
  Reduced model         -123.82         1       4.40312      3          0.2211

           AIC:         249.421


                                Goodness  of  Fit
                                                                    Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ----------------------------------------------------------------------
    0.0000     0.2638        13.188    10.000          50       -1.023
    8.9000     0.2751        13.755    17.000          50        1.028
   36.0000     0.3086        15.428    16.000          50        0.175
  110.0000     0.3922        19.612    19.000          50       -0.177

 Chi^2 = 2.17      d.f. = 2        P-value = 0.3387


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        60.4331

            BMDL =        26.8451


BMDU did not converge for BMR = 0.100000
BMDU calculation failed
            BMDU = Inf
```

1

D.1.5.2. Michaelis-Menten fit

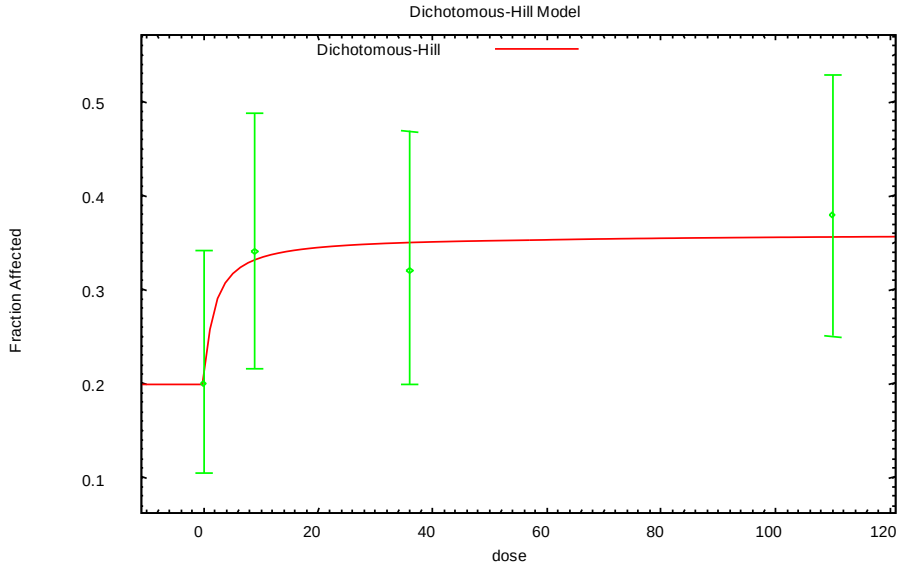


Figure D-12. Michaelis-Menten model fit to MCL incidence in female rats (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
 ================================================================
         Dichotomous Hill Model. (Version: 1.0; Date: 09/24/2006)
         Input Data File: C:\Usepa\BMDS21\dhl_JISA1993_RF_MCL_admc_DichHill_slope1_0.1.(d)
================================================================

   The form of the probability function is:

   P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

        where: 0 <= g < 1, 0 < v <= 1

               v is the maximum probability of response predicted by the model,

               and v*g is the background estimate of that probability.


   Dependent variable = Response
   Independent variable = Dose
   Slope parameter is set to 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  User Inputs Initial Parameter Values
                              v =          0.6
                              g =         0.38
                      intercept =           -4
                          slope =        -9999   Specified
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	v	g	intercept
v	1	-0.53	-0.76
g	-0.53	1	0.32
intercept	-0.76	0.32	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
v	0.358282	0.0647079	0.231457	0.485107
g	0.558478	0.186157	0.193618	0.923338
intercept	-0.531551	4.74243	-9.82655	8.76345

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test d.f.	P-value
Full model	-121.619			
Fitted model	-121.795	0.353046	1	0.5524
Reduced model	-123.82	4.40312	3	0.2211

AIC: 249.59

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2001	10.005	10	50	-0.001636
8.9000	0.3329	16.645	17	50	0.1067
36.0000	0.3511	17.557	16	50	-0.4613
110.0000	0.3559	17.794	19	50	0.3563

Chi^2 = 0.351193 d.f. = 1 P-value = 0.5534

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.74056

Benchmark dose computation failed. Lower limit includes zero.

Table D-7. Model predictions for combined male and female rat MCL (JISA, 1993),[a] using administered tetrachloroethylene concentrations as dose metric

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Comments	Conclusions
	p-value [b]	Largest standardized residual(s)	AIC				
Administered Tetrachloroethylene Concentration (ppm)							
Michaelis-Menten	**0.68**	**−0.3, mid-dose**	**503.6**	**7.7**	**1.4**	**Best fit to combined data.**	
LogLogistic	0.35	−0.9, control	503.4	5.1	0.003	Unrestricted slope parameter[c]	Fit at control response not useful.
Multistage, one-stage,	0.28	−1.1, control	504.0	32.0	20.9	No statistical improvement from higher order stages	
Gamma	0.96		503.4	4.5	0.001	Unrestricted power parameter	
Weibull	0.98		503.4	4.8	0.002	Unrestricted power parameter	
Probit	0.20	−1.3, control	504.7	40.7	29.7	—	
Logistic	0.19	−1.3, control	504.8	41.6	30.5	—	
LogProbit	0.07	−1.6, control	506.8	55.2	38.6	Inadequate overall fit	
Tetrachloroethylene AUC in blood (mg-hr/L-day)[d]							
Michaelis-Menten[e]	**0.68**	**−0.3, mid-dose**	**503.6**	**17.4**	**3.0**	Best fit above repeated with preferred dose metric.	

[a] Incidence data and human equivalent continuous exposures provided in Table 5-7 and in output below.
[b] Values <0.10 fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ± 2 units) are considered. Best fit model is highlighted in bold; output for best fit models provided in following pages.
[c] Lower limit for slope or power parameters is ≥ 1 to avoid infinite slopes at zero dose. However, fits with restricted parameters may not provide BMDLs with adequate statistical coverage. Fits with unrestricted power or slope parameters did not provide a usable BMDL.
[d] Due to the proportionality of tetrachloroethylene AUC in blood, the preferred dose metric, to administered concentration, administered concentration was used as the dose metric until the final model selection was made.
[e] Dichotomous-Hill model with slope fixed at 1.

1
2

Analyses to evaluate combining the male and female rat MCL data:

1. Following the strategy of Stiteler et al. (1993), the data sets were evaluated for statistical compatibility by applying the generalized likelihood ratio method to the results of fitting a common dose-response model (Michaelis-Menten) to the separate and combined data sets (using administered concentration as dose metric):

	Female Rat MCLs	Male Rat MCLs	Females + Males
Maximum log-likelihoods (LLs), and sum	−121.795 (3 df)	-124.841 (3 df)	−246.636 (6 df)
Overall LL from combined data set			−248.79 (3 df)
X^2 = 2 × absolute difference in LLs.			X^2 = 2.15 (p = 0.54)

2. Logistic regression was used to test whether the datasets differed significantly between males and females. The advantage of this approach is that it does not require assuming a specific functional form to represent the dose response relationship. Dose and sex were treated as categorical variables using PROC LOGISTIC in SAS:

Effect	DF	Wald Chi-Square	Pr > ChiSq
dose	3	14.6302	0.0022
sex	1	1.6634	0.1971

The p-value of 0.197 for sex indicates no significant relationship of sex in the pattern of responses.

D.1.6. Modeling Output for Male and Female Rats, MCL (JISA, 1993)

D.1.6.1. With administered tetrachloroethylene concentration (ppm) as dose metric

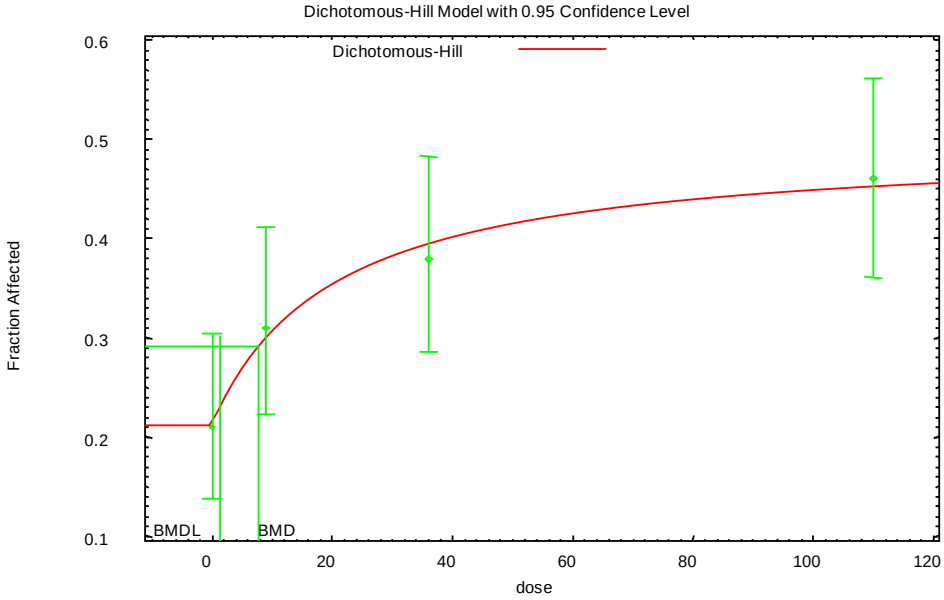


Figure D-4: Dichotomous-Hill model fit to MCL incidence in male and female rats (JISA, 1993), with BMD and BMDL at 10% extra risk.

```
=====================================================================
        Dichotomous Hill Model. (Version: 1.0; Date: 09/24/2006)
=====================================================================

  The form of the probability function is:

  P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

       where: 0 <= g < 1, 0 < v <= 1

              v is the maximum probability of response predicted by the model,

              and v*g is the background estimate of that probability.


  Dependent variable = Response
  Independent variable = Dose
  Slope parameter is set to 1

  Total number of observations = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008


                User Inputs Initial Parameter Values
                          v =          0.6
                          g =         0.38
                  intercept =           -4
```

slope = -9999 Specified

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	v	g	intercept
v	1	-0.6	-0.86
g	-0.6	1	0.3
intercept	-0.86	0.3	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
v	0.496794	0.0951495	0.310304	0.683283
g	0.428222	0.100989	0.230288	0.626157
intercept	-3.00428	1.19179	-5.34015	-0.668408

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test d.f.	P-value
Full model	-248.707			
Fitted model	-248.79	0.167701	1	0.6822
Reduced model	-256.414	15.4153	3	0.001494

AIC: 503.581

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2127	21.274	21	100	-0.06691
8.9000	0.2997	29.970	31	100	0.2249
36.0000	0.3948	39.479	38	100	-0.3025
110.0000	0.4528	45.278	46	100	0.1451

Chi^2 = 0.167615 d.f. = 1 P-value = 0.6822

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

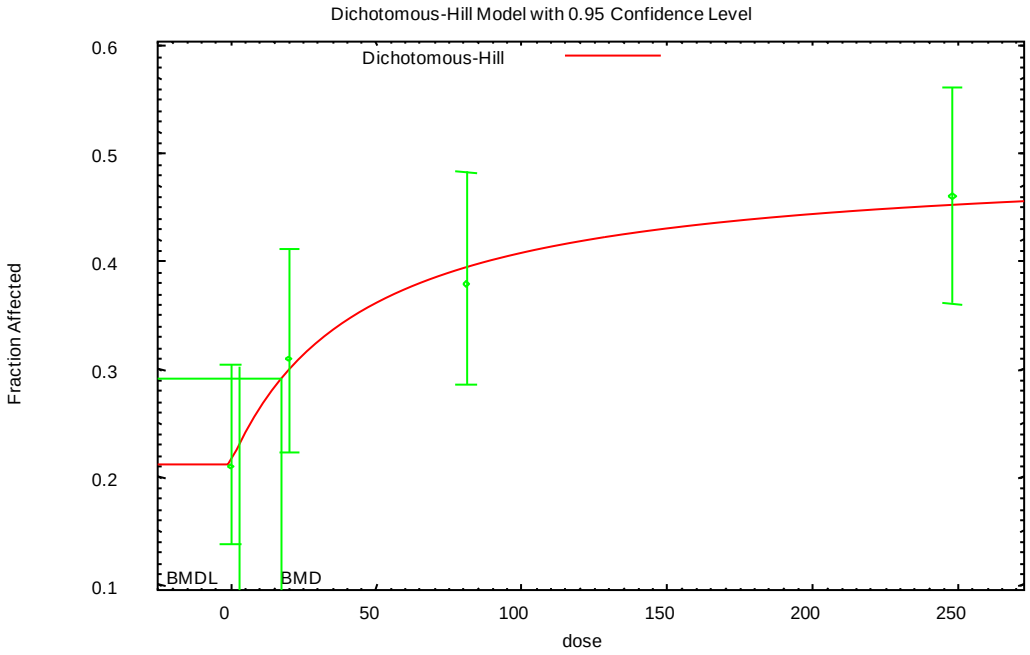
Confidence level = 0.95

BMD = 7.7341

BMDL = 1.35558

1

D.1.6.2. With tetrachloroethylene AUC in blood as dose metric




```
=================================================================
        Dichotomous Hill Model. (Version: 1.0; Date: 09/24/2006)
        Input Data File: C:\Usepa\BMDS21\dhl_JISA1993_RMF_MCL_percAUC_DichHill_slope1_0.1.(d)

=================================================================

  The form of the probability function is:

  P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

       where: 0 <= g < 1, 0 < v <= 1

              v is the maximum probability of response predicted by the model,

              and v*g is the background estimate of that probability.


  Dependent variable = Response
  Independent variable = Dose
  Slope parameter is set to 1

  Total number of observations = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008


               User Inputs Initial Parameter Values
                           v =          0.6
                           g =         0.38
                   intercept =           -4
                       slope =        -9999   Specified


          Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	v	g	intercept
v	1	-0.6	-0.86
g	-0.6	1	0.3
intercept	-0.86	0.3	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
v	0.496603	0.0949265	0.31055	0.682655
g	0.428392	0.100947	0.230539	0.626245
intercept	-3.81314	1.19145	-6.14833	-1.47795

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test d.f.	P-value
Full model	-248.707			
Fitted model	-248.791	0.168004	1	0.6819
Reduced model	-256.414	15.4153	3	0.001494

AIC: 503.581

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.2127	21.274	21	100	-0.06697
20.0000	0.2997	29.969	31	100	0.225
81.0000	0.3948	39.480	38	100	-0.3028
248.0000	0.4528	45.277	46	100	0.1453

Chi^2 = 0.167918 d.f. = 1 P-value = 0.6820

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 17.382

BMDL = 3.04513

D.2. Model Selection Details for Male Rat Tumors (NTP, 1986)

Table D-8. Model predictions for male rat tumors (NTP, 1986),[a] using administered tetrachloroethylene concentration as dose metric and multistage model

Model	Goodness of fit			BMD_{10} (ppm)	$BMDL_{10}$ (ppm)	Conclusions
	p-value[a]	Largest standardized residual(s)	AIC[b]			
Kidney tumors						
One-, two-**stage**	0.75	0.3, low-dose	64.1	110	50	No statistical improvement from adding higher-order parameter; one-stage model selected
Brain gliomas						
One-stage	**0.11**	-1.3, low-dose	**45.7**	**180**	**73**	No statistical improvement from adding higher-order parameter; one-stage model selected.
Two-stage	0.18	-1.3, low-dose	44.6	138	45	
Testicular interstitial cell tumors						
One-, two-**stage**	0.40	0.7, low-dose	155.8	13.0	6.1	No statistical improvement from adding higher-order parameter; one-stage model selected
MCL						
One-, two-stage	0.18	1.1, low-dose	184.8	12.1	6.5	Only a one-stage model resulted.

[a] Incidence data and human equivalent continuous exposures provided in Table 5-7 and in output below.
[b] Values <0.05 fail to meet conventional goodness-of-fit criteria.
[c] The highest response in these data sets was less than 10% extra risk; however because the best fit models were linear, use of BMD_{10} and $BMDL_{10}$ was equivalent to using a BMR within the data range.

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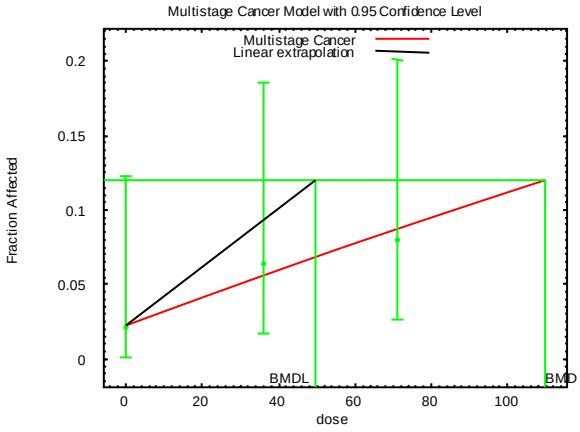
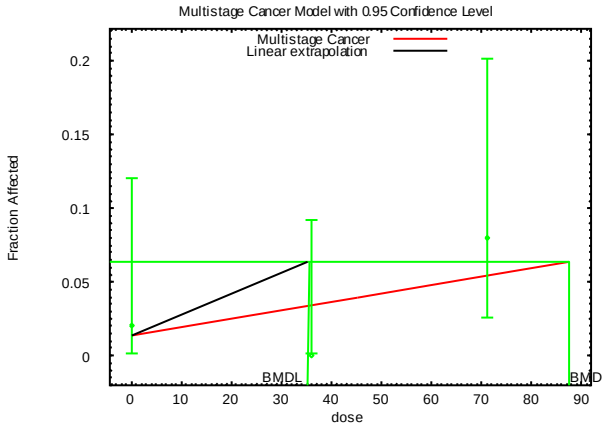
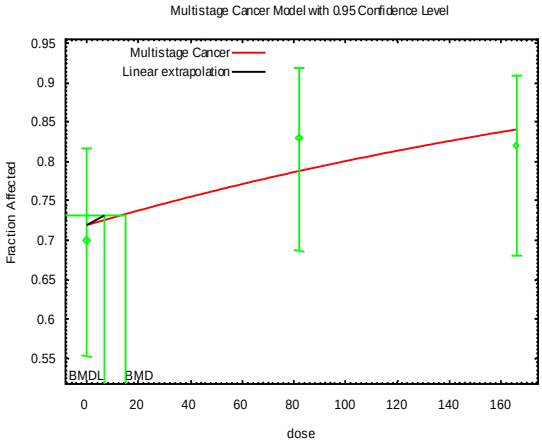


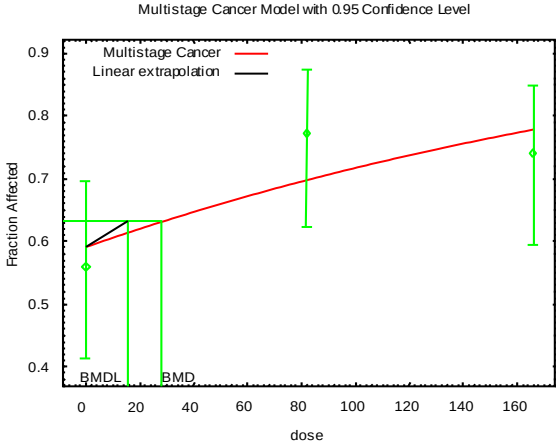
a. One-stage model fit to kidney tumors. See section D.2. for model output.



b. One-stage model fit to brain gliomas. See section D.2. for model output.



c. One-stage model fit to testicular interstitial cell tumors. See section D.2. for model output.



d. One-stage model fit to MCLs. See section D.2. for model output.

Figure D-5. Multistage model fits to tumor incidences at multiple sites in male rats—kidney tumors, brain gliomas, testicular interstitial cell tumors, and MCL (NTP, 1986). Graphs show BMD and BMDL at 10% extra risk.

D.2.1. **Modeling Output For Male Rats (NTP, 1986): MCLs, Brain Gliomas, Kidney Tumors, Testicular Interstitial Cell Tumors and Combined Tumors at 10% Extra Risk, Using Administered Concentration and Multistage Modeling (Discussed in Section 5.4.4.1)**

D.2.2. Kidney Tumors

```
 ================================================================
         MS_COMBO. (Version: 1.5 Beta;  Date: 01/25/2011)
         Input Data File: C:\Usepa\BMDS21\New.(d)
 ================================================================
  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

  The parameter betas are restricted to be positive


  Dependent variable = kidney
  Independent variable = hec

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =    0.0247493
                       Beta(1) =  0.000885764


          Asymptotic Correlation Matrix of Parameter Estimates

            Background      Beta(1)

Background           1        -0.78

   Beta(1)       -0.78            1


                              Parameter Estimates

                                                      95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    Background        0.0220312            *               *                   *
       Beta(1)      0.000959208            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -29.9768         3
   Fitted model          -30.025         2     0.0964903      1          0.7561
```

```
 Reduced model          -31.01         1       2.06651      2          0.3558

          AIC:           64.05

 Log-likelihood Constant             25.932650402661093


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size        Residual
  ----------------------------------------------------------------------------
   0.0000     0.0220         1.080     1.000          49       -0.077
  36.0000     0.0552         2.596     3.000          47        0.258
  71.0000     0.0864         4.321     4.000          50       -0.161

 Chi^2 = 0.10      d.f. = 1        P-value = 0.7533


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        109.841

            BMDL =        49.5786

            BMDU =   5.15876e+007

Taken together, (49.5786, 5.15876e+007) is a 90     % two-sided confidence
interval for the BMD
```

D.2.3. **Brain Gliomas**

```
 ================================================================
         MS_COMBO. (Version: 1.5 Beta;  Date: 01/25/2011)
         Input Data File: C:\Usepa\BMDS21\New.(d)
  ================================================================
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = gliomas
   Independent variable = hec

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =   0.00303212
                        Beta(1) =  0.000882936
```

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.7
Beta(1)	-0.7	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0135755	*	*	*
Beta(1)	0.0005865	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-18.8404	3			
Fitted model	-20.8724	2	4.06391	1	0.04381
Reduced model	-21.8534	1	6.02604	2	0.04914

AIC: 45.7448

Log-likelihood Constant 16.259161091237132

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0136	0.679	1.000	50	0.393
36.0000	0.0342	1.641	0.000	48	-1.303
71.0000	0.0538	2.690	4.000	50	0.821

Chi^2 = 2.53 d.f. = 1 P-value = 0.1119

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 179.643

BMDL = 72.6378

BMDU = 2.38388e+101

Taken together, (72.6378, 2.38388e+101) is a 90 % two-sided confidence interval for the BMD

D.2.4. **Testicular Tumors**

```
 ================================================================
         MS_COMBO. (Version: 1.5 Beta;  Date: 01/25/2011)
         Input Data File: C:\Usepa\BMDS21\New.(d)
================================================================
```

```
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = testtumor
   Independent variable = hec

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 Default Initial Parameter Values
                    Background =     0.728853
                       Beta(1) =   0.00723542


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.71

   Beta(1)        -0.71            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    Background         0.717295            *               *                   *
       Beta(1)       0.00809268            *               *                   *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -75.5554         3
   Fitted model         -75.9206         2      0.730362      1          0.3928
  Reduced model         -77.0228         1       2.93491      2          0.2305

           AIC:         155.841

 Log-likelihood Constant             69.650407128412709


                                Goodness  of  Fit
                                                                    Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------
    0.0000     0.7173        35.865    35.000          50       -0.272
   36.0000     0.7887        37.071    39.000          47        0.689
   71.0000     0.8409        42.043    41.000          50       -0.403

 Chi^2 = 0.71      d.f. = 1        P-value = 0.3990


   Benchmark Dose Computation
```

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        13.0192

            BMDL =         6.0591

            BMDU =   8.43867e+014

Taken together, (6.0591 , 8.43867e+014) is a 90     % two-sided confidence
interval for the BMD
```

D.2.5. **MCLs**

```
 ================================================================
         MS_COMBO. (Version: 1.5 Beta;  Date: 01/25/2011)
         Input Data File: C:\Usepa\BMDS21\New.(d)
 ================================================================

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1)]

   The parameter betas are restricted to be positive


   Dependent variable = M_mcl
   Independent variable = hec

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =     0.612363
                        Beta(1) =   0.00746075


           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.72

   Beta(1)        -0.72            1


                                Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    Background         0.588403            *               *                   *
       Beta(1)       0.00873731           *               *                   *

* - Indicates that this value is not calculated.
```

```
                      Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -88.7862         3
   Fitted model        -89.6897         2       1.80709      1          0.1789
  Reduced model        -91.7227         1       5.87302      2         0.05305

           AIC:         183.379

 Log-likelihood Constant             82.552836454191464


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.5884        29.420    28.000          50       -0.408
   36.0000     0.6995        33.575    37.000          48        1.078
   71.0000     0.7787        38.933    37.000          50       -0.659

 Chi^2 = 1.76      d.f. = 1        P-value = 0.1843


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        12.0587

            BMDL =        6.54184

            BMDU =   1.67846e+007

Taken together, (6.54184, 1.67846e+007) is a 90     % two-sided confidence
interval for the BMD
```

D.2.6. **Combined BMD and BMDL for Male Rat Tumors**

```
**** Start of combined BMD and BMDL Calculations.****

  Combined Log-Likelihood                    -216.50768590007982

  Combined Log-likelihood Constant            194.39505507650239


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        5.73369

            BMDL =        3.48718
```

D.3. Comparison of PODs Resulting from the Use of Models Alternative to the Multistage Model, for Tumor Sites in the JISA (1993) Bioassay

Note: See Section D.1 for alternative modeling for female rat MCLs and combined male and female rat MCLs.

Table D-9. Comparison of model predictions for hepatocellular tumors in mice (JISA, 1993), using administered tetrachloroethylene concentration (ppm) as the dose metric,[a] across a range of dichotomous models

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Comments[b]
	p-value[a]	Largest standardized residual(s)	AIC			
Male mice (input data in Table 5-5)						
Gamma	0.14	−1.0, control 1.1, low-dose	241.1	10.2	0.4	Power parameter unrestricted
Weibull	0.15	−1.0, control 1.1, low-dose	241.0	9.5	0.7	Power parameter unrestricted
Michaelis-Menten[d]	0.13	−1.0, control 1.1, low-dose	241.0	2.5	1.3	—
LogLogistic	0.14	−1.0, control 1.1, low-dose	241.1	10.6	1.5	Slope parameter unrestricted
LogProbit	0.14	−1.1, control 1.0, low-dose	241.1	11.0	2.1	—
Multistage	0.27	1.2, low-dose −1.0, mid-dose	239.5	3.9	2.7	Lowest residual at control (−0.5)
Logistic	0.35	−0.7, control 1.1, low-dose	238.9	6.0	4.7	—
Probit	0.36	−0.7, control 1.1, low-dose	238.9	6.1	4.8	—
Female mice (input data in Table 5-5)						
Multistage	0.36	−1.1, mid-dose	152.9	5.0	3.8	—
Gamma	0.96	−0.04, low-dose	152.8	9.5	4.3	—
Weibull	0.93	−0.07, control	152.8	9.5	4.3	—
LogLogistic	0.98	0.02, control	152.8	9.5	4.7	Slope parameter unrestricted
Michaelis-Menten		0.01, control	154.8	9.5	4.7	—
LogProbit	0.95	0.04, low-dose	152.8	9.5	5.0	—
Probit	0.91	0.4, mid-dose	151.0	11.8	9.7	—
Logistic	0.84	0.5, mid-dose	151.2	13.1	10.6	—

[a] Only one dose metric used, due to near proportionality of relevant dose metrics.
[b] Goodness-of-fit *p*-values <0.05 for a preferred model, or <0.10 when considering suite of models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered.
[c] Lower limit ≥1for slope or power parameters avoids biologically implausible infinite slopes at zero dose. However, fits with restricted parameters may not provide BMDLs with nominal (95%) statistical coverage.
[d] Dichotomous-Hill model with slope fixed at 1

Table D-10. Comparison of model predictions for male mice, hemangiomas or hemangiosarcomas (JISA, 1993),[a] using administered tetrachloroethylene concentration as dose metric,[b] across a range of dichotomous models

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Comments[d]
	p-value[c]	Largest standardized residual(s)	AIC			
Michaelis-Menten[e]	0.21	−1.0, low-dose	143.7	16.1	4.1	Better fit than restricting or unrestricting slope parameter
LogLogistic	0.19	−1.0, low-dose	141.9	20.7	5.4	Slope parameter unrestricted
LogProbit	0.21	−1.0, low-dose	143.7	19.2	5.4	
Weibull	0.18	−1.0, low-dose	143.9	21.3	5.5	Power parameter unrestricted
Gamma	0.18	−1.0, low-dose	143.9	21.7	5.6	Power parameter unrestricted
Multistage	0.38	−1.0, low-dose 0.9, mid-dose	142.0	24.4	13.3	Lowest residual at control (0.4)
Probit	0.32	−1.1, low-dose 1.0, mid-dose	142.4	30.6	20.9	—
Logistic	0.31	−1.1, control 1.0, low-dose	142.4	31.6	22.1	—

[a] Incidence data and human equivalent continuous exposure estimates provided in Table 5-5.
[b] Only one dose metric used, due to proportionality of relevant dose metrics.
[c] Goodness-of-fit *p*-values <0.05 for a preferred model, or <0.10 when considering suite of models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within $\pm$2 units) are considered.
[d] Lower limit $\geq$1for slope or power parameters avoids biologically implausible infinite slopes at zero dose. However, fits with restricted parameters may not provide BMDLs with nominal (95%) statistical coverage.
[e] Dichotomous-Hill model with slope fixed at 1

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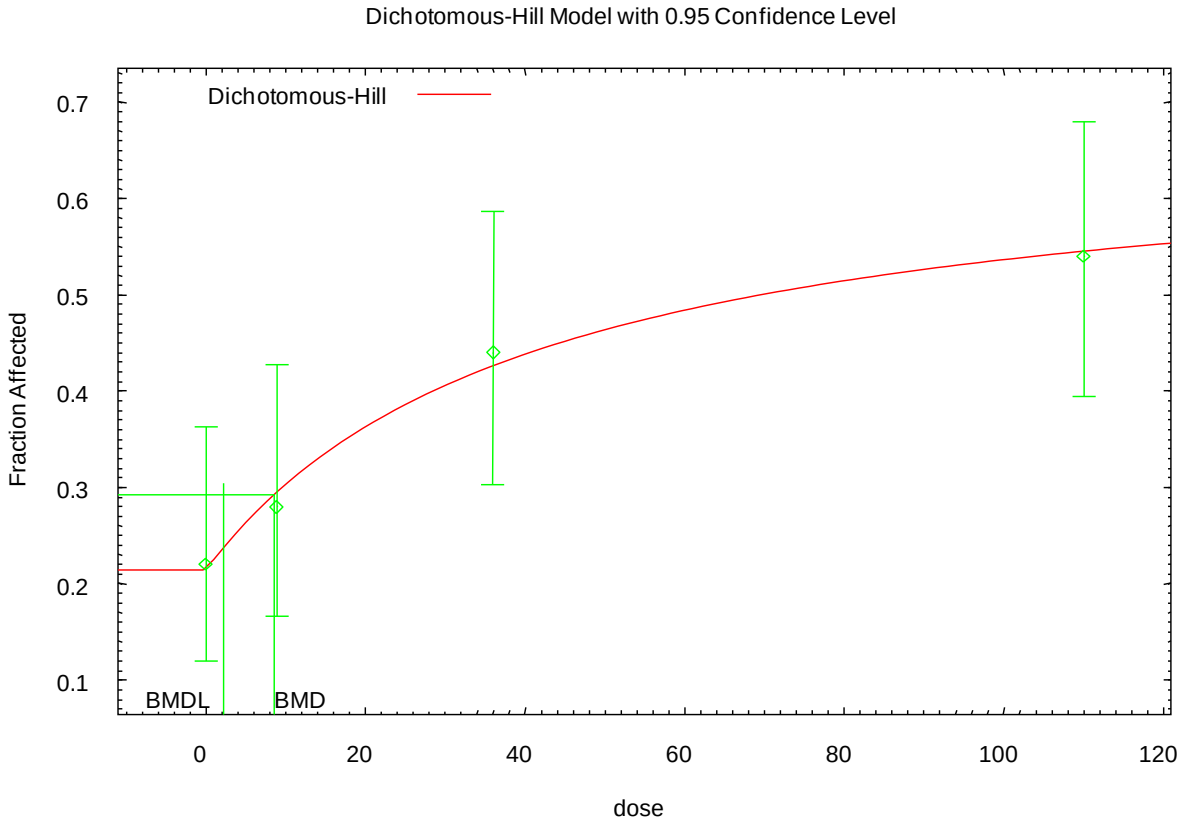
Table D-11. Comparison of model predictions for MCL in male rats (JISA, 1993),[a] using administered tetrachloroethylene concentration as dose metric,[b] across a range of dichotomous models

Model	Goodness of fit			BMD_{10}	$BMDL_{10}$	Comments
	p-value[c]	Largest standardized residual(s)	AIC			
Gamma	0.51	−0.4, low-dose 0.4, mid-dose	256.0	6.9	0.062	Power parameter unrestricted; BMDL quite low
Weibull	0.54	−0.4, low-dose 0.4, mid-dose	256.0	7.1	0.11	Power parameter unrestricted
LogLogistic	0.59	0.4, mid-dose	255.9	7.8	0.18	Slope parameter unrestricted
LogProbit	0.63	0.4, mid-dose	255.8	8.5	0.28	—
Michaelis-Menten[d]	0.74	(0.1, control) −0.2, low-dose	255.7	8.6	2.2	—
Multistage	0.51	1.0, mid-dose	254.9	20.5	13.2	—
Probit	0.34	−0.8, control 1.2, mid-dose	255.7	29.3	21.6	—
Logistic	0.32	−0.8, control 1.2, mid-dose	255.8	30.0	22.1	—

[a] Incidence data and human equivalent continuous exposure estimates provided in Table 5-7.
[b] Only one dose metric used, due to proportionality of the available dose metrics.
[c] Goodness-of-fit *p*-values <0.05 for a preferred model, or <0.10 when considering suite of models, fail to meet conventional goodness-of-fit criteria. In addition, visual fit and residuals (within ±2 units) are considered.
[d] Dichotomous-Hill model with slope fixed at 1

1
2




```
 ======================================================================
          Dichotomous Hill Model. (Version: 1.0; Date: 09/24/2006)
          Input Data File: C:\Usepa\BMDS21\dhl_JISA1993_RM_MCL_admc_DichHill_slope1_0.1.(d)
======================================================================

   The form of the probability function is:

   P[response] = v*g +(v-v*g)/[1+EXP(-intercept-slope*Log(dose))]

        where: 0 <= g < 1, 0 < v <= 1

               v is the maximum probability of response predicted by the model,

               and v*g is the background estimate of that probability.


   Dependent variable = Response
   Independent variable = Dose
   Slope parameter is set to 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



                User Inputs Initial Parameter Values
                            v =          0.6
```

```
                          g =         0.38
                  intercept =           -4
                      slope =        -9999   Specified


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -slope
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )

                       v            g    intercept

         v             1        -0.71         -0.9

         g         -0.71            1         0.47

 intercept          -0.9         0.47            1


                                Parameter Estimates

                                                          95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
              v         0.668921         0.205885            0.265395             1.07245
              g          0.32044         0.110376            0.104107            0.536774
      intercept         -3.72152          1.21769            -6.10815             -1.3349


                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test d.f.   P-value
     Full model         -124.787
    Fitted model        -124.841     0.108028      1          0.7424
   Reduced model        -131.791      14.0088      3        0.002893

          AIC:          255.682


                    Goodness  of  Fit

                                                                 Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
   ---------------------------------------------------------------------
    0.0000      0.2143        10.717          11          50      0.09737
    8.9000      0.2949        14.745          14          50       -0.231
   36.0000      0.4260        21.299          22          50       0.2005
  110.0000      0.5448        27.239          27          50     -0.06785

 Chi^2 = 0.107657     d.f. = 1        P-value = 0.7428


   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =        8.63516

            BMDL =       2.20116
```

References