NTP Monograph

on the Systematic Review of Occupational Exposure to Cancer Chemotherapy Agents and Adverse Health Outcomes

March 2019

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Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

NTP conducts literature-based evaluations to determine whether exposure to environmental substances (e.g., chemicals, physical agents, and mixtures) may be associated with adverse health effects. These evaluations result in hazard conclusions or characterize the extent of the evidence and are published in the NTP Monograph series, which began in 2011. NTP Monographs serve as an environmental health resource to provide information that can used to make informed decisions about whether exposure to a substance may be of concern for human health.

NTP conducts these health effects evaluations following pre-specified protocols that apply the general methods outlined in the "Handbook for Conducting a Literature-Based Health Assessment Using the OHAT Approach for Systematic Review and Evidence Integration." [†] The protocol describes project-specific procedures tailored to each systematic review in a process that facilitates evaluation and integration of scientific evidence from published human, experimental animal, and mechanistic studies.

The key feature of the systematic review approach is the application of a transparent framework to document the evaluation methods and the basis for scientific judgements. This process includes steps to comprehensively search for studies, select relevant evidence, assess individual study quality, rate confidence in bodies of evidence across studies, and then integrate evidence to develop conclusions for the specific research question. Draft monographs undergo external peer review prior to being finalized and published.

NTP Monographs are available free of charge on the NTP website and cataloged in PubMed, a free resource developed and maintained by the National Library of Medicine (part of the National Institutes of Health). Data for these evaluations are included in the Health Assessment and Workspace Collaborative.

For questions about the monographs, please email NTP or call 984-287-3211.

[†]OHAT is the abbreviation for Office of Health Assessment and Translation, which is within the Division of the National Toxicology Program at the National Institute of Environmental Health Sciences.

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This report has been reformatted to meet new NTP publishing requirements;
its content has not changed.

About This Review

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Peer Review

The National Toxicology Program (NTP) conducted a peer review of the draft NTP *Systematic Review of Occupational Exposure to Cancer Chemotherapy Agents and Adverse Health Outcomes* by letter in March 2018 by the experts listed below. Reviewer selection and document review followed established NTP practices. The reviewers were charged to:

(1) Determine whether the scientific information cited in the draft monograph is technically correct and clearly stated, and whether NTP has objectively presented and assessed the scientific evidence.

(2) Determine whether the scientific evidence presented in the draft monograph supports NTP's conclusions regarding the level of evidence from human studies for adverse health effects associated with occupational exposure to cancer chemotherapy agents.

(3) Review and comment on NTP's presentation of workplace monitoring and biomonitoring data as well as proposed research needs based on the assessment of the available scientific data on health effects and exposure monitoring.

NTP carefully considered reviewer comments in finalizing this monograph.

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Publication Details

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Conflict of Interest

Individuals identified as collaborators in the About This Review section have certified that they have no known real or apparent conflict of interest related to cancer chemotherapy agents.

Abstract

Introduction: Many cancer chemotherapy agents are known carcinogens, genetic toxicants, and developmental toxicants. Secondary malignancies, such as therapy-related acute myeloid leukemia, are caused by cancer chemotherapy agents administered to patients for the treatment of cancer. Occupational exposure to these agents was first documented in the 1970s and continues to occur, despite the issuance of safe handling guidelines in 1980s.

Objectives: Based on the evidence of carcinogenicity and genetic toxicity associated with direct administration of cancer chemotherapy agents and current evidence of occupational exposure, the National Toxicology Program (NTP) conducted a systematic review to: (1) evaluate whether occupational exposure (e.g., medical, manufacturing, research, and veterinary) is associated with any adverse health outcomes in humans, and (2) summarize the prevalence and levels of chemotherapy agents in the workplace as measured by environmental monitoring and biomonitoring for possible worker exposures.

Methods: The evaluation was conducted following the Office of Health Assessment and Translation (OHAT) method. A literature search was performed up to February 23, 2017, using PubMed, Embase, Scopus, Toxline, and Web of Science. Relevant human studies were data extracted and assessed for risk of bias. Bodies of evidence were assessed to develop confidence ratings and level-of-evidence conclusions that reflect the certainty in the evidence that occupational exposure to cancer chemotherapy agents are associated with health effects on a per outcome basis.

Results and Evidence Synthesis: The literature search and screening process identified 110 epidemiological studies relevant to assessing possible adverse health outcomes. Most studies addressing health outcomes evaluated potential DNA damage (n = 66; specifically, structural chromosomal aberrations (CA) and micronucleus (MN) induction and comet assay endpoints) and spontaneous abortion (n = 16). In addition to DNA damage, groups of studies were identified to evaluate the potential association between occupational exposure to cancer chemotherapy agents and adverse health outcomes, including cancer (three studies) and adverse effects on reproduction (30 studies). Additional health outcomes included acute effects, immune effects, and liver and kidney toxicity. One hundred sixty-one studies were identified to assess workplace exposure based on reporting of environmental contamination (107 studies) and urine and/or blood monitoring of these agents (82 studies).

Discussion and Conclusions: NTP concluded that there is a **moderate level of evidence** that occupational exposure to chemotherapy agents is associated with increased incidence of spontaneous abortion, particularly when evaluating studies of nursing and pharmacy personnel. NTP also concluded that there is a **moderate level of evidence** that exposure to chemotherapy agents in the workplace is associated with genetic toxicity in humans based on consistent reports significantly higher levels of structural CA (% of cells with CA and number of CA), MN induction (number of cells with MN and number of MN) and DNA damage measured by comet assay (% tail DNA, tail length, tail moment, and DNA damage index) in exposed personnel. There was inadequate evidence for NTP to reach level-of-evidence conclusions on the remaining health outcomes, including cancer, primarily due to few studies per outcome and heterogeneity in the data. Despite current safety guidelines, cancer chemotherapy agents were commonly detected in environmental samples of the workplace (e.g., surface wipes and air sampling) and biosamples (e.g., urine or blood) of workers handling these agents, including data collected as

recently as 2014 to 2016. Considering the potential for occupational exposure to these agents and the association between exposure and DNA damage and spontaneous abortions, there is a continued need to reduce exposures through training in safe handling procedures and provision and use of personal protective equipment and associated safety containment equipment. Health surveillance of occupationally exposed personnel would also benefit from improved exposure characterization methods, such as use of daily diaries that are assessed and validated to estimate exposure levels and additional environmental monitoring and biomonitoring data that include analytical chemistry approaches to assess multiple agents. There is also a need to better understand the sources (i.e., activities or physical locations) of worker exposure, especially in settings that have not been adequately studied (e.g., home care, veterinary clinics).

Introduction

Cancer chemotherapy agents are designed to kill or halt the progression of cancer cells through various mechanisms of action. Due to their mechanisms of action, many cancer chemotherapy agents are reported to induce carcinogenicity and mutagenicity. Forty-two cancer chemotherapy agents are identified by the International Agency for Research on Cancer (IARC) as known (n = 18; IARC Class 1), probable (n = 11; IARC Class 2A), or possible (n = 13; IARC Class 2B) carcinogens in humans (IARC 2012; 2016). Cancer chemotherapy agents administered therapeutically for the treatment of cancer are known to cause secondary cancers, primarily therapy-related acute myeloid leukemia (Mistry et al. 2005; Morton et al. 2013; Pedersen-Bjergaard 2005; Pedersen-Bjergaard et al. 2002; Sill et al. 2011). In addition, most cancer chemotherapy agents are reported to be teratogenic and/or to induce embryo toxicity in experimental studies of laboratory animal models and limited observational reports in women administered cancer chemotherapy for treatment of cancer during pregnancy [reviewed in (NTP 2013)]. A summary of the published carcinogenicity, mutagenicity, teratogenicity, and embryo toxicity of different cancer chemotherapy drug classes following direct, intentional exposure of these agents to human patients or experimental animals are presented in Table 1. Given the observed adverse health outcomes observed following intentional, direct administration of these agents to patients, the National Toxicology Program (NTP) evaluated the literature for potential adverse health outcomes in employees who are occupationally exposed to cancer chemotherapy agents.

Table 1. Carcinogenicity, Mutagenicity, and Developmental Toxicity of Cancer Chemotherapy Agents by Drug Class Based on Direct, Intentional Exposure to Humans and Laboratory Animals

Drug Class[a]	Carcinogenicity[b]	Genetic Toxicity[b,c]	Developmental Toxicity[d]	
			Teratogenicity	Embryotoxicity
Alkylating Agents	+[e]	+	+	+
Antimetabolites	+	+	+	+
Biological	inadequate data[f]	−[g]	−	−[h]
Anthracycline Antibiotics	+	+	+	+
Hormone Therapies	+	+	+	+
Mitotic Function Inhibitors	inadequate data	+	+	+
Topoisomerase II Function Inhibitors	+	+	+	+
Tyrosine Kinase Inhibitors	inadequate data	inadequate data	+	+

[a]Examples of agents in each drug class: alkylating agents (e.g., cyclophosphamide), antimetabolites (e.g., hydroxyurea), biologicals (e.g., cytokines, such as interferon alpha, and monoclonal antibodies, such as trastuzumab), anthracycline antibiotics (e.g., doxorubicin), hormone therapies (e.g., tamoxifen), mitotic function inhibitors (e.g., vincristine), topoisomerase function inhibitors (e.g., etoposide), and tyrosine kinase inhibitors (e.g., imatinib, adalimumab).
[b]Data reviewed in: (IARC 1966; 1980; 1981; 1990; 2000).
[c]Data reviewed in: (NTP 2008; 2016).
[d]Data reviewed in: (NTP 2013).
[e]Evidence of an effect for at least one agent in this drug class.
[f]Inadequate data; inconsistent data or a lack of data for one or more agents in this drug class.
[g]Lack of an effect for agents in this drug class.
[h]Trastuzumab is a reproductive developmental toxicant, which induced oligohydramnios when administered in second and/or third trimester.

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Occupational exposure to cancer chemotherapy agents may occur in medical, veterinary, and manufacturing settings among personnel involved in the production, preparation and administration of these agents (Hall et al. 2013; Kiffmeyer et al. 2013; Kopp et al. 2013b) as well as other workers involved with the care of patients administered chemotherapy (e.g., unit clerks, volunteers, ward aides, dieticians, and shipper/receivers) (Hon et al. 2014). Potential routes of occupational exposure to these agents include dermal, ingestion, and inhalation. While levels of such exposures are thought to be much lower than those administered to cancer patients, occupational exposure likely involves more than one chemotherapy agent or combination therapy, and it may occur more frequently and over a longer time. Furthermore, occupational exposures are often unrecognized due to lack of systematic environmental monitoring and biomonitoring programs (OSHA 1999).

Evidence for occupational exposure began appearing in the 1970s with reports of elevated mutagenic activity in the urine of health care workers who prepared and administered such agents [reviewed in (Connor and McDiarmid 2006)]. Subsequent studies reported evidence of genetic toxicity such as chromosome aberrations, sister chromatid exchanges, and DNA damage in workers handling these agents, as well as the detection of cancer chemotherapy agents or their metabolites in workers' urine. Guidelines for safe handling of cancer chemotherapy agents were first published in the 1980s by national health care worker agencies in Australia and the United States [reviewed in (Connor and McDiarmid 2006)]. The Occupational Safety and Health Administration in the United States published guidelines for safe handling of cancer chemotherapy agents in 1986 (OSHA 1986), and the guidelines were updated in 1999 to include all hazardous drugs (OSHA 1999). Beginning in the 1990s, numerous publications documented surface contamination of safety cabinets, countertops, floors, and equipment with cancer chemotherapy agents. While improved handling procedures and engineering controls have reduced contamination, Connor et al. (2010) reported that surface contamination persists in pharmacy and nursing areas of some hospital-based cancer centers. In addition, the potential for occupational exposure to cancer chemotherapy agents has increased with greater usage of chemotherapy for non-cancer disease conditions [e.g., autoimmune diseases (Zack 2012)], the development of new surgical techniques involving administration of chemotherapy directly into the peritoneal cavity (Villa et al. 2015), and greater usage of chemotherapy by veterinary clinics to treat cancer in companion animals (Klahn 2014).

A number of health outcomes have been assessed in health care workers exposed to cancer chemotherapy agents, including cancer, genetic damage, reproductive and pregnancy outcomes, and acute effects (e.g., hair loss, nausea) [reviewed in (Connor and McDiarmid 2006)]. The association between occupational exposure to cancer chemotherapy agents and some of these health effects have been evaluated in a literature review and meta-analysis (Dranitsaris et al. 2005), a systematic review (Quansah and Jaakkola 2010), and a recent narrative literature review by Connor et al. (2014). The review and meta-analysis by Dranitsaris and colleagues (2005) evaluated the literature on cancer, pregnancy outcomes, and acute toxic effects in nurses, pharmacists, and pharmacy technicians/assistants who work with cancer chemotherapy agents. They reported that there was insufficient literature to reach conclusions on cancer, acute effects, congenital malformations, or stillbirth; however, they did find a significant association between occupational exposure and spontaneous abortions (odds ratio (OR) = 1.46, 95% confidence interval (CI) = 1.11–1.92) (Dranitsaris et al. 2005). A systematic review and meta-analysis by Quansah and Jaakkola (2010) evaluated the association between occupational exposures and

work conditions of nurses only, including cancer chemotherapy agents and risk of spontaneous abortion. The meta-analysis on spontaneous abortion by Quansah and Jaakkola (2010) did not reach statistical significance (OR = 1.21, 95% CI = 0.80−1.83); however, they included a different combination of studies than the systematic review by Dranitsaris et al. (2005). Finally, a narrative review by Connor et al. (2014) provided a survey of the literature on occupational exposure to cancer chemotherapy agents and reproductive health, including spontaneous abortion, congenital anomalies as well as other reproductive outcomes (e.g., fertility, time to pregnancy, birth weight). Overall, confidence in the findings was limited for outcomes other than spontaneous abortion (e.g., congenital malformations) due to low sample size and heterogeneity in the study designs (Connor et al. 2014; Dranitsaris et al. 2005; Quansah and Jaakkola 2010).

Accurate characterization of exposure is one of the major challenges in assessing the adverse health effects of occupational exposure to cancer chemotherapy. Occupational exposure to cancer chemotherapy agents is a complex exposure involving many different cancer chemotherapy agents per day or per week, and each agent may have different potencies to induce the same or different adverse health effects. Furthermore, usage of personal protective equipment and safety containment equipment can influence the level of occupational exposure. Exposure is generally characterized by job title or industrial hygiene data in occupational settings; however, this information alone (i.e., job title or position) does not provide much detail on level of exposure. More informative approaches for exposure characterization of occupational exposure to cancer chemotherapy agents include the use of a validated questionnaire or use of a daily diary where the subject reports on the types of drugs handled, levels handled (i.e., doses administered), frequency of handling, unusual events (e.g., spills or needle sticks), and use of protective measures (e.g., personal protective equipment) that are assessed and validated to estimate exposure levels (Albertini et al. 2000; Nieuwenhuijsen 2003). Positive environmental monitoring results (e.g., surface wipes, air samples, dermal pads) provide strong evidence for the potential for occupational exposure, but they may or may not correlate to internal doses to personnel based on possible modifying variables such as an individual's use of personal protective equipment or availability of safety containment equipment, among other variables. Biomonitoring of urine or blood samples may determine the internal dose of levels of a cancer chemotherapy agent(s) or its metabolites, which identify that exposure has occurred; however, biomonitoring measurements likely provide confirmation of only the most recent exposure. A positive biomonitoring result requires that there be sufficient intake (which may be reduced by good work practices and usage of personal protective equipment) to exceed the limit of detection (LOD) for the agent tested, and the time between exposure and sample collection must be consistent with any biological processing (e.g., metabolism or excretion of the cancer chemotherapy agent). Additional limitations of monitoring studies (environmental monitoring and biomonitoring) of cancer chemotherapy agents are that they typically test only one or a handful of cancer chemotherapy agents, while multiple agents are handled, and biomonitoring studies generally evaluate only the parent drugs (e.g., cyclophosphamide) and not their metabolites. However, recent studies of environmental monitoring and biomonitoring of occupational exposure to cancer chemotherapy agents demonstrate that surface contamination continues to occur (Hon et al. 2011), and can lead to detectable internal dose levels (Hon et al. 2015).

Objectives and Research Strategy

Objectives

The primary objective (Objective 1) of this evaluation was to undertake a systematic review to develop level-of-evidence conclusions regarding whether occupational exposure to cancer chemotherapy agents is associated with adverse health effects in humans. The types of adverse health outcomes considered are described in more detail below (see section below, PECO Statement). The secondary objective (Objective 2) was to survey the literature to determine the levels of workplace contamination by cancer chemotherapy agents and the detection of parent compound or metabolites of these agents in occupationally exposed personnel to provide context for the health outcome literature. The exposure monitoring literature was not evaluated for risk of bias as this was beyond the scope of this evaluation. As possible, environmental and biosample monitoring data from these studies were used to compare the levels reported prior to the publication of the OSHA Guidelines for Handling Hazardous Drugs in 1986 to the present time (OSHA 1986). Limitations of the systematic review were noted for Objective 1 and, for both objectives 1 and 2, the limitations of the evidence base and research needs were described.

Many commonly used cancer chemotherapy agents have already been recognized as known or probable human carcinogens by IARC (2012) and the NTP's Report on Carcinogens (NTP 2016); thus, this review did not pursue hazard identification. Instead, this review is intended to provide public health information that may be useful to workers, employers, and organizations where occupational exposure may occur to these compounds to support efforts to lower exposure. For example, genetic toxicity studies can identify the occurrence of DNA damage following exposure to occupational exposure to cancer chemotherapy agents. These data are sometimes used as surrogates for direct exposure measurements and they can also be used to provide information on potential health risks (e.g., cancer or fetal loss). This review of reproductive health outcomes associated with occupational exposure to cancer chemotherapy may also be useful to inform safety protocols for working with these agents while pregnant. The scope of this Office of Health Assessment and Translation (OHAT) evaluation is broad with the inclusion of any adverse health outcome and expands beyond the previously published reviews (Dranitsaris et al. 2005; Quansah and Jaakkola 2010), which were limited to acute effects, cancer, and/or effects on reproduction. Furthermore, the evaluation did not limit the types of exposed occupations to only medical personnel; instead, it included all reported occupational exposures to cancer chemotherapy agents (e.g., medical, manufacturing, research, veterinary, and home health care).

Specific Aims

Objective 1

- Identify literature reporting adverse health effects associated with occupational exposure to cancer chemotherapy agents.
- Extract data from relevant studies.
- Assess the internal validity (risk of bias) of individual studies assessing health outcomes.
- Summarize the extent of evidence available.

- Synthesize the evidence for adverse health outcomes, including performance of quantitative meta-analyses if appropriate, and evaluate sources of heterogeneity.

- Rate confidence in the body of evidence for adverse health outcomes according to one of four statements: (1) high, (2) moderate, (3) low, or (4) very low/no evidence available.

- Translate confidence ratings into level of evidence for adverse health outcomes according to one of four statements: (1) high, (2) moderate, (3) low, or (4) inadequate.

- Describe limitations of the systematic review, limitations of the evidence base, and identify data gaps and key research needs.

Objective 2

- Collect and summarize the available information on levels of cancer chemotherapy agents detected in environmental monitoring studies (e.g., surface wipes, air samples of work environment) and biomonitoring (e.g., urine or blood levels) of occupationally exposed personnel.

- Describe limitations of the evidence base and identify data gaps and key research needs for exposure characterization.

Methods

Problem Formulation and Protocol Development

Problem formulation activities and the systematic review methodology used to conduct this review were posted in a protocol in October 2015 (Appendix I). The protocol was based on: (1) deliberation with NTP staff and consultation with scientists at other federal agencies represented on the NTP Executive Committee;[1] (2) discussions by the evaluation design team and other technical experts with backgrounds in occupational exposure to hazardous drugs (including cancer chemotherapy agents) and systematic review (see About This Review); (3) public review of the proposed evaluation during the April 16–18, 2014 meeting of the NTP Board of Scientific Counselors (BSC);[2] (4) guidance outlined in the OHAT Handbook for Conducting a Literature-Based Health Assessment (https://ntp.niehs.nih.gov/go/systematic_review); and (5) external peer review of the draft protocol. A summary of the methods is presented below.

PECO Statement

A PECO (**P**opulation, **E**xposure, **C**omparators, and **O**utcomes) statement was developed as an aid to identify search terms and inclusion/exclusion criteria for Objective 1 (Table 2).

Table 2. PECO Statement for Objective 1

Element	Type of Evidence
Population	Humans who may be exposed to cancer chemotherapy agents in their workplace, without restriction based on age or sex
Exposure	Exposure to cancer chemotherapy agents, including antineoplastic agents, synthetic hormones (e.g., tamoxifen), biologicals, and targeted therapies (e.g., imatinib) based on indirect measures such as job title and direct measures such as biomonitoring data (e.g., urine, blood, or other specimens), when available
Comparators	A comparison population exposed to lower levels (or no exposure/exposure below detection levels) of cancer chemotherapy agents in their workplace
Outcomes	**Primary outcomes:** Any adverse health effect (e.g., cancer, reproductive and developmental toxicity, immune system effects, kidney toxicity, liver toxicity, and acute effects [i.e., alopecia, nausea]) and genetic biomarkers of effect (specifically, chromosomal aberrations, micronucleus induction, and DNA damage measured by the comet assay) **Secondary outcomes:** Cellular, biochemical, or clinical chemistry changes in immune system, liver, kidney, reproductive, or other organ systems

[1]The NTP Executive Committee provides programmatic and policy oversight to the NTP Director and meets once or twice a year in closed forum. Members of this committee include the heads (or their designees) from the following federal agencies: Consumer Product Safety Commission (CPSC), Department of Defense (DoD), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Cancer Institute (NCI), National Center for Environmental Health/Agency for Toxic Substances and Disease Registry (NCEH/ATSDR), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA).

[2]During that meeting, the BSC members considered the evaluation a high priority and no public comments were received.

The NTP evaluation included cancer chemotherapy agents, such as antineoplastic agents (e.g., alkylating agents, anthracycline antibiotics, antimetabolites), hormone therapies (e.g., tamoxifen), biologicals (e.g., interferon alpha, trastuzmab), and targeted therapies (e.g., tyrosine kinase inhibitor imatinib). The evaluation did not include occupational exposure to targeted radionuclide therapy (also called radiopharmaceuticals) (Gudkov et al. 2015).

For the evaluation of adverse health effects associated with occupational exposure to cancer chemotherapy agents (Objective 1), the primary focus was on clinical diseases and disorders (e.g., cancer, spontaneous abortion, congenital malformations, abnormal functioning of the immune system, kidney, liver), and recognized acute effects observed in patients receiving cancer chemotherapy (e.g., alopecia, nausea) and genetic toxicity. Only three genetic toxicity assays were included in this evaluation because they test for a broad range of types of DNA damage induced by drugs or chemicals that induce genetic damage, including: structural chromosomal aberrations (CA), DNA damage as measured by comet assay, and micronucleus induction (structural and numerical chromosomal alterations). CA and micronucleus (MN) induction have been identified as good predictors of future cancer incidence (Bonassi et al. 2007; Bonassi et al. 2004; Norppa et al. 2006), and cancer chemotherapy agents are reported to induce CA or MN induction under experimental (e.g., in vitro or animal studies) or controlled exposure conditions (i.e., patients administered cancer chemotherapy agents for treatment of cancer) (Suspiro and Prista 2011). The comet assay is becoming more widely used in human biomonitoring to measure DNA damage as a biomarker of effect following exposure to chemicals known to induce genetic toxicity (Collins et al. 2014). However, a causal link between DNA damage detected by comet assay and subsequent induction of cancer has yet to be determined [reviewed in (Collins et al. 2014)]. The evaluation also collected information on secondary (less direct) health outcomes that are not as clearly indicative of an adverse effect, but they provide biological support and plausibility for the corresponding primary health outcomes (e.g., biochemical or clinical chemistry changes in organ systems). The evaluation did not include other biomarkers of effect (e.g., sister chromatid assay, hypoxanthine-guanine phosphoribosyltransferase [HPRT] mutations), or mechanisms of toxicity (e.g., oxidative stress, apoptosis) because there were fewer studies available, and/or their relevance to later health outcomes was less established. The evaluation also did not include studies evaluating urine mutagenesis, which is considered a biomarker of exposure.

For Objective 2, the evaluation included a literature survey of the studies reporting environmental monitoring of cancer chemotherapy agents in hospital, clinic facilities, or other occupational settings, as well as studies designed to detect the presence of cancer chemotherapy agents or their metabolites in urine or blood of personnel handling these agents or possibly exposed to such contamination. Publications that reported on levels of environmental monitoring or biomonitoring efforts were reviewed, and the data were extracted into tables (see Supplemental Files in Appendix I). These environmental monitoring and biomonitoring publications were not systematically reviewed (e.g., no risk-of-bias assessment or evaluation of confidence in the body of evidence) as that was beyond the scope of the current evaluation. The purpose of this literature survey was to gain an understanding of: (1) the frequencies and levels of positive environmental monitoring, the locations where contamination was detected, and the chemotherapy agents that were monitored and detected; (2) the extent to which worker exposures could be verified by the presence of chemotherapy agents or their metabolites in blood or urine, and (3) any possible changes in the frequency of detection or amounts of cancer chemotherapy

agent detected in environmental monitoring/biomonitoring since implementation of the OSHA safe handling guidelines (OSHA 1986). Data on glove contamination or comparisons of the permeability of different glove materials are not included because the focus of this evaluation was on residual surface contamination, and not on these protective barriers that would be discarded following exposure. Also, studies validating new analytical techniques in the absence of measuring actual samples were also excluded from the review of environmental monitoring or biomonitoring studies.

Literature Search

The literature search was developed in collaboration with a librarian trained in systematic review methodology. Five electronic databases were searched using a search strategy tailored for each database: Embase, PubMed, Scopus, Toxline, and Web of Science. The search terms for PubMed are reported in Appendix A and the search strategy for other databases in protocol are reported in the protocol (Appendix I). No language restrictions or publication year limits were imposed, and the databases were searched on October 23, 2014 with a final updated search on February 23, 2017. The reference lists of all included studies, relevant reviews, commentaries, and other non-research articles as well as the NIOSH webpages detailing Occupational Exposure to Antineoplastic Agents and Other Hazardous Drugs (http://www.cdc.gov/niosh/topics/antineoplastic/default.html) were manually searched for additional relevant publications.

Study Selection

Evidence Selection Criteria

Studies were eligible for inclusion if they satisfied the eligibility criteria in the PECO statement (Objective 1) or contain relevant environmental monitoring or biomonitoring assessment information (Objective 2). Inclusion and exclusion criteria used to screen articles for relevance and eligibility at both the title-and-abstract and full-text screening stages are summarized in Table 2. The following additional exclusion criteria were applied: (1) articles without original data (e.g., editorials or reviews); (2) studies published in abstract form only (grant awards and conference abstracts); and (3) retracted articles. There were no language restrictions for the studies reporting health outcomes (Objective 1). For studies evaluating only environmental monitoring or biomonitoring (Objective 2), only studies written in English language were included because NTP was not conducting a systematic review of the exposure-only literature.

Screening Process

References retrieved from the literature search were screened for relevance and eligibility against the evidence selection criteria using DistillerSR® (Evidence Partners; https://www.evidencepartners.com/products/distillersr-systematic-review-software/), a database software program. Screeners from the evaluation team were trained with an initial pilot phase undertaken to improve clarity of the evidence selection criteria and to improve accuracy and consistency among screeners. Two trained screeners (one of whom was the project lead) independently screened the references at the title-and-abstract level to determine whether a reference met the evidence selection criteria. References that were not excluded by reviewing the title and abstract were screened by a full-text review, including references that were considered

of unclear relevance based on the title-and-abstract review. Screening conflicts were resolved through discussion. Following full-text review, the remaining studies were "included" and used for the evaluation.

Data Extraction

Extraction Process

Data were collected (i.e., extracted) from included studies by one member of the evaluation team and checked by a second member for completeness and accuracy. Any discrepancies in the data extraction were resolved by discussion. Information that was inferred, converted, or estimated during data extraction is annotated, e.g., using brackets [n = 10]. Authors were contacted when details were missing on key study findings. The data extraction files note if an attempt was made to contact study authors by email for missing data considered important for evaluating key study findings, and whether a response from the author was received.

Data Availability

Data extraction was completed using the Health Assessment Workspace Collaborative (HAWC), an open-source and freely available web-based interface application, for visualization and warehousing.[3] The data extraction results for included studies are publicly available (https://hawcproject.org/assessment/196/) and can be downloaded in Excel format through HAWC (NTP 2015a). Data extraction elements are listed separately for human, animal, and in vitro studies in the protocol (Appendix I) (NTP 2015b).

Quality Assessment of Individual Studies

Risk of bias was assessed for individual studies using a tool developed by OHAT (https://ntp.niehs.nih.gov/go/systematic_review); the risk-of-bias criteria were customized for the evaluation (e.g., to address occupational exposure scenarios to cancer chemotherapy agents). The OHAT risk-of-bias tool has questions tailored to specific study design types to assess risk of bias in six categories, including selection bias, confounding bias, performance bias, attrition bias, detection bias, and selective reporting (Rooney et al. 2014). Studies were independently evaluated by two trained assessors who answered all applicable risk-of-bias questions with one of four options (Figure 1) following pre-specified criteria. The criteria describe aspects of study design, conduct, and reporting required to reach risk-of-bias ratings for each question and specify factors that can distinguish among ratings (e.g., what separates "definitely low" from "probably low" risk of bias). Risk-of-bias assessments for confounding, exposure characterization, and outcome assessment were considered especially critical.

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[3]HAWC (Health Assessment Workspace Collaborative): A Modular Web-based Interface to Facilitate Development of Human Health Assessments of Chemicals (https://hawcproject.org/portal/).

Symbol	Description
++	**Definitely *Low* *risk* of bias**: There is direct evidence of <u>low risk</u> of bias practices.
+	***Probably* *Low* *risk* of bias:** There is indirect evidence of low risk of bias practices **OR** it is deemed that deviations from low risk of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias.
- / NR	***Probably High* risk of bias:** There is indirect evidence of high risk of bias practices (indicated with "-") **OR** there is insufficient information provided about relevant risk of bias practices (indicated as not reported (NR)). Both symbols indicate probably high risk of bias.
---	***Definitely High* *risk* of bias**: There is direct evidence of high risk of bias practices.

Figure 1. Risk-of-bias Assessment Ratings

Answers to the risk-of-bias (study quality) questions results in one of four risk-of-bias ratings.

Any discrepancies in ratings between assessors were resolved through discussion to reach the final recorded risk-of-bias rating for each question along with a statement of the basis for that rating. Members of the evaluation team were consulted for assistance if additional expertise was necessary to reach final risk-of-bias ratings based on specific aspects of study design or performance reported for individual studies. Information or study procedures that were not reported were assumed not to have been conducted, resulting in an assessment of "probably high" risk of bias. NTP queried authors by email to obtain missing information, and responses received were used to update risk-of-bias ratings.

The OHAT method identifies some risk-of-bias questions as more important than others because there is evidence that these areas of bias generally have a larger impact on the credibility of study results in environmental health literature (Rooney et al. 2016). The key questions for observational human studies are: confounding, exposure characterization, and outcome assessment (including blinding of outcome assessors).

Rating Confidence in Bodies of Evidence

Groups or studies (bodies of evidence) were assessed to develop confidence ratings that reflect the certainty in the evidence that occupational exposure to chemotherapy agents are associated with health effects for each health outcome using the GRADE system as adapted by OHAT (Rooney et al. 2014). Thus, for each health outcome, bodies of evidence were assessed to develop confidence ratings that reflect the certainty in the evidence that occupational exposure to cancer chemotherapy agents are associated with health effects. More detailed guidance on reaching confidence ratings in the body of evidence as "high," "moderate," "low," or "very low" is provided in the OHAT Handbook for Conducting a Literature-Based Health Assessment (https://ntp.niehs.nih.gov/go/systematic_review, see STEP 5). In brief, available studies on an outcome were initially grouped by key study design features, and each grouping of studies was given an initial confidence rating by those features (Column 1 of Figure 2), including controlled exposure, exposure prior to outcome, individual outcome data, and comparison group used. For example, cohort studies (either prospective or retrospective) are generally assigned an initial

confidence rating of "moderate" because they have three factors (exposure prior to outcome, individual outcome data, and comparison group). Cross-sectional studies are, generally, assigned an initial confidence rating of "low" because they only have two factors (individual data and comparison group). The cross-sectional study design generally cannot assure that exposure occurred prior to outcome; therefore, there is decreased confidence that the relationship between exposure and outcome is causal. Concerns about possible reverse causation or the potential influence of the outcome on the exposure can limit confidence in the results of cross-sectional studies. However, there are several factors that could increase the confidence that data from cross-sectional studies more strongly supports the causal association between exposure and outcome and, thus, increase the initial confidence rating to "moderate." Two examples of factors that could increase the confidence in data from cross-sectional studies are (1) the outcome was rapid (e.g., occurring within minutes or hours of exposure) (see section below, Adjustment of Initial Confidence Ratings of Cross-sectional Studies Evaluating Genetic Toxicity), and (2) the exposure was persistent (e.g., exposure would have preceded outcome even in a cross-sectional study design).

Potential downgrading of the confidence rating was considered for factors that decrease confidence in the results (Column 2 of Figure 2, [high risk of bias, unexplained inconsistency, indirectness or lack of applicability, imprecision, and publication bias]), and potential upgrading of the confidence rating was considered for factors that increase confidence in the results (Column 3 of Figure 2, [large magnitude of effect, dose-response, consistency across study designs/populations, consideration of residual confounding, and other factors that increase confidence in the association or effect]). Consideration of consistency across study designs or human populations is not included in the GRADE guidance (Guyatt et al. 2011); however, it is considered in the modified version of GRADE used by OHAT (Rooney et al. 2014).

Member of the evaluation review team made the confidence ratings assessments. Any discrepancies between reviewers were resolved by consensus and by consultation with technical advisors, as needed. Confidence ratings are summarized in evidence profile tables for each outcome.

Adjustment of Initial Confidence Ratings of Cross-sectional Studies Evaluating Genetic Toxicity

For the evaluation of the three genetic toxicity assays, cross-sectional studies were assigned an initial confidence rating of "moderate" because there was compelling evidence to conclude that occupational exposure preceded outcome and reverse causation was highly unlikely. It is highly likely that the cross-sectional study design ensures that occupational exposure to the cancer chemotherapy agent preceded the health outcome for genetic toxicity assays based on three factors: (1) the rapid induction of DNA damage, (2) inclusion in most studies of only subjects who worked full time the week that their blood samples were drawn, and (3) an employment duration ranging from at least a month to more than one year at the time the study was conducted. Due to the rapid induction of genetic damage, for studies designed to measure DNA damage using the comet assay, it is recommended that blood samples be collected within 3 to 4 hours of exposure termination. For studies designed to measure induction of chromosomal damage or micronuclei, it is recommended that blood samples be obtained within 2 days of acute exposure (Albertini et al. 2000). Furthermore, reverse causation is unlikely in the cross-sectional

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studies of genetic toxicity as participants are not likely to know their DNA damage status such that it would influence their response to a survey of exposures.
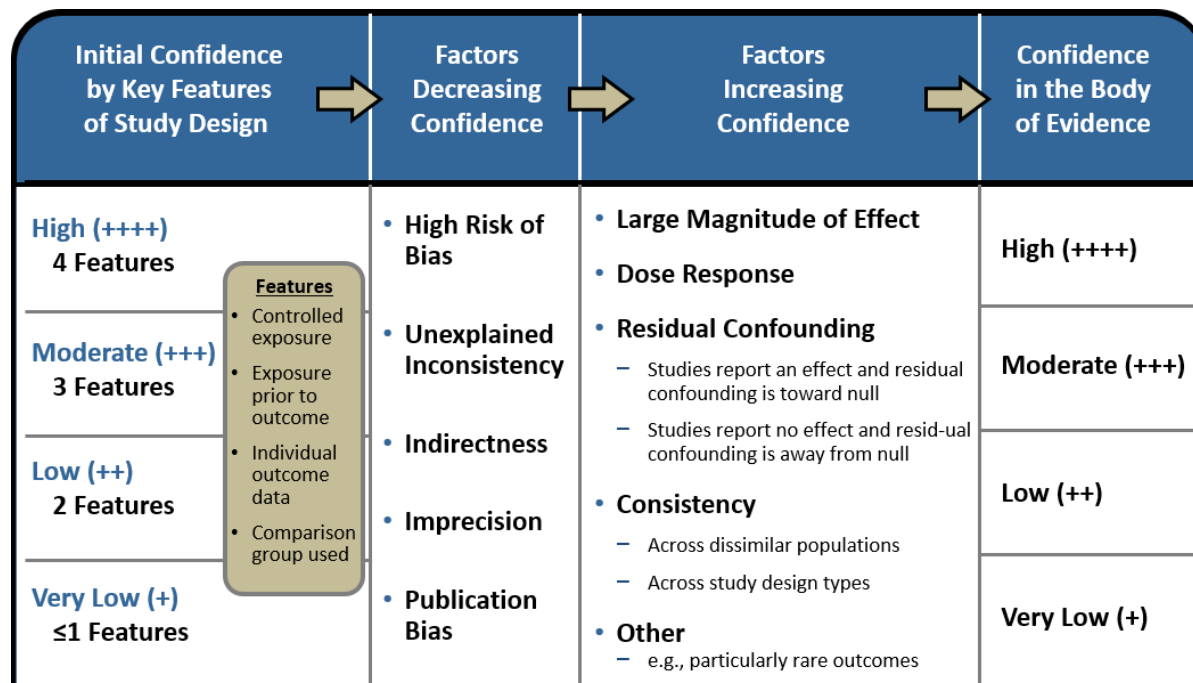
Figure 2. Assessing Confidence in the Body of Evidence

This figure describes how confidence in bodies of evidence (i.e., groups of studies) are considered on an outcome basis.

Preparation of Level-of-evidence Conclusions

The confidence ratings were translated into level-of-evidence conclusions that reflect the confidence in the bodies of evidence and the direction of effect (i.e., health effect or no health effect). These conclusions indicate the confidence in the available evidence that occupational exposure to chemotherapy agents are associated with health effects for each type of health outcome, separately, according to one of four statements: (1) high, (2) moderate, (3) low, or (4) inadequate (Figure 3 and Table 3).
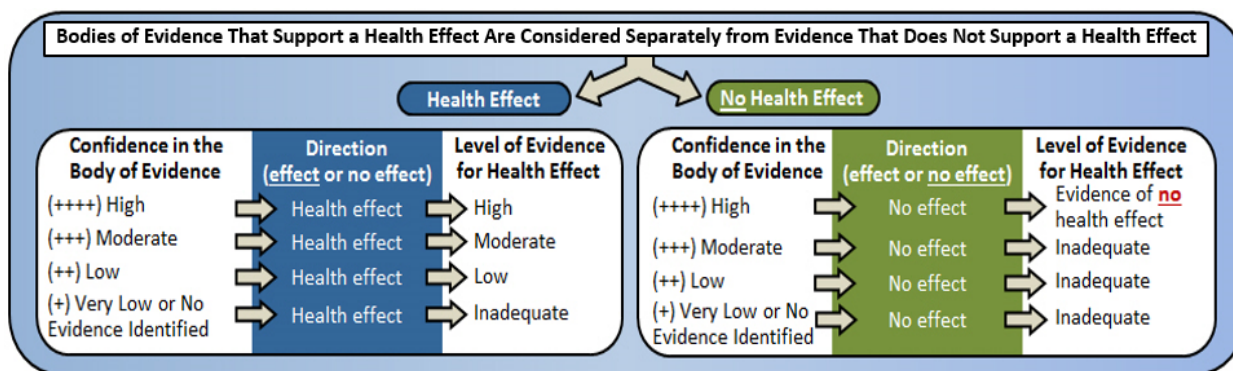
Figure 3. Translation of Confidence Ratings into Evidence of Health Effect Conclusions

Table 3. Definitions of Level-of-evidence Descriptors

Evidence Descriptors	Definition
High Level of Evidence	There is high confidence in the body of evidence for an association between occupational exposure to cancer chemotherapy agents and the health outcome(s).
Moderate Level of Evidence	There is moderate confidence in the body of evidence for an association between occupational exposure to cancer chemotherapy agents and the health outcome(s).
Low Level of Evidence	There is low confidence in the body of evidence for an association between occupational exposure to cancer chemotherapy agents and the health outcome(s), or no data are available.
Inadequate Evidence	There is insufficient evidence available to assess if occupational exposure to cancer chemotherapy agents is associated with the health outcome(s).
Evidence of No Health Effect	There is high confidence in the body of evidence that occupational exposure to cancer chemotherapy agents is <u>not</u> associated with the health outcome(s).

Results and Evidence Synthesis

Literature Search Results

The electronic database searches retrieved 5,584 unique references, and an additional 58 references were identified by experts and by reviewing published reviews and reference lists of included studies. From the total references retrieved: 4,433 were excluded during the title-and-abstract screening and 953 were excluded during the full-text review. The screening results are outlined in a study selection diagram with reasons for exclusion documented at the full-text review (Figure 4). A total of 110 studies reported primary or secondary health outcomes, which were data extracted and processed for risk-of-bias (Objective 1); the included health studies are listed in Appendix B, including 12 non-English language studies that were professionally translated to English language. A total number of 171 studies evaluated contamination of the workplace (environmental monitoring) or biomonitoring of personnel handling cancer chemotherapy agents (Objective 2), including 18 studies that reported on both environmental monitoring and biomonitoring.
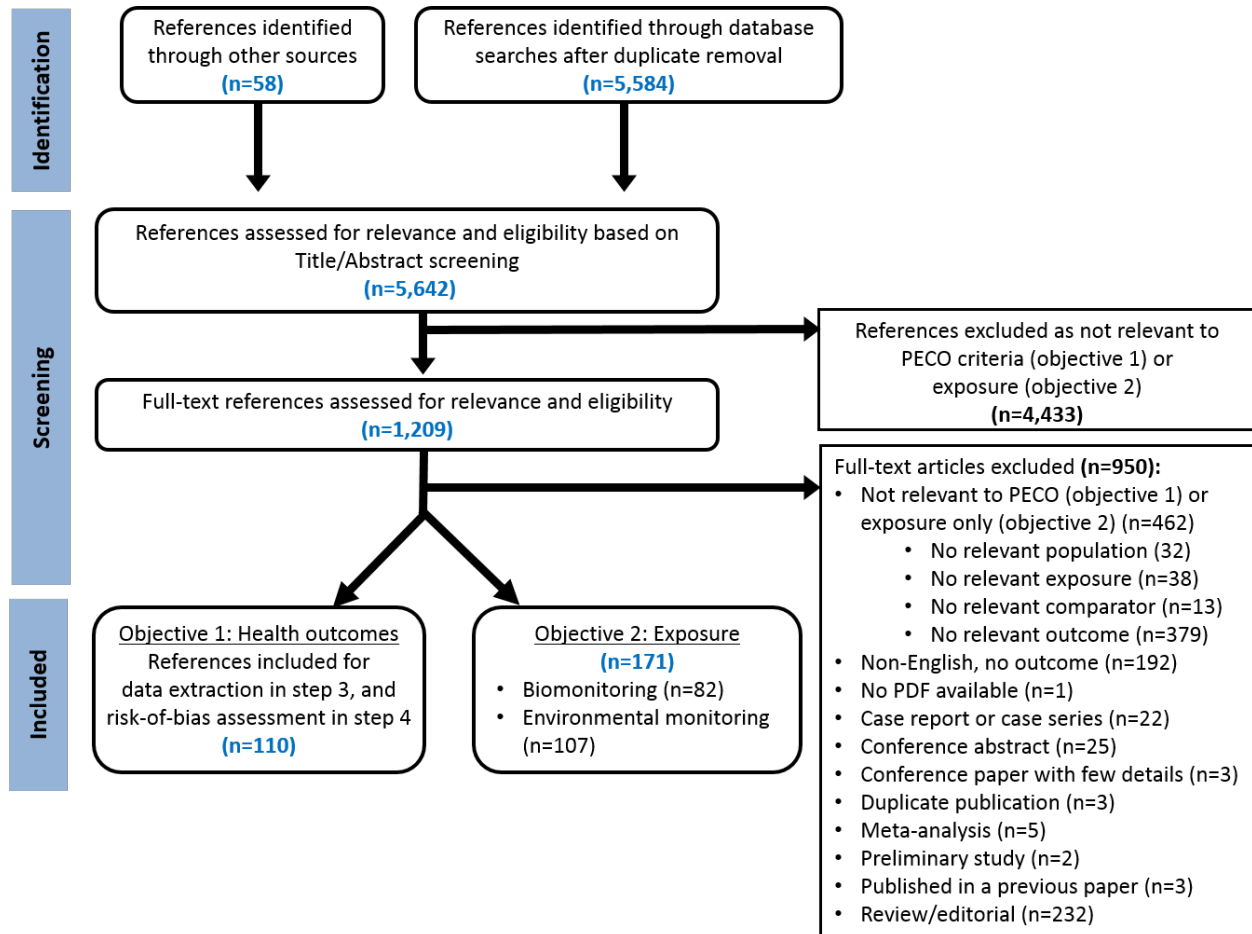
Figure 4. Study Selection Diagram

The total number of included studies was 251, including 110 studies reporting on health outcomes. Seventeen studies on health outcome also reported on biomonitoring (n = 7), environmental monitoring (n = 3), or both (n = 7). Eighteen exposure studies reported on both biomonitoring and environmental monitoring.

Twenty-one studies were excluded from the body of evidence of health effects in reaching health effects conclusions because of methodological considerations and the relatively large body of evidence that reported data using preferred methods. Studies were excluded from the evidence synthesis step because they did not use the preferred measurements for genetic toxicity, including: the inclusion of gaps for CA (Goloni-Bertollo et al. 1992; Mahrous et al. 1998), and the number of binucleated lymphocytes with one, two, three or four micronuclei without analyzing the total binucleated lymphocytes with micronuclei (Fucic et al. 1998). Eight studies, including Fucic et al. (1998), reporting on CA were excluded because they only reported the number of individual types of CA per 100 cells, instead of the total number of CA per 100 cells (Benhamou et al. 1988; Boughattas et al. 2010; Fucic et al. 1998; Harris et al. 1992; Oestreicher et al. 1990; Sarto et al. 1990; Stiller et al. 1983; Waksvik et al. 1981). While the OECD protocol recommends reporting of the frequency of individual CA (OECD 2016a), these studies did not consistently report on the same types of individual CA or grouped data (e.g., chromosome breaks, chromatid breaks), which made it difficult to compare between the studies. Six studies were excluded because they included preliminary data (Maluf and Erdtmann 2000a; Villarini et al. 2012) or they included data that were published in prior publications. For example, Cavallo et al. (2007; 2009) were excluded because they evaluated the effect of gene polymorphisms on micronuclei and comet assay data published in a prior publications (Cavallo et al. 2005; Ursini et al. 2006), and two studies reporting on number of CA per 100 cells scored (Mušák et al. 2009a; Mušák et al. 2009b) were excluded because the data were published in (Mušák et al. 2006). One study was excluded because it reported on combined, instead of individual outcomes: adverse pregnancy outcomes combined, which included spontaneous abortion, stillbirth and congenital malformations (Rogers and Emmett 1987). Finally, four studies reporting on the percentage of cells with CA of the same population of nurses in Hungary were excluded due to a lack of adjustment for significant effects of co-exposure to ionizing radiation on exposed subjects, which made it unclear whether the significant finding of higher percentage of cells with CA was due to occupational exposure to cancer chemotherapy agents or to the co-exposed individuals (Tompa et al. 2016; Tompa et al. 2006a; Tompa et al. 2015; Tompa et al. 2006b).

The main findings for each category of health outcome are summarized below, and the number of studies per health outcome are reported in Table 4. The results and evidence synthesis sections include a detailed analysis of the evidence on spontaneous abortion and genetic toxicity. The risk-of-bias assessment of individual studies and for the body of evidence were considered in developing the confidence ratings for each health effect. The key risk-of-bias questions were: confounding, exposure characterization, and outcome assessment (see protocol in Appendix I); they are discussed in the consideration of the body of evidence for each health effect. While no study was excluded based on concerns for risk of bias, confidence conclusions were considered with and without the high risk-of-bias studies (e.g., studies rating probably high or definitively high risk of bias for two key risk-of-bias questions) to assess the influence of the high risk-of-bias studies. The risk-of-bias assessment for all included studies is in Appendix C.

Table 4. Categories of Health Outcomes for 110 Included Studies

Health Outcome[a]	DNA Damage[b]	Reproductive and Developmental Toxicity	Immune System Alterations	Acute Effects	Kidney Toxicity	Liver Toxicity	Cancer	Cardiac System Toxicity
Primary (Direct)	66 studies[b]	30 studies (e.g., spontaneous abortion)	1 study (e.g., immune-related diseases)	10 studies (e.g., nausea)	1 study (e.g., kidney disease)	1 study (e.g., liver disease)	3 studies	1 study (e.g., cardiovascular disease)
Secondary (Indirect)	–	–	10 studies (e.g., lymphocyte activation)	–	4 studies (e.g., kidney biochemistry)	3 studies (e.g., liver biochemistry)	–	1 study (e.g., cardiac functional endpoints)

[a]Individual studies often reported more than one health outcome.
[b]DNA damage studies included only those evaluating chromosomal aberrations (n = 29), micronucleus induction (n = 35), and DNA damage measured by the comet assay (n = 21).

Health Outcomes with Inadequate Evidence

For many of the health outcomes, there is inadequate evidence to determine whether there is an association with occupational exposure to cancer chemotherapy. The published studies were considered inadequate to evaluate potential reproductive or development toxicity on endpoints other than spontaneous abortion because most of the studies had a small number of cases for each health outcome, and some outcomes had very few studies. These outcomes included: cancer, congenital malformations, menstrual irregularities, ectopic pregnancy, stillbirth, preterm birth, low birth weight/small for gestational age, sex ratio, and time to pregnancy or infertility. The body of evidence was inadequate to evaluate potential effects on the immune system (e.g., hematotoxicity) because there was heterogeneity in the endpoints examined and, when evaluated in more than one study, the results were inconsistent. The body of evidence was also inadequate for liver or kidney toxicity because these health effects were only reported in one or two studies with inconsistent results. In addition, the number of cases were low (e.g., n = 3–6 cases out of 44 exposed medical personnel for liver or kidney toxicity, respectively), and there was considerable heterogeneity in the endpoints examined. The results, evidence synthesis and risk-of-bias assessment for the health outcomes with inadequate evidence are in Appendix E.

Spontaneous Abortion

Spontaneous abortion (also called miscarriage) is the noninduced termination of a pregnancy before 20 weeks of gestation. NTP identified 16 studies reporting on spontaneous abortion in women or spouses of men occupationally exposed to cancer chemotherapy agents. Among the studies in this evaluation, spontaneous abortion was most commonly defined as spontaneous pregnancy loss at ≤20 weeks of gestation; however, one study defined spontaneous abortion as pregnancy loss at less than 24 weeks of gestation (Zhang et al. 2016) and two studies defined it as pregnancy loss at less than 28 weeks of gestation (McDonald et al. 1988b; Stücker et al. 1990). The level-of-evidence conclusion is based only on studies that reported spontaneous abortions, and did not include studies that reported spontaneous abortion and stillbirth as a combined outcome (McAbee et al. 1993; Rogers and Emmett 1987).

Summary

Based on the available studies, there is *moderate confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with spontaneous abortion. Seven of the 16 studies identified were considered to be more informative regarding exposure assessment because the studies identified exposed nursing or pharmacy staff based on the task they performed (e.g., prepared and administered cancer chemotherapy agents) and, in some studies, the frequency of handling these agents (e.g., number of times hourly or weekly) (Fransman et al. 2007c; Lawson et al. 2012; Peelen et al. 1999; Selevan et al. 1985; Stücker et al. 1990; Valanis et al. 1999; Zhang et al. 2016). The body of evidence from these seven studies was used for rating confidence in the conclusions because of their exposure characterization and concerns for high risk of bias for exposure characterization as well as other key risk-of-bias factors (confounding and outcome assessment) in the remaining nine studies. The results were inconsistent for the nine studies that evaluated occupational exposure to any chemical or work stressor (e.g., shift work, heavy lifting) (Hemminki et al. 1985; McDonald et al. 1988b; Schaumburg and Olsen 1990b; Taskinen et al. 1994; Taskinen et al. 1986) or risk-of-bias issues regarding exposure characterization (Skov et al. 1992; Walusiak et al. 2003) and/or outcome assessment (Elshamy et al. 2010; Medková 1991a). There were no changes from the initial rating of moderate confidence in the body of evidence (seven studies) after considering factors that may increase or decrease confidence (Figure 5). The final rating of moderate confidence in the body of evidence translates directly into a *moderate level of evidence* that occupational exposure to cancer chemotherapy agents is associated with a higher risk of spontaneous abortion.

Overview

The available 16 epidemiological studies in the body of evidence that evaluated the association between occupational exposure to cancer chemotherapy and spontaneous abortions included four retrospective cohort studies, four case-control studies, and eight cross-sectional studies of 13 unique study populations (Table 5). While all studies evaluated the pregnancy outcomes of occupationally exposed female subjects, two studies also evaluated spontaneous abortion among female spouses of occupationally exposed male subjects (Valanis et al. 1999; Walusiak et al. 2003). The majority of the studies evaluated nurses, one study evaluated pharmaceutical employees (Taskinen et al. 1986), and one evaluated laboratory workers (Taskinen et al. 1994). The studies were conducted in 11 countries: Denmark (two studies), Finland (four studies; two studies overlapped in population being evaluated), the Netherlands (two studies evaluated the same population and same data), the United States (two studies), and one study each from Canada, China, Czech Republic, Egypt, France, and Poland. All the studies used retrospective exposure characterization that relied primarily on job title and self-reported questionnaires with questions about work tasks, exposures, and use of safety equipment (e.g., biological safety cabinets and personal protective equipment during or prior to pregnancy). Two studies evaluating the same study population also reported on biomonitoring or environmental monitoring: swipe tests for cyclophosphamide, ifosfamide, 5-flurouracil and urine biomonitoring for cyclophosphamide (Peelen et al. 1999), and glove and hand wash sampling for cyclophosphamide (Fransman et al. 2007c). The occurrence of spontaneous abortion was identified from medical records (five studies) or via questionnaire (interviewer-led questionnaire, four studies; self-reported questionnaire, six studies). Data collection on the study participants ranged from the years of 1970 to 2013: five studies (four unique populations) reported data prior to 1985, two studies overlapped with 1985 U.S. guidance on handling hazardous drugs, and eight

studies (six unique populations) reporting data collected after 1985. Six of these studies also reported data on other reproductive outcomes, cancer, and/or acute effects (see Appendix E for discussion of the other health outcomes).

Evidence Synthesis

The evidence synthesis for spontaneous abortion was based on 16 studies, including: four retrospective cohort studies (Lawson et al. 2012; McDonald et al. 1988b; Schaumburg and Olsen 1990b; Skov et al. 1992), four case-control studies (Hemminki et al. 1985; Selevan et al. 1985; Taskinen et al. 1994; Taskinen et al. 1986), and eight cross-sectional studies (Elshamy et al. 2010; Fransman et al. 2007c; Medková 1991a; Peelen et al. 1999; Stücker et al. 1990; Valanis et al. 1999; Walusiak et al. 2003; Zhang et al. 2016) (Table 5). The results were consistent for a higher risk of spontaneous abortions associated with cancer chemotherapy agents when evaluating studies of nursing or pharmacy personnel with higher handling activities of these agents (Figure D-1) (Fransman et al. 2007c; Lawson et al. 2012; Peelen et al. 1999; Selevan et al. 1985; Stücker et al. 1990; Valanis et al. 1999). For example, a case-control study of Finnish nurses reported significantly greater odds of spontaneous abortion (OR = 2.3, 95% CI = 1.2–4.39) in nurses with high usage of cancer chemotherapy drugs compared to nurses with less than once weekly exposure in the first trimester (Selevan et al. 1985). A cross-sectional study in France by Stucker et al. (1990) reported significantly higher odds of spontaneous abortion (adjusted odds ratio (adjOR) = 1.7, 95% CI = 1.0–2.8) in exposed nurses employed in a cancer center or hospital oncology wards compared to unexposed nurses from consulting medical, cardiology, endocrinology, and general medical units. Similarly, a cross-sectional study of female nurses, nurses' aides, pharmacists, and pharmacy technicians in the United States reported significantly increased odds of spontaneous abortion (adjOR = 1.5, 95% CI = 1.2–1.8) in medical personnel who either prepared or administered doses, and/or handled the excreta of patients administered cancer chemotherapy agents during pregnancy than unexposed subjects (Valanis et al. 1999). In a study evaluating the influence of occupational exposure in the Nurses' Health Study II in the United States, Lawson et al. (2012) reported significantly greater odds of spontaneous abortion in nurses exposed ≥1 hour per day to cancer chemotherapy agents (adjOR= 1.94, 95% CI = 1.32–2.86), with the highest odds of spontaneous abortion occurring at <12 weeks of gestation; the analyses were adjusted for other co-exposures and work conditions (i.e., anesthetic gases, sterilizing agents, anti-viral agents, ionizing radiation, and shift work).

Further support for a relationship between occupational exposure to cancer chemotherapy agents and spontaneous abortion was reported in a cross-sectional study of nurses handling cancer chemotherapy agents employed in an oncology ward and non-oncology ward compared to unexposed nurses in a hospital in China at the beginning of the implementation of a pharmacy intravenous admixture service (PIVAS) versus an open plan treatment area, with a follow-up study 2 years later (Zhang et al. 2016). The PIVAS was a closed system that reduced exposure by adding safety equipment (e.g., biological safety cabinets, sealed bags for transport of prepared drugs), increased use of personal protective equipment when handling these agents, and protocols for storage, transport, disposal, and management of spills as well as safety training. Prior to implementation of the PIVAS, the rate of spontaneous abortions was non-significantly higher in nurses handling cancer chemotherapy in oncology (14.6%) compared to unexposed nurses (9.4%). In a follow-up study 2 years later, the authors observed a significant reduction in the rate of spontaneous abortions in nurses working in the oncology ward 2 years after PIVAS implementation (4.6%) compared to the rates before PIVAS (14.6%), as well as compared to

spontaneous abortion rates in oncology nurses from a hospital in China with no PIVAS (22.3%) (Zhang et al. 2016).

In contrast, two studies of one population observed no association of spontaneous abortion (Fransman et al. 2007c; Peelen et al. 1999). Peelen et al. (1999) reported a slightly higher, but not statistically significant, odds of spontaneous abortion in oncology nurses from 121 hospitals in the Netherlands based on job title and work tasks (OR = 1.4, 95% CI = 0.8–2.6). In a second analysis of the same data from the Dutch oncology nurses, Fransman et al. (2007c) reported no association of spontaneous abortions with estimated dermal exposure to cyclophosphamide; the dermal exposure estimate was based on job title tasks, use of PPE as well as glove and hand contamination. The author commented that the study may have underestimated exposure of the nurses because the administered dose levels of cancer chemotherapy agents have decreased over time, and the outcome data were collected in 1990–1997, while the glove and hand monitoring studies were conducted in 1996–1997 and 2001–2003.

Table 5. Studies Reporting on Spontaneous Abortion

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Elshamy et al. (2010)	Cross-sectional (Nurses, Egypt, 2006, F)	35 exposed, 29 unexposed	Job title, length of employment, self-administered questionnaire about drug handling, frequency of handling, number of accidents with cancer chemotherapy in past year, usage of personal protective equipment, and training. *Note: Only 42.9% of nurses reported using gloves when handling patient waste, and 45.7% of nurses admitted to eating in the drug preparation area*	Self-reported questionnaire; no definition of abortions was provided [assumed it was spontaneous abortion]	Chi-square test with continuity correction, if indicated	Significantly (p<0.05) higher rates of spontaneous abortions in exposed (22.6%; 8 cases) versus unexposed (10.3%; 3 cases)
Fransman et al. (2007c)	Cross-sectional (Nurses, the Netherlands, 1990–1997, F) *Note: Same data as Peelen 1997*	Exposed: 279 background, 146 low, 145 medium, 134 high; 555 unexposed	Estimated dermal exposure based on job title, self-reported questionnaire, and glove usage in first month of pregnancy (or during time trying to get pregnant), combined with data on CP glove monitoring conducted in 1996–1997 and glove and hand monitoring in 2003–2007; categorized as: unexposed, background, low (≤0.20 μg CP/wk), medium (>0.20−0.74 μg CP/wk) or high exposure (>0.74 μg CP/wk)	Self-reported questionnaire on most recent pregnancy; defined as pregnancy loss at <20 weeks of gestation	Logistic regression analysis; adjusted a priori for age at conception, parity, smoking, alcohol consumption, coffee intake during 1st trimester of pregnancy, vitamin/folic acid use during pregnancy as well as work factors (e.g., co-exposures)	No difference in odds of spontaneous abortions compared to unexposed pregnancies (log-linear association OR = 1.01, 95% CI = 0.93–1.10; 36 exposed cases). Using dermal exposure estimates, the odds of spontaneous abortion for exposed pregnancies were: low exposure, adjOR = 1.2 (95% CI = 0.6–2.7); medium exposure, adjOR = 0.8 (95% CI = 0.3–2.0); and high exposure, adjOR = 1.2 (95% CI 0.6–2.7)

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Hemminki et al. (1985)	Case-control (Nurses, 1973–1979, Finland, F) Note: population overlaps with Selevan 1985	169 cases, 469 controls; only 53 pregnancies exposed	Central Registry of Health Care Personnel and a questionnaire to head hospital nurses regarding each subjects' occupational exposures (type of occupational exposure, shift work, etc.) *Note: Exposed nurses were from non-oncology departments (i.e., anesthesia, intensive care, operating room, or internal medicine) where exposure was relatively uncommon*	Medical records	Logistic model of conditional likelihood function adjusted for shift work and co-exposures (e.g., ionizing radiation)	No difference in odds of spontaneous abortion between cytostatic agents ≥ once weekly and unexposed (OR = 0.8, 95% CI = 0.3–1.7; 12 exposed cases versus 41 unexposed cases)
Lawson et al. (2012)	Cohort, retrospective (Nurses' Health Study II, USA, 1993–2002, F)	775 cases, 6,707 live births; 302 exposed, 7,180 unexposed	Job title and self-reported questionnaire, including questions for each trimester of pregnancy on exposure to 5 occupational exposures: anesthesia, cancer chemotherapy agents, anti-viral drugs, sterilizing agents, and X-ray radiation	Self-reported questionnaire on most recent pregnancy; defined as pregnancy loss at <20 weeks of gestation	Logistic regression adjusted for age; multivariate analysis included all 5 work exposures, parity, shift work, and hours worked	Significantly higher odds of spontaneous abortion in nurses exposed ≥1 hour per day compared to unexposed pregnancies (adjOR = 1.94, 95% CI = 1.32–2.86; 48 exposed cases); appeared to be due to spontaneous abortions occurring at <12 weeks

Systematic Review of Occupational Exposure to Cancer Chemotherapy Agents

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
McDonald et al. (1988b)	Cohort, retrospective (Working women, 1982–1984, Canada, F)	22,713 (only 63 pregnancies exposed to cancer chemotherapy agents)	Job title and interviewer-led questionnaire, and chemical exposure information from published and unpublished studies, and occupational surveillance by local health departments and Montreal surveillance for cancer, and other reports *Note: Medical questionnaire also asked nurses or physicians if they administered cancer chemotherapy agents in the month after the first missed menstrual period*	Interviewer-led questionnaire on previous pregnancies; defined as pregnancy at <28 weeks of gestation	Poisson regression; evaluated factors: age, gravidity, history of previous abortion, ethnic group, educational level as well as smoking habit and alcohol consumption	No association with spontaneous abortion compared to unexposed pregnancies (O/E = 0.97, 13 exposed cases); maternal age, gravidity, previous spontaneous abortion, smoking, and alcohol consumption were significant factors [but the data do not appear to be adjusted for these significant factors]
Medková (1991a)	Cross-sectional (Physicians, nurses, auxiliary workers, Czech Republic, Year NR, FM)	74 exposed, 11 unexposed (to partners of exposed subjects)	Job title and interviewer-led questionnaire (≥5 years, n = 25; 6–10 years, n = 14; 11–15 years, n = 4; and 16–20 years, n = 1) *Note: All exposed personnel used gloves and gowns; isolated room for drug preparation only used by 25% of exposed subjects*	Interviewer-led questionnaire; [no definition provided for early and late spontaneous abortion]	NR	Higher number of early spontaneous abortions compared to unexposed pregnancies (early: 8 exposed vs. 0 unexposed); whereas, there were 2 late spontaneous abortions in unexposed versus 0 in exposed

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Peelen et al. (1999)	Cross-sectional (Nurses, the Netherlands, 1990–1997, F) *Note: Same data as Fransman et al. 2007c*	249 exposed, 1,010 unexposed	Job title, self-reported questionnaire, biomonitoring, and environmental monitoring	Self-reported questionnaire on most recent pregnancies; [definition same as Fransman et al. 2007c]	[Logistic regression]; adjusted for age, coffee consumption, smoking, alcohol consumption, pregnancy, physical strain, and co-exposures (e.g., ionizing radiation, disinfectants), as needed	Non-significant, but slightly higher, odds of spontaneous abortion compared to unexposed pregnancies (adjOR = 1.4, 95% CI = 0.8–2.6; 18 exposed cases); 30% of urine samples from exposed nurses tested positive for CP and 40% tested positive for IF; unexposed subjects were not tested
Schaumburg and Olsen (1990b)	Cohort, retrospective (Pharmacy assistants, Denmark, 1979–1984, F)	1,882 births, 177 spontaneous abortions, 109 induced abortions; only 8 pregnancies exposed to cancer chemotherapy agents	Membership in national union of pharmacy assistants and self-reported questionnaire	Medical records	Unconditional logistic regression model	No spontaneous abortions were reported for the 8 pregnancies of occupationally exposed personnel
Selevan et al. (1985)	Case-control (Nurses, Finland, 1973–1980, F)	124 cases, 321 controls; only 92 pregnancies exposed	Central Registry of Health Care Personnel and self-reported questionnaire *Note: Exposed nurses identified as having high usage of cancer chemotherapy agents*	Medical records	Conditional logistic regression; factors considered: smoking, alcohol use, medications in first trimester, gravidity, prior fetal loss, exposure prior to pregnancy	Significantly higher odds of spontaneous abortion with first trimester exposure (OR = 2.3, 95% CI = 1.2–4.39; 18 exposed cases); prior fetal loss was significant factor and results were the same when adjusted for this factor; exposure prior to pregnancy NS

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Skov et al. (1992)	Cohort, retrospective (Nurses, Denmark, 1977–1988, F)	281 exposed, 809 unexposed	Employment records of 5 oncology hospitals, and data from head nurses regarding drug handling and administration of individual subjects; evaluated data as exposed versus unexposed and by level of exposure [details not provided] versus unexposed	Medical records	Logistic regression analysis with adjustment for maternal age	No difference in odds of spontaneous abortion compared to unexposed nurses (adjOR = 0.74, 95% CI = 0.40–1.38; 18 exposed cases); spontaneous abortion rate was similar when considering first pregnancies only; no exposure-response observed
Stücker et al. (1990)	Cross-sectional (Nurses, France, 1985–1986, F)	139 exposed, 357 unexposed	Job title and interviewer-led questionnaire *Note: At time of study, no special protective equipment was in operation and use of PPE was not uniform*	Interviewer-led questionnaire; defined as pregnancy loss at <28 weeks of gestation	Logistic regression analysis; evaluated effect of maternal age, parity and smoking, exposure duration and frequency of handling	Significantly higher odds of spontaneous abortion in the first exposed pregnancy compared to unexposed pregnancies (adjOR = 1.7, 95% CI = 1.0-2.8); 36 exposed cases; exclusion of 24 cases prior to pregnancy did not change significance (rate ratio = 1.7, 95% CI = 1.1–2.5)

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Taskinen et al. (1986)	Case-control (Pharmaceutical industry workers, Finland, 1973–1980, F)	44 cases, 130 controls; only 6 exposed pregnancies	Factory physician completed-questionnaire on exposure during pregnancy through health cards, labor protection chiefs, and department foremen regarding occupation, main tasks, exposures, lifting, standing, or sitting; employed at least one week during the first trimester	Medical records	Logistic regression analysis based on conditional maximum likelihood	No statistically significant higher odds of spontaneous abortions compared to unexposed pregnancies (OR = 2.8, 95% CI = 0.6–1.4; 3 exposed cases)
Taskinen et al. (1994)	Case-control (Laboratory assistants, Finland, 1970–1986, F)	206 cases, 329 controls; only 8 exposed pregnancies	Employment records and self-reported questionnaire regarding frequency of specific exposures during first trimester	Medical records	Logistic regression based on conditional likelihood; covariate included smoking, alcohol use, employment status	No statistically significant higher odds of spontaneous abortion compared to unexposed pregnancies (adjOR = 4.0, 95% CI = 0.8–19.3; 5 exposed cases)

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Valanis et al. (1999)	Cross-sectional (Nurses, nurses' aides, pharmacists, and pharmacy technicians, USA, 1988–1989, FM)	1,448 exposed, 5,297 unexposed	Job title and self-reported questionnaire *Note: Exposed subjects were involved in mixing, administering, and/or handling the excreta of patients administered cancer chemotherapy agents*	Self-reported questionnaire; defined as pregnancy loss at ≤20 weeks	Logistic regression for (1) independence model and (2) generalized estimating equations model; all models adjusted for age, gravidity at time of pregnancy, maternal smoking during pregnancy; outcome of prior fetal loss	Significantly higher odds of spontaneous abortion in pregnancies of exposed female subjects exposed during pregnancy (adjOR = 1.5, 95% CI = 1.2–1.8; 223 exposed cases) or prior to pregnancy (adjOR = 1.5, 95% CI = 1.3–1.9) compared to unexposed pregnancies; pregnancies of exposed female subjects affected more than pregnancies of spouses of exposed male subjects
Walusiak et al. (2003)	Cross-sectional (Physicians, nurses, orderlies, Year NR, Poland, FM)	84 exposed, 169 unexposed	Job title and self-reported questionnaire (11.0 ± 9.3 years, range 5–44 years)	[Interviewer-led] questionnaire; defined as pregnancy loss at <24 weeks of gestation	Mann-Whitney U-test	Greater, but NS, number of spontaneous abortions compared to unexposed nurses (unexposed = 9 cases, 5.3% prevalence; exposed = 7 cases, 8.3% prevalence)

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Pregnancies (Unless Otherwise Stated)	Exposure Measure	Outcome Assessment	Analysis	Results
Zhang et al. (2016)	Cross-sectional (Nurses, China, 2011 pre-PIVAS and 2013 (post-PIVAS) in Hospital A, F)	Pre-PIVAS: 106 unexposed, 30 exposed non-oncology, 82 exposed oncology; Post-PIVAS: 108 unexposed, 29 exposed non-oncology, 87 exposed oncology, and 112 exposed oncology nurses at Hospital B)	Job title and self-reported questionnaire (≥2 years in current job) *Note: All exposed nurses involved in mixing and/or administration of cancer chemotherapy agents*	Self-reported questionnaire; pregnancy loss at <24 weeks of gestation	[Student] t-test, Chi-square, and Wilcoxon [signed-rank sum] test	No difference in rate of spontaneous abortion compared to unexposed nurses prior to PIVAS at Hospital A; after implementation of PIVAS, the rate of spontaneous abortions in exposed oncology nurses was significantly (p<0.05) lower compared to pre-PIVAS values as well as non-significant reductions in the rates for unexposed and exposed non-oncology nurses. Significantly (p<0.01) higher rate of spontaneous abortions was reported for exposed oncology nurses at Hospital B (no PIVAS) compared to post-PIVAS exposed oncology nurses at Hospital A

adjOR = adjusted odds ratio; CI = confidence interval, CP = cyclophosphamide, F = female, IF = ifosfamide; M = male, NR = not reported, NS = not significant, OR = odds ratio, PIVAS = pharmacy intravenous admixture service, and USA = United States of America, wk = week.

The remaining nine studies evaluating spontaneous abortion were less informative for a variety of reasons. Hemminki et al. (1985) conducted a case-control study of the same population of nurses in France as Selevan et al. (1985) to evaluate the association with occupational exposure to anesthesia gases, sterilizing agents, ionizing radiation, cancer chemotherapy agents, and other exposures. The authors observed no association between occupational exposure to cancer chemotherapy agents and spontaneous abortion (Hemminki et al. 1985); however, the authors stated that the nurses were from hospital departments with reduced exposure to cancer chemotherapy agents (i.e., anesthesia surgery, intensive care, operating room or internal medicine department of a general hospital) relative to the nurses with high levels of handling and administering these agents reported in the study by Selevan et al. (1985). A retrospective study of oncology nurses in five hospitals in Denmark from 1977–1988 reported that spontaneous abortion was not associated with occupational exposure to cancer chemotherapy agents when evaluating exposed versus unexposed nurses or in an exposure level (low, moderate, high exposure) analysis conducted by head nurses consulting hospital drug-handling logs (Skov et al. 1992). However, the authors did not provide details on how they categorized the nurses into the exposure levels, and there was no information on use of personal protective equipment; the authors hypothesized that part of the lack of effect might be due to the implementation of safety handling procedures for cancer chemotherapy agents after 1980.

One retrospective cohort study of 2,168 pregnancies of pharmacy assistants in Denmark observed no spontaneous abortions among the eight pregnancies exposed to cancer chemotherapy agents; however, the workers may not have been highly exposed (characterized as daily or weekly exposure versus unexposed) (Schaumburg and Olsen 1990b). No association of spontaneous abortion with occupational exposure to cancer chemotherapy agents was observed in a cross-sectional study assessing occupational exposures of nurses and doctors in Canada; however, there was no information provided about the tasks or frequency of drug handling of the exposed individuals (McDonald et al. 1988b). Two case-control studies evaluating the influence of various occupational exposures of pharmaceutical workers (Taskinen et al. 1986) and laboratory assistants (Taskinen et al. 1994) reported higher, but non-significant, odds for spontaneous abortion with exposure to cancer chemotherapy agents; however, these studies included very few exposed pregnancies (6–8 pregnancies) with very few cases (3–5 cases) and the range of exposure during pregnancy was insufficient to determine a difference between groups (controls: 1–2 days per week versus exposed: ≥3 days per week). A cross-sectional study of physicians, nurses, and auxiliary workers handling cancer chemotherapy agents in the Czech Republic reported a higher occurrence of early spontaneous abortions in exposed subjects compared to unexposed spouses of the exposed subjects across all pregnancies (Medková 1991a); however, the authors did not provide a definition of early spontaneous abortion, no statistical analyses were reported, and there were only two unexposed subjects with pregnancy outcome data compared to 38 exposed subjects with pregnancy outcome data. A cross-sectional study of doctors, nurses, and orderlies in Poland reported that there was no difference in spontaneous abortion in the exposed subjects versus the unexposed personnel (Walusiak et al. 2003). The authors reported that doctors were the least exposed of the medical personnel, but they do not explain how they characterized exposure and they did not run an analysis with only the nurses and orderlies (Walusiak et al. 2003). Finally, a cross-sectional study of oncology nurses in Egypt employed in the same position for >10 years reported a significantly (p<0.05) higher rate of abortions—which was not defined, but was presumed to be spontaneous abortions—relative to controls (22.6%) compared to unexposed nurses (10.3%); the authors

reported poor adherence to safety measures of the exposed nurses, such as eating in the drug administration area (45.7%) and only 42.9% used gloves when cleaning up spills or handling patient waste.

Risk-of-bias Assessment

Risk-of-bias assessments were conducted on all studies included in the evidence synthesis for spontaneous abortion (Figure D-2 and Figure D-3). Approximately 60% of the studies reporting on the occurrence of spontaneous abortion were rated probably low risk of bias for confounding (e.g., appropriate confounders were considered and adjusted when necessary), exposure characterization, and outcome assessment.

Most studies (10 of 16) were rated probably low or definitely low risk of bias for confounding. Schaumburg and Olsen (1990b) did not adjust for confounders or control for multiple exposures among the pharmacy assistants working with cancer chemotherapy drugs on a daily or weekly basis; however, this study was rated as probably low risk of bias because no spontaneous abortions were observed among the eight exposed pregnancies. One study was rated as probably high risk of bias (Medková 1991a); the author did not adjust for differences in age or smoking, and it was not clear whether both the male employees and their pregnant spouses were smokers or whether second hand smoke was addressed. Five studies were rated probably high risk of bias for lack of adjustment for confounding variables (Elshamy et al. 2010; McDonald et al. 1988b; Skov et al. 1992; Taskinen et al. 1986; Walusiak et al. 2003). One study of female pharmaceutical workers did not appear to adjust for possible co-exposures (e.g., ionizing radiation) in their analysis, and the authors did not report whether they evaluated for confounders of smoking or alcohol consumption (Taskinen et al. 1986). McDonald et al. (1988b) identified significant differences in the prevalence of several confounders (i.e., maternal age, gravidity, previous spontaneous abortion, smoking, and alcohol consumption) between the exposed and unexposed nurses and doctors, but did not report whether they adjusted for these confounders. Skov et al. (1992) did not evaluate smoking or alcohol consumption in their retrospective cohort of oncology nurses; however, the authors comment that nurses were likely to have similar rates of these two possible confounders, regardless of occupational exposure. A study of oncology nurses in Egypt did not report an assessment of potential confounders for either exposed or controls (e.g., smoking, ionizing radiation) (Elshamy et al. 2010). Finally, Walusiak et al. (2003) reported data on the sex, age, and smoking status of the exposed and unexposed nurses in their study, but did not present any statistical analysis evaluating possible differences in these confounders.

Ten of 16 studies were rated probably low risk of bias for exposure characterization. For example, Fransman et al. (2007c) estimated exposure using data on self-reported tasks of oncology nursing staff (preparation, administration, handling patient urine, washing a patient, removing bed sheets, cleaning toilets) and PPE use with task-based exposure measurements of glove and hand (dermal) contamination of cyclophosphamide. In another study, Lawson et al. (2012) characterized exposure from the Nurses' Health Study, a well-established cohort, using a self-reported questionnaire with questions regarding occupational exposure to cancer chemotherapy agents as well as other genetic toxicant exposures (e.g., anesthetic gases, sterilizing agents, x-rays), shiftwork, and anti-viral medication. The questionnaire included examples for each class of exposures, which has been demonstrated to improve the accuracy of the exposure recall (Teschke et al. 2002). While use of questionnaires (self-report or interviewer-

led) to characterize exposure in retrospective cohort studies can be influenced by recall bias, support for accurate recall of exposure by medical staff has been demonstrated by a study of pharmacists whose self-reported questionnaire was corroborated by their supervisor (McDiarmid et al. 1992). Six studies were rated probably high risk of bias for exposure characterization (Hemminki et al. 1985; McDonald et al. 1988b; Skov et al. 1992; Taskinen et al. 1994; Taskinen et al. 1986; Walusiak et al. 2003). Two studies were rated probably high risk of bias for a lack of details regarding exposure characterization; for example, Walusiak et al. (2003) only provided job title as the description of physicians, nurses, and orderlies handling cancer chemotherapy agents although they stated that doctors were less exposed, and Skov et al. (1992) provided no description of the semi-quantitative categories of exposure of oncology nurses from two hospitals (Skov et al. 1992). Two studies did not provide a sufficient range or variance in exposure measures across groups (Taskinen et al. 1994; Taskinen et al. 1986); e.g., these studies compared female laboratory workers (Taskinen et al. 1994) or pharmaceutical factory workers (Taskinen et al. 1986) exposed (1994) 1–2 days per week (considered rarely handled) versus ≥3 days per week (considered frequently handled) during pregnancy. Another study reported the exposure of each participant was assessed by questionnaire of the head nurse of the hospital on behalf of the study participants, which may lead to high potential for recall bias (Hemminki et al. 1985). Finally, McDonald et al. (1988b) exposure was assessed by interviewer-led questionnaire to doctors and nurses regarding what chemicals (including antineoplastic agents) they were exposed to while at work in the first four weeks past their first missed menstrual period; thus, the study assessed only whether they were exposed or not exposed to cancer chemotherapy agents with no details about frequency of use or personal protective equipment use.

Regarding outcome assessment, most studies included in the evidence synthesis were rated definitely low risk of bias or probably low risk of bias because they assessed outcome by identifying cases from hospital discharge records or collected data from questionnaires from which the participants were not aware of the connection between outcome and exposure. For example, Fransman et al. (2007c) and Peelen et al. (1999) conducted their self-reported questionnaire of oncology nurses in the Netherlands as a study of reproductive outcomes in nurses. The interviewer-led questionnaire by Stucker et al. (1990) presented the purpose of the study as an assessment of reproductive characteristics in hospital personnel. Similarly, exposure was not likely to influence the outcome assessment from the Nurses' Health Study II as it is a well-established cohort study, which collects data on all types of lifestyle, exposure and health data (Lawson et al. 2012). While recall error can be a limitation of questionnaires assessing health outcomes, women have accurate recall of pregnancy outcomes (Axelsson 1990; Joffe et al. 1993), and nurses have accurate recall of health data (Colditz et al. 1986; Colditz et al. 1987). Thus, even when participants were advised of the purpose of the study as in three studies reporting on spontaneous abortion (McDonald et al. 1988b; Valanis et al. 1999; Walusiak et al. 2003), it would not likely influence their recall of spontaneous abortion or other pregnancy outcomes. Two studies were rated as probably high risk of bias due to a lack of definitions for early and late spontaneous abortions (Medková 1991a) or abortions [presumed to be spontaneous abortions] (Elshamy et al. 2010).

Confidence Ratings and Level-of-evidence Conclusions

The initial rating of moderate confidence in the body of evidence for spontaneous abortion was not downgraded or upgraded for any factor (Figure 5). The confidence rating was based on seven

studies with the lowest risk of bias (defined as none or no more than one probably high risk-of-bias rating for one of three key questions of confounding, exposure characterization, and outcome assessment) and the most highly exposed personnel (Fransman et al. 2007c; Lawson et al. 2012; Peelen et al. 1999; Selevan et al. 1985; Stücker et al. 1990; Valanis et al. 1999; Zhang et al. 2016). The remaining studies had higher risk of bias and/or provided less detail to determine level of drug handling; thus, there were no changes in the initial rating of moderate confidence in the body of evidence after considering factors that may increase or decrease confidence (Figure 5). Thus, the final rating was moderate confidence in the body of evidence. The final rating of moderate confidence directly translates into a moderate level of evidence that occupational exposure to cancer chemotherapy agents is associated with spontaneous abortion.

Initial Confidence for Each Body of Evidence (# of Studies)	Factors Decreasing Confidence ("–" if no concern; "↓" if serious concern to downgrade confidence)					Factors Increasing Confidence ("–" if not present; "↑" if sufficient to upgrade confidence)					Final Confidence Rating
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Residual Confounding	Consistency	Other	
Spontaneous Abortion[a,b]											
Initial Moderate (4 cohort [retrospective], 4 case-control[c])	–	–	–	–	–	–	–	–	–	–	Moderate
Initial Low (6 cross-sectional[d])	–	–	–	–	–	–	–	–	–	–	Low

Figure 5. Confidence in the Body of Evidence for Spontaneous Abortions

[a]Spontaneous abortion references: (Fransman et al. 2007c; Hemminki et al. 1985; Lawson et al. 2012; Medková 1991a; Peelen et al. 1999; Schaumburg and Olsen 1990b; Selevan et al. 1985; Skov et al. 1992; Stücker et al. 1990; Taskinen et al. 1994; Taskinen et al. 1986; Valanis et al. 1999; Walusiak et al. 2003; Zhang et al. 2016).
[b]The final confidence in the body of literature was based on seven high-quality studies of highly exposed workers that reported higher case numbers of spontaneous abortions, including: one retrospective cohort (Lawson et al. 2012), one case-control (Selevan et al. 1985), and five cross-sectional studies (Fransman et al. 2007c; Lawson et al. 2012; Peelen et al. 1999; Selevan et al. 1985; Stücker et al. 1990; Valanis et al. 1999; Zhang et al. 2016).
[c]One research group conducted case-control studies of the same population of nurses in France; however, the nurses evaluated in each study were slightly different: Selevan et al. (1985) evaluated nurses with high usage of cancer chemotherapy agents and Hemminki et al. (1985) studied the occupational exposure in nurses from departments of the hospitals with lesser exposure to these agents.
[d]Two cross-sectional studies evaluated the same study population and data set using different exposure characterization methods: job title and work tasks only (Peelen et al. 1999) or estimated dermal exposure based on job title, work tasks and measured glove and skin contamination (Fransman et al. 2007c).

Genetic Toxicity: DNA Damage

Genetic toxicity assays have been used to evaluate whether occupational exposure to cancer chemotherapy agents results in chromosomal or DNA damage. These types of assays are often used in surveillance programs as biomarkers of exposure (i.e., to determine if occupational exposure to the chemical(s) of interest has occurred) (Kirsch-Volders et al. 2011; Mateuca et al. 2006). Nearly all of the classes of cancer chemotherapy agents are known to induce genetic toxicity [reviewed in Suspiro and Prista (2011) and Alam et al. (2011)]. NTP evaluated the

effects of occupational exposure to cancer chemotherapy agents on three types of genetic toxicity assays in this review: induction of structural CA, MN, and DNA damage measured by the alkaline comet assay. All three of these assays have standardized testing protocols validated by the OECD, and are used to evaluate genetic toxicity in both epidemiological studies and laboratory animal toxicity testing of environmental and occupational exposures (OECD 2016a; 2016b; 2016c). Both CA and MN induction are considered early biomarkers of effect of cancer incidence (Bonassi et al. 2007; Bonassi et al. 2004; Norppa et al. 2006) and are frequently included in support of a carcinogenic agent listing in IARC and NTP's Report on Carcinogens (IARC 1966; 1980; 1981; 1990; 2000; NTP 2016). There is much interest in the comet assay to measure DNA damage as a biomarker of effect in environmental and occupational biomonitoring due to its affordability and relative ease of use (Valverde and Rojas 2009; Zare Sakhvidi et al. 2016); however, its association to cancer has not been established. All three assays rely on cells obtained in samples of peripheral blood.

The NTP evaluation identified 66 studies of 53 unique populations reporting structural CA, MN induction, and/or DNA damage measured by the comet assay (Table F-1). The available epidemiological studies in the body of evidence that evaluated the association between occupational exposure to cancer chemotherapy and the three DNA damage assays included: one prospective cohort study of pharmacists (Roth et al. 1994), one longitudinal cohort study of nurses (Mader et al. 2009), and 64 cross-sectional studies of medical personnel (e.g., nurses, physicians, pharmacists, pharmacy technicians) as well as chemists, laboratory assistants, and production or manufacturing workers). Most of the studies evaluated nursing or pharmacy personnel, while drug production, manufacturing employees, chemists, and laboratory assistants were the least studied (only four studies). The studies varied greatly in size (from 12 to 594 subjects), and length of time in job position (1 month to 30 years). The studies originated from 27 different countries, mainly in Europe (n = 42); there were three studies from the United States (all on the same study population) and one study from Canada.

Overall Summary of Genetic Toxicity Evidence

Summary: Based on the available studies, there is a *moderate confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with genetic toxicity. A clear majority of studies reported significant effects of structural CA (22 of 29 studies measuring either percentage of cells with CA and number of CA per 100 cells scored), MN induction (24 of 36 studies measuring either number of micronucleated cells or number of MN per 1,000 cells scored) or DNA damage by comet assay (18 of 21 studies reporting on either percentage of tail DNA, tail length, tail moment and DNA damage (Table F-1). Of the 18 studies that reported on measurements of more than one of the three genetic toxicity assays, 16 reported consistent effects. The initial rating of moderate confidence in the body of evidence for each genetic toxicity assay was not downgraded or upgraded for various factors (Figure 6, Figure 7, and Figure 8). Therefore, the final rating of moderate confidence in the body of evidence directly translates into a rating of a *moderate level of evidence* that occupational exposure to cancer chemotherapy agents is associated with genetic toxicity as measured by structural CA, MN induction, and DNA damage measured by comet assay.

Overall Risk-of-bias Assessment of Genetic Toxicity Evidence

Risk-of-bias ratings of individual genetic toxicity studies are available in Figure D-4 and Figure D-5. A general discussion of the common issues for this dataset on the key risk-of-bias

questions (confounding, exposure characterization, and outcome assessment) is included below. Additional detailed discussion of specific risk-of-bias issues that impact the bodies of evidence for individual measures (i.e., structural CA, MN induction, and DNA damage measured by comet assay) are presented in the following sections.

Risk-of-bias assessment of potential confounders included age, sex, smoking, and co-exposure to other known or suspected genetic toxicants (e.g., anesthetic gases, ionizing radiation, and organic solvents). Most studies (73%) measuring CA, MN induction or DNA damage measured by comet assay controlled for these potential confounders resulting in definitely low or probably low risk of bias. Among the remaining 27% of studies, 14 studies (21%) were identified as probably high risk of bias due to lack of reporting on one or more confounders and modifiers, or the authors did not statistically analyze whether the confounders or modifiers were significantly different between the exposure groups (Figure D-4 and Figure D-5). Six percent of studies (four studies) were rated as definitely high risk of bias for lack of adjustment of confounding or modifying variables, including age, sex, smoking status (Cooke et al. 1991; Ensslin et al. 1997; Kašuba et al. 1999; Kopjar and Garaj-Vrhovac 2001), or genetic toxicant co-exposures [e.g., ionizing radiation (Kašuba et al. 1999)].

Risk-of-bias assessment of the exposure characterization assessed the consistency and reliability of the exposure measures regarding the use of established test methods and whether exposure was assessed in a relevant time-window for development of the outcome. Most of the studies assessing genetic toxicity as probably low risk of bias for exposure characterization because they reported data on work tasks (e.g., preparing drugs, administering drugs, or cleaning up patient excreta) and drug handling (e.g., drug types, frequency of handling, doses, duration of exposure); the data were usually collected by self-reported or interviewer-led questionnaire. Data on work practices, safety equipment availability, and use of personal protective equipment also supported a rating of probably low risk of bias. Three studies characterized exposure using a daily diary in which exposed subjects recorded their work activities and usual events (e.g., accidents), which improved the exposure characterization by allowing for an analysis of number of drug-handling events, handling events for the drugs that were measured, lifetime handling of antineoplastic drugs, job classification, and class of drugs (alkylating, non-alkylating) (Connor et al. 2010) or an incidence rate ratio of CA per the frequency of drug-handling events (based on a daily diary of exposure) (McDiarmid et al. 2010; McDiarmid et al. 2014); these studies were also rated probably low risk of bias because frequency of drug-handling events is considered an acceptable approach for exposure assessment of mixed exposures such as cancer chemotherapy agents (Albertini et al. 2000; Nieuwenhuijsen 2003). Two studies were rated probably high risk of bias because they only reported on the job title of the exposed population, but did not provide any further details characterizing the exposure (Garaj-Vrhovac and Kopjar 1998; Mušák et al. 2006).

Risk-of-bias evaluation of the outcome assessment considered the use of established methods, whether the outcome had been assessed consistently across all groups and whether the outcome assessors had been blinded to the study groups or exposure levels prior to assessing the outcomes. Most of the studies measuring DNA damage as CA, MN induction or DNA damage measured by comet assay were rated probably or definitely low risk of bias for outcome assessment. All studies used standard methods for assessing CA, MN induction, and DNA damage by comet assay (see protocol in Appendix I). Most studies reported the OECD recommended measurements or common measurements for each of these genetic toxicity assays and assessed outcomes consistently across all groups. Most studies also reported blinding of the

outcome assessor. In addition, the outcome assessment was automated for some studies reporting on MN induction and comet assay; thus, for these studies, there was less of a concern if there was a lack of reporting on whether blinding occurred. Eight studies were also rated probably high risk of bias for lack of details regarding assessment methods for MN (Ensslin et al. 1997) or sample processing for comet assay (Cornetta et al. 2008; Deng et al. 2006; Deng et al. 2005; Mader et al. 2009; Ündeğer et al. 1999; Yang et al. 2002a; Yin et al. 2010). Only one study (Ursini et al. 2006) received a ranking of definitely high risk of bias for outcome assessment for maintaining blood samples at room temperature until processing; this action may have biased the results toward the null because DNA repair enzymes are known to begin working within 30 minutes of sample collection unless they are chilled. The authors reported no difference in tail moment between the exposed and unexposed groups (Ursini et al. 2006).

Overall Confidence Ratings and Level-of-evidence Conclusions for Genetic Toxicity

Across the three measures of genetic toxicity (increased structural CA, MN induction, and DNA damage measured by the comet assay), there is *moderate confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with genetic toxicity. The body of evidence across a total of 66 studies presents a consistent pattern of findings of higher levels of CA, MN induction, and DNA damage measured by comet assay in occupationally exposed subjects. Furthermore, studies that evaluated more than one genetic toxicity assay (e.g., CA, MN, or DNA damage measured by comet assay) were largely consistent in the direction of their results: 14 of 18 studies reported significantly higher levels of DNA damage across multiple assays and two studies reported no difference between exposure groups; two studies reported inconsistent effects across more than one genetic toxicity assay. A potential upgrade in the overall confidence for genetic toxicity was considered based on consistent evidence across multiple effect measures. However, no change was made in the confidence rating because these three indications of genetic toxicity are closely related measures of an effect without support for an independent mechanism. Two of the genetic toxicity assays (CA and MN induction) had the same mechanism of action, and comet assay is a biomarker of effect, which has not yet been associated with any downstream health outcome. The final rating of moderate confidence directly translates into a *moderate level of evidence* that occupational exposure to cancer chemotherapy agents is associated with genetic toxicity.

Structural Chromosomal Aberrations

The NTP evaluation identified 29 studies of 26 unique populations reporting structural CA (i.e., breaks, deletions, duplications, translocations, inversions, and rings) resulting from direct DNA breakage, replication on a damaged DNA template, inhibition of DNA synthesis and other mechanisms (e.g., inhibition of topoisomerase II enzymes) in peripheral blood lymphocytes arrested at metaphase. The evaluation focused the level-of-evidence conclusions on studies reporting on the two measurements of CA: percent of cells with CA per 100 cells scored (excluding chromosomal gaps), which are referred to here as percentage of cells with CA (excluding gaps) (Figure D-6), and the number of CA per 100 cells scored (excluding gaps) (Figure D-7). The percentage of cells with CA (excluding gaps) is a measure of the frequency of cells that exhibited any type of CA, and is a recommended measurement for CA by the OECD (2016a). The number of CA per 100 cells (excluding gaps) scored is a less precise, but commonly reported, measure than percentage of cells with CA (without gaps) because some cells have more than one CA; however, it is included because it is commonly reported in the published literature. Chromosomal and chromatid gaps (also called gaps or achromatic lesions)

are lightly stained bands in the chromosomes and chromatids and are not accepted as a measure of damage because they occur naturally in apparently unexposed populations, their identification is highly subjective, and the implication of gaps is not known. The OECD Test Guideline 473 for the in vitro mammalian CA test recommends to count the gaps, but not to include them in the measure of total CA (OECD 2016a). NTP also considered studies that measured aberrations in chromosome 5, 7, or 11 to support the CA data because a higher number of aberrations in these three chromosomes have been reported in patients following administration of cancer chemotherapy agents for treatment of cancer [reviewed in McDiarmid et al. (2010)].

Summary

Based on the available studies, there is a *moderate confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with increased structural CA. A clear majority of studies reporting on percentage of cells with CA and number of aberrations per 100 cells scored reported significantly higher effects in individuals with occupational exposure to chemotherapy agents (Table F-1). Eleven of 14 studies reporting on percentage of cells with CA and 11 of 17 studies reporting on the number of aberrations per 100 cells scored reported significantly higher effects on exposed subjects compared to control subjects. Four studies evaluated both CA measurements and reported similar results for each endpoint (El-Ebiary et al. 2013; Jakab et al. 2001; Kopjar et al. 2009; Sorsa et al. 1988). Similarly, a preliminary study by Mušák et al. (2006) reported a non-significant (p = 0.07) number of CA in healthcare workers in Slovakia, which was corroborated by a larger study of the same population that reported significantly higher percentage of cells with CA compared to unexposed subjects (Mušák et al. 2013). Furthermore, two studies evaluating CA in chromosomes 5, 7, and 11 also support higher number of CA for individuals with occupational chemotherapy exposure. Specifically, samples from the same population of nursing and pharmacy personnel reported a significantly higher number of CA on chromosome 5 following occupational exposure to alkylating (McDiarmid et al. 2010) as well as non-alkylating agents compared to unexposed subjects (McDiarmid et al. 2014). The initial rating of moderate confidence in the body of evidence was not downgraded or upgraded for various factors (Figure 6). Therefore, the final rating of moderate confidence in the body of evidence directly translates into a rating of a *moderate level of evidence* that occupational exposure to cancer chemotherapy agents is associated with structural CA.

Overview

The NTP evaluation identified 29 studies of 26 unique populations reporting structural CA (% of cells with CA, number of CA/100 cells scored, or incidence rate ratio of CA) resulting from direct DNA breakage, replication on a damaged DNA template, inhibition of DNA synthesis and other mechanisms (e.g., inhibition of topoisomerase II enzymes) in peripheral blood lymphocytes arrested at metaphase. The available epidemiological studies in the body of evidence that evaluated the association between occupational exposure to cancer chemotherapy and CA included: 28 cross-sectional studies of medical personnel as well as chemists, laboratory assistants, and production or manufacturing workers, and one prospective cohort study of pharmacists (Table F-1). The majority of the studies evaluated nurses or pharmacy personnel, while drug production or manufacturing employees were the subject of only three studies. The studies varied greatly in continent where the study was conducted (Europe = 20 studies, Middle East = five studies, North America = three studies, and Asia = one study), size (from 12 to 594 subjects), and length of time in job position (>6 months to 25 years). Some of the studies also

measured other DNA damage endpoints, such as MN induction or comet assay (see following sections for discussion of these other health outcomes).

Evidence Synthesis

The evidence synthesis for percentage of cells with CA (excluding gaps) was based on 14 studies (Table F-1), including one prospective cohort study of pharmacists (Roth et al. 1994) and 13 cross-sectional studies evaluating nurses, pharmacists, physicians, and other health workers as well as studies evaluating employees of drug production and manufacturing facilities (Anwar et al. 1994; Burgaz et al. 2002; El-Ebiary et al. 2013; Hola et al. 1988; Jakab et al. 2001; Kopjar et al. 2009; Medková 1990; Mušák et al. 2013; Nikula et al. 1984; Pohlová et al. 1986; Rubeš et al. 1998; Sessink et al. 1994a; Sorsa et al. 1988). The results show a consistent increase in CA as measured by an increase in the percentage of cells with CA in occupationally exposed subjects. Eleven of the 14 studies reported significantly higher percentage of cells with CA in exposed subjects relative to controls (Figure D-6). Of the three studies reporting no difference between exposed and unexposed subjects, a study of exposed nurses in Turkey reported a non-significant higher percentage of cells with CA compared to unexposed, and exposure was a significant factor in the analysis of variance (Burgaz et al. 2002). The remaining two studies attributed the lack of effect on CA to the availability of safety equipment and use of personal protective equipment by the exposed subjects. A single prospective cohort of pharmacists in Finland reported no difference between exposed subjects and controls (Roth et al. 1994); the authors reported that all exposed subjects used personal protective equipment and prepared the drugs in a vertical laminar flow safety cabinet in an isolated negative-pressured laboratory, separate from other work areas. Sorsa et al. (1988) attributed the lack of difference in percentage off cells with CA to improvements in the proper exposure prevention practices; however, the controls in the factory had higher number of CA than controls from outside the factory.

The evidence synthesis for the number of CA per 100 cells scored (excluding gaps) was based on 17 cross-sectional studies of nurses, pharmacists, and physicians handling cytostatic agents as well as workers in production and manufacturing of these agents (Table F-1) (Bouraoui et al. 2011; Cavallo et al. 2005; Cooke et al. 1991; El-Ebiary et al. 2013; Grummt et al. 1993; Jakab et al. 2001; Kopjar et al. 2009; Krepinsky et al. 1990; Mahmoodi et al. 2017; Milković-Kraus and Horvat 1991; Moretti et al. 2015; Mušák et al. 2006; Sorsa et al. 1988; Stücker et al. 1986; Testa et al. 2007; Thulin et al. 1995; Yang et al. 2002b). The results show a consistent increase in CA as measured by the number of CA per 100 cells in occupationally exposed subjects. Eleven of the 17 cross-sectional studies reported that occupational exposure to cancer chemotherapy agents resulted in a significantly higher number of CA per 100 cells scored (Figure D-7). Of the six studies that did not report a significant association for CA, a study of health workers in Slovakia reported that exposed subjects tended (p = 0.07) to have a higher number of CA than controls (Mušák et al. 2006); the authors subsequently published a larger study of the same population that found a significantly higher percentage of cells with ≥1 CA (Mušák et al. 2013). Two studies of drug production workers in Finland (Sorsa et al. 1988) and Sweden (Thulin et al. 1995) reported similar number of CA compared to unexposed workers; the authors stated that employees wore appropriate personal protective equipment and used safety equipment (e.g., personal fresh-air devices, gas-protective suits). Cooke et al. (1991) attributed the lack of difference between exposed pharmacists and nurses and the control subjects in the United Kingdom to the appropriate use of personal protective equipment and safety equipment (i.e., biological safety cabinets), and the fact the exposed nurses were only responsible for

administering, but not preparing, the cancer chemotherapy doses. In a study of nurses in France, Stucker et al. (1986) suggested that the lack of effect on the number of CA may be due to less frequent handling of cancer chemotherapy agents in the pneumology department of this study, relative to studies that examine medical staff working in oncology departments. Finally, Krepinsky et al. (1990) suggested that the variability in the dose and frequency of handling of cancer chemotherapy agents among the exposed nurses in may have contributed to the observation of no difference compared to unexposed nurses.

Further support for an association between occupational exposure to cancer chemotherapy agents and induction of CA was provided by McDiarmid and colleagues, who examined the number of aberrations at chromosomes 5, 7, and 11 in a group of nurses, pharmacists, and pharmacy technicians in three university-based hospital cancer centers in the United States (McDiarmid et al. 2010; McDiarmid et al. 2014). The exposed subjects were asked to maintain a 6-week daily diary of the types and frequency of cancer chemotherapy drugs they handled as well as any unusual events (e.g., accidents). The data were presented as incidence rate ratios (IRR) that described the association between the number of CA predicted by the model at the select drug-handling frequencies compared with the number of CA at zero drug-handling events (controls). Significantly higher IRRs of aberrations were observed in chromosome 5 as the number of handling events increased for either alkylating agents (McDiarmid et al. 2010) or non-alkylating agents (e.g., anthracycline antibiotics, biologics, antimetabolites) (McDiarmid et al. 2014). The IRRs of aberrations at chromosome 7 and 11 were also increased in a dose-related manner for either alkylating agents or non-alkylating agents, but did not reach statistical significance (McDiarmid et al. 2010; McDiarmid et al. 2014).

Risk-of-bias Assessment

Risk of bias was assessed for all 29 included studies reporting on percentage of cells with CA, number of CA per 100 cells scored, (Figure D-8 and Figure D-9) and number of aberrations on chromosome 5, 7, or 11 (data not graphed).

Most studies were rated probably low risk of bias for confounding because they evaluated the key confounders and addressed differences in age, sex, smoking status, and possible co-exposure to other genetic toxicants (e.g., ionizing radiation). One study was rated definitely high risk of bias for confounding because the authors did not adjust for age although they reported that controls were significantly older than exposed pharmacists, which could bias the results toward the null (Cooke et al. 1991); the authors reported no difference in number of CA/100 cells. Nine studies receiving a rating of probably high risk of bias for confounding due to either lack of adjustment for confounding variables or insufficient information on how confounders were assessed (Hola et al. 1988; Jakab et al. 2001; Medková 1990; Mušák et al. 2006; Rubeš et al. 1998; Sessink et al. 1994a; Stücker et al. 1986; Thulin et al. 1995; Yang et al. 2002b). Lack of adjustment for confounders did not appear to influence the outcome for one study; thus, it was rated as probably low risk of bias for confounding (Nikula et al. 1984). Specifically, a study of nurses from Finland reported that 6 of 16 unexposed subjects were exposed to other chemicals (e.g., organic solvents) while exposed subjects were not similarly co-exposed (Nikula et al. 1984); the co-exposure did not appear to influence the results toward the null as the exposed subjects had a significantly greater percentage of cells with CA.

Most studies were rated probably low risk of bias for exposure characterization because exposure was based on job title in combination with work tasks (e.g., preparation and/or administration of

cancer chemotherapy agents, handling patient excreta) and drug handling (e.g., frequency of drug handling, doses administered). Many studies also collected and reported on the level of safety protection available (e.g., biological safety cabinet, isolated room for drug preparation) and personal protective equipment used (e.g., gloves, masks, aprons). Two studies were ranked probably low risk of bias for exposure characterization because the authors further characterized exposure by requiring exposed participants to maintain a 6-week daily diary of the agents used, the frequency of handling each agent as well as any usual events (e.g., accidents) (McDiarmid et al. 2010; McDiarmid et al. 2014), which allowed the authors to analyze the data number of handling events. Biomonitoring further supported a rating of probably low risk of bias because a majority of the exposed subjects (eight of 12 exposed drug manufacturing workers) had levels of cyclophosphamide in their urine above the LOD, while urine samples from all control subjects were below the LOD (Sessink et al. 1994a). Three other studies reporting on biomonitoring of urine samples did not provide further support for a rating of probably low risk of bias rating because two studies reported very few of the urine samples had levels of the agent(s) above the LOD (Cavallo et al. 2005; Moretti et al. 2015), and another study detected cyclophosphamide in the urine samples 12 of the 12 exposed subjects tested, but did not test samples from unexposed subjects (Burgaz et al. 2002).

For outcome assessment, all studies included in the evidence synthesis followed a standard protocol and most studies included blinding of outcome assessors to the exposure status of the participants resulting in a rating of probably low risk of bias. Five studies did not report whether there was blinding for outcome assessment [two studies measuring percentage of cells with CA (Hola et al. 1988; Rubeš et al. 1998) and three studies reporting on the number of CA/100 cells (Krepinsky et al. 1990; Stücker et al. 1986; Yang et al. 2002b)], which resulted in a rating of probably high risk of bias for outcome assessment.

Confidence Ratings and Level-of-evidence Conclusions

The initial rating of moderate confidence in the body of evidence for CA, including percentage of cells with CA and number of CA per 100 cells scored, was not downgraded or upgraded for various factors (Figure 6). The final rating of moderate confidence in the body of evidence did not change when NTP excluded the study with definitely high risk of bias for confounding (Cooke et al. 1991).

Initial Confidence for Each Body of Evidence[a] (# of Studies)	Factors Decreasing Confidence ("-" if no concern; "↓" if serious concern to downgrade confidence)					Factors Increasing Confidence ("-" if not present; "↑" if sufficient to upgrade confidence)					Final Confidence Rating
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Residual Confounding	Consistency	Other	
% Cells with CA[b]											
Initial Moderate (1 cohort [prospective], 13 cross-sectional)	–	–	–	–	–	–	–	–	–	–	Moderate
Number of CA/100 cells scored[c]											
Initial Moderate (1 cohort [prospective], 12 cross-sectional)	–	–	–	–	–	–	–	–	–	–	Moderate
Number of aberrations on chromosome 5, 7 or 11/100 cells scored[d]											
Initial Moderate (2 cross-sectional)	–	–	–	–	–	–	–	–	–	–	Moderate

Figure 6. Confidence in the Body of Evidence for Structural Chromosomal Aberrations (Excluding Gaps)

[a]Initial confidence of cross-sectional studies of genetic toxicity started as moderate due to the determination that knowledge of exposure status would not influence the results of the CA assays.
[b]% cells with CA references: (Anwar et al. 1994; Burgaz et al. 2002; El-Ebiary et al. 2013; Hola et al. 1988; Jakab et al. 2001; Kopjar et al. 2009; Medková 1990; Mušák et al. 2013; Nikula et al. 1984; Pohlová et al. 1986; Roth et al. 1994; Rubeš et al. 1998; Sessink et al. 1994a; Sorsa et al. 1988).
[c]Number of CA references: (Bouraoui et al. 2011; Cavallo et al. 2005; Cooke et al. 1991; El-Ebiary et al. 2013; Grummt et al. 1993; Jakab et al. 2001; Kopjar et al. 2009; Krepinsky et al. 1990; Mahmoodi et al. 2017; Milković-Kraus and Horvat 1991; Moretti et al. 2015; Mušák et al. 2006; Sorsa et al. 1988; Stücker et al. 1986; Testa et al. 2007; Thulin et al. 1995; Yang et al. 2002b).
[d]Number of aberrations on chromosome 5, 7, or 11 references (presented as incidence rate ratios): (McDiarmid et al. 2010; McDiarmid et al. 2014).

Micronucleus Induction

The NTP evaluation identified 35 studies of 32 unique populations reporting MN induction and focused the level-of-evidence conclusions on studies reporting on the number of micronucleated cells per 1,000 cells scored (also called number of cells with micronuclei (MN)) and the number of MN per 1,000 cells scored. This assay detects MN in the cytoplasm of interphase cells, which may arise from acentric chromosome fragments or whole chromosomes that cannot migrate to the poles during cell division. Micronucleus induction signify structural or numerical chromosomal alterations that have been transmitted to daughter cells. The number of micronucleated cells per 1,000 cells scored is the most precise measure and is recommended by the 2014 OECD Testing Guidelines for the In Vitro Micronucleus Test (OECD 2016b). NTP also evaluated the number of MN per 1,000 cells scored because it is a frequently reported endpoint; however, this measure is considered slightly less reliable because a cell can have more than one micronucleus. Micronuclei induction was evaluated in two cells types: binucleated lymphocytes and buccal cells. The NTP evaluation used the abbreviation MN for both the singular (micronucleus) and plural forms (micronuclei) of the word, as applicable.

Summary

Based on the available studies, there is *moderate confidence in the body of evidence* that occupational exposure to cancer chemotherapy is associated with greater MN induction. Eleven of 13 studies measuring the number of cells with MN and 16 of 26 studies reporting on the number of MN per 1,000 cells scored reported significantly greater effects in exposed subjects compared to unexposed subjects (Table F-1). Four studies evaluated both measurements of MN and reported similar results for each endpoint (Deng et al. 2006; Deng et al. 2005; Kašuba et al. 1999; Kopjar et al. 2009). In addition, three sets of studies—(Boughattas et al. 2010; Bouraoui et al. 2011), (Garaj-Vrhovac and Kopjar 1998; Kašuba et al. 1999), and (Sorsa et al. 1988; Yager et al. 1988)—evaluated the three similar or overlapping populations and reported consistent results with the exception of Yager et al. (1988), which included an extra group of oncology nurses with a high number of MN compared to Sorsa et al. (1988). The initial rating of moderate confidence in the body of evidence was not downgraded or upgraded for various factors (Figure 7). The final confidence rating in the body of evidence directly translates into a rating of *moderate level of evidence* that occupational exposure to cancer chemotherapy agents is associated with MN induction.

Overview

The available epidemiological studies in the body of evidence that evaluated the association between occupational exposure to cancer chemotherapy and MN induction included 34 cross-sectional studies of medical personnel as well as chemists, laboratory assistants, and production or manufacturing workers; and one prospective cohort study of pharmacists (Table F-1). Most studies evaluated nurses, while drug production or manufacturing employees were the least studied (four studies). The studies varied greatly in country of origin (Europe = 20, Middle East = 5, Asia = 4, South America = 3, and North and Central America = 2), size (from n = 20 to 156), and length of time in job position (1 month to 30 years). Some of the studies also measured other DNA damage endpoints, such as CA or comet assay (see other sections of Results and Evidence Synthesis for discussion of these other health outcomes).

Evidence Synthesis

The evidence synthesis for the number of cells with MN per 1,000 cells scored was based on 13 studies (Table F-1): one prospective cohort study of pharmacists (Roth et al. 1994) and 12 cross-sectional studies evaluating nurses, doctors, pharmacists and production workers (Anwar et al. 1994; Boughattas et al. 2010; Buono-Michel et al. 2000; Deng et al. 2006; Deng et al. 2005; Kašuba et al. 1999; Kopjar et al. 2009; Machado-Santelli et al. 1994; Maluf and Erdtmann 2000b; Rodríguez-Montero et al. 2016; Rombaldi et al. 2009; Yang et al. 2002b). The results show a consistently higher number of cells with MN per 1,000 cells scored in exposed subjects relative to controls (Figure D-10). Eleven of the 13 studies reported a significantly higher number of cells with MN in exposed subjects relative to controls. Of the two studies reporting negative a lack of effect on MN, a study of nurses and pharmacists in Brazil reported no difference in the number of cells with MN compared to unexposed subjects following an adjustment in the work schedule to limit exposure and the hiring of additional employees (Maluf and Erdtmann 2000b); four years prior, this population reported a significantly higher number of cells with MN in exposed subjects than controls. A prospective cohort of pharmacists in Finland reported no difference between exposed subjects and controls (Roth et al. 1994), which the authors attribute to the use of personal protective equipment and the availability of a vertical

laminar flow safety cabinet for drug preparation in an isolated negative-pressured laboratory, separate from other work areas.

The evidence synthesis for the number of MN/1,000 cells scored was based on 26 cross-sectional studies evaluating 23 unique populations of nurses, doctors, pharmacists and drug production workers (Table F-1) (Bolognesi et al. 2005; Bouraoui et al. 2011; Burgaz et al. 1999; Cavallo et al. 2005; Cornetta et al. 2008; Deng et al. 2006; Deng et al. 2005; El-Ebiary et al. 2013; Ensslin et al. 1997; Garaj-Vrhovac and Kopjar 1998; Harris et al. 1992; Hessel et al. 2001; Kašuba et al. 1999; Kevekordes et al. 1998; Kopjar et al. 2009; Ladeira et al. 2014; Laffon et al. 2005; Mahmoodi et al. 2017; Moretti et al. 2015; Moretti et al. 2013; Mrđanović et al. 2012; Pilger et al. 2000; Rekhadevi et al. 2007; Sorsa et al. 1988; Thiringer et al. 1991; Yager et al. 1988). The results show a consistent increase in MN induction as measured by an increase in the number of MN/1,000 cells scored in exposed subjects relative to control subjects (Figure D-11 and Figure D-12). Sixteen of 26 studies reported a significantly higher number of MN/1,000 cells scored in exposed subjects compared to controls. Of the nine studies reporting no effect of exposure, a study of exposed medical workers including nurses, pharmacy personnel, one physician, and one orderly in Germany did not observe any difference in the number of MN compared to unexposed office workers (Hessel et al. 2001); frequency of drug handling of the exposed subjects was not reported. Moretti et al. (2013) reported no significant differences in the number of MN between exposed workers in a hospital in Italy responsible for preparation, transport, administration, and disposal of cancer chemotherapy agents unexposed blood donors, but did report a significantly higher level of DNA damage measured by tail intensity in exposed subjects. Eight studies reported a lack of effect of occupational exposure on the number of MN in nursing and pharmacy personnel that used personal protective equipment and/or prepared drugs in vertical laminar flow safety cabinets (Bolognesi et al. 2005; Cavallo et al. 2005; Ensslin et al. 1997; Harris et al. 1992; Laffon et al. 2005; Moretti et al. 2013; Pilger et al. 2000; Thiringer et al. 1991). Harris et al. (1992) also observed that nurses with low and moderate exposure that used gloves <100% of the time had significantly higher number of MN compared to nurses using gloves 100% of the time. Finally, one study of drug production and manufacturing workers, and associated laboratory technicians in Finland reported a non-significant higher number of MN compared to unexposed workers following exposure safety protection improvements (Sorsa et al. 1988). Of note, two studies reported contrasting results for number of MN from studies overlapping in the population under study. While Sorsa et al. (1988) reported no effect on the number of MN, Yager et al. (1988) tested the same population and included an extra group of exposed workers in their study (oncology nurses) who had a higher number of MN than the other exposed groups; the authors combined the data for all the exposed workers and observed a significantly higher number of MN when analyzed by an ANOVA of the log-transformed data (Yager et al. 1988).

Risk-of-bias Assessment

Risk-of-bias assessment was conducted on all studies included in the evidence synthesis for MN induction presented number of cells with MN per 1,000 cells scored and number of MN per 1,000 cells scored (Figure D-13 and Figure D-14). Similar to the body of evidence for CA, most studies on MN induction were rated probably low risk of bias for confounding (e.g., appropriate confounders were considered and adjusted when necessary) and outcome assessment (e.g., the assessors were generally blinded to treatment), as well as probably high risk of bias for exposure

characterization due to exposure classification by job position without confirmation of exposure from biomonitoring measurements.

Most studies were rated as probably low risk of bias for confounding. Two studies were rated as definitely high risk of bias for confounding (Ensslin et al. 1997; Kašuba et al. 1999). In a study reporting no difference in the number of MN per 1,000 cells scored between exposed pharmacists (n = 13 subjects) and controls (n = 13 subjects) in Germany, Ensslin et al. (1997) did not adjust for reported differences in sex and smoking status between exposed and control subjects (women: controls = 11 of 13 and exposed = 8 of 13; smoking: controls = 4 of 13 and exposed = 1 of 13), which could have biased the results toward the null. Kašuba et al. (1999) did not adjust for a higher number of exposed subjects co-exposed to ionizing radiation (7 of 20) compared to controls exposed (1 of 16), which could have biased the results away from the null; this study observed a significantly higher number of MN per 1,000 cells scored in exposed nurses relative to control subjects. Four studies did not report confounding variables or the methods used to collect data on confounding (Deng et al. 2006; Garaj-Vrhovac and Kopjar 1998; Harris et al. 1992; Yager et al. 1988; Yang et al. 2002b). One study was rated probably low risk of bias even though the authors did not adjust for significant covariates. Hessel et al. (2001) did not directly adjust the results for a significantly greater number of men in the controls versus the exposed pharmacy personnel in Germany, which could have biased the results away from the null: however, there was no difference in the number of MN/1,000 cells scored between exposure groups.

Similar to studies assessing CA, most studies were rated probably low risk of bias for exposure characterization because exposure was based on job title in combination with work tasks (e.g., preparation and/or administration of cancer chemotherapy agents, handling patient excreta) and drug handling (e.g., frequency of drug handling, doses administered). Many studies also collected and reported on the level of safety protection available (e.g., biological safety cabinet, isolated room for drug preparation) and personal protective equipment used (e.g., gloves, masks, aprons). Urine biomonitoring results did not provide further support for a rating of probably low risk of bias for five studies testing urine samples from both exposed and unexposed subjects (Bolognesi et al. 2005; Cavallo et al. 2005; Ensslin et al. 1997; Moretti et al. 2015; Pilger et al. 2000) as none of the studies reported positive samples for a majority of the exposed subjects. Another MN study that measured cyclophosphamide in urine of exposed and unexposed occupationally exposed hospital, pharmacy, and medical personnel reported no correlation between a positive urine sample ≥ LOD versus urine samples that measured < LOD (Hessel et al. 2001). Two studies reported positive biomonitoring results in a majority of exposed subjects, but did not test unexposed subjects (Burgaz et al. 1999; Rekhadevi et al. 2007); specifically, cyclophosphamide was above the LOD in urine samples of 19 of 25 (Burgaz et al. 1999) and 42 of 52 exposed nurses (Rekhadevi et al. 2007).

Regarding risk of bias for outcome assessment, 11 studies did not report blinding and the authors did not respond to NTP's request for information (Bolognesi et al. 2005; Boughattas et al. 2010; Buono-Michel et al. 2000; Cornetta et al. 2008; Deng et al. 2006; Deng et al. 2005; Ensslin et al. 1997; Garaj-Vrhovac and Kopjar 1998; Kašuba et al. 1999; Yager et al. 1988; Yang et al. 2002b).

Confidence Ratings and Level-of-evidence Conclusions

The initial rating of moderate confidence in the body of evidence for MN, including number of cells with MN/1,000 cells scored and number of MN/1,000 cells scored, was not downgraded or upgraded for various factors (Figure 7). The final rating of moderate confidence in the body of evidence did not change when NTP excluded the studies with definitely high risk of bias for confounding.

Initial Confidence for Each Body of Evidence[a] (# of studies)	Factors Decreasing Confidence ("–" if no concern; "↓" if serious concern to downgrade confidence)					Factors Increasing Confidence ("–" if not present; "↑" if sufficient to upgrade confidence)					Final Confidence Rating
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Residual Confounding	Consistency	Other	
Number of cells with micronuclei (MN)/1,000 cells scored[b,c]											
Initial Moderate (1 cohort [prospective], 12 cross-sectional)	–	–	–	–	–	–	–	–	–	–	**Moderate**
Number of MN/1,000 cells scored[d,e]											
Initial Moderate (26 cross-sectional)	–	–	–	–	–	–	–	–	–	–	**Moderate**

Figure 7. Confidence in the Body of Evidence for Micronucleus Induction

[a]Initial confidence of cross-sectional studies of genetic toxicity started as moderate due to the determination that knowledge of exposure status would not influence the results of the MN assays.
[b]Number of cells with MN/1,000 binucleated lymphocytes scored references: (Anwar et al. 1994; Boughattas et al. 2010; Buono-Michel et al. 2000; Deng et al. 2006; Deng et al. 2005; Kašuba et al. 1999; Kopjar et al. 2009; Maluf and Erdtmann 2000b; Rombaldi et al. 2009; Roth et al. 1994; Yang et al. 2002b).
[c]Number of cells with MN/1,000 buccal cells scored references: (Machado-Santelli et al. 1994; Rodríguez-Montero et al. 2016).
[d]Number of MN/1,000 binucleated lymphocytes scored references: (Bolognesi et al. 2005; Bouraoui et al. 2011; Burgaz et al. 1999; Cavallo et al. 2005; Cornetta et al. 2008; Deng et al. 2006; Deng et al. 2005; El-Ebiary et al. 2013; Ensslin et al. 1997; Garaj-Vrhovac and Kopjar 1998; Harris et al. 1992; Hessel et al. 2001; Kašuba et al. 1999; Kevekordes et al. 1998; Kopjar et al. 2009; Ladeira et al. 2014; Laffon et al. 2005; Mahmoodi et al. 2017; Moretti et al. 2015; Moretti et al. 2013; Mrđanović et al. 2012; Pilger et al. 2000; Rekhadevi et al. 2007; Sorsa et al. 1988; Thiringer et al. 1991; Yager et al. 1988).
[e]Number of MN/1,000 buccal cells scored references: (Bolognesi et al. 2005; Burgaz et al. 1999; Cavallo et al. 2005; Rekhadevi et al. 2007).

DNA Damage Measured by the Comet Assay

The NTP evaluation identified 21 studies of 18 unique populations reporting DNA damage measured by the comet assay. The level-of-evidence conclusions were based on studies reporting the following four measurements: the percent of tail DNA (also called % tail intensity), tail length (μm), tail moment, and DNA damage index. The percent of tail DNA corresponds to the fraction of DNA intensity of the comet tail relative to total intensity (head plus tail); this comet assay measurement is recommended for use by the OECD Testing Guideline for In Vivo Mammalian Comet Assay (OECD 2016c). Tail length is the maximum length of DNA migration and is measured either from the center of the head or the leading edge of the head to the tip of the tail. Tail moment may be measured as extent tail moment (% tail DNA multiplied by tail length) or Olive tail moment (% tail DNA multiplied by tail moment length; tail moment is calculated as

length from the center of the head to the center of the tail). Tail length and tail moment are considered acceptable measurements if an image analysis software system is used to score slides. However, tail moment is not a recommended measurement for comet assay due to variability in the methods to calculate tail moment (OECD 2016c) and the fact that tail moment has no units attached to it. Another commonly reported measurement of comet assay was a DNA damage index, which was a sum of the cells with DNA damage weighted by the severity of damage; this method is not among the recommended measured by the OECD (2016c). The majority of studies evaluated either lymphocytes or leukocytes. For accurate comet assay results, the OECD guidelines state that samples must be kept ice-cold, or frozen, until processing. Otherwise, enzymes will act to repair any damaged DNA and may cause the test results to be inaccurate.

Summary

Based on the available studies, there is a *moderate confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with increased DNA damage measured by the comet assay. Five of seven studies reporting on percent of tail DNA, 10 of 11 studies reporting on tail length (μm), and five of five studies reporting a DNA damage index reported significantly higher rates of DNA damage compared to unexposed subjects (Table F-1). Only two of seven studies reporting on tail moment reported significantly higher levels of DNA damage in exposed subjects than controls; however, tail moment is not recommended measurement by the OECD due to variability in methods to calculate tail moment (OECD 2016c). Seven studies evaluated two or more tail measurements (Connor et al. 2010; Deng et al. 2006; Deng et al. 2005; Kopjar and Garaj-Vrhovac 2001; Sasaki et al. 2008; Villarini et al. 2011; Yin et al. 2010); however, only three studies reported consistent results between each endpoint (Connor et al. 2010; Kopjar and Garaj-Vrhovac 2001; Yin et al. 2010); tail length and tail moment were the most common endpoint with no difference compared to unexposed subjects. The initial rating of moderate confidence in the body of evidence was not downgraded or upgraded for various factors (Figure 8). The final rating of moderate confidence in the body of evidence directly translates into a rating of *moderate level of evidence* that occupational exposure to cancer chemotherapy agents is associated with DNA damage measured by comet assay.

Overview

The available epidemiological studies in the body of evidence that evaluated the association between occupational exposure to cancer chemotherapy and DNA damage measured by comet assay included one prospective cohort study (Mader et al. 2009) and 20 cross-sectional studies of medical personnel as well as chemists, laboratory assistants, and production or manufacturing workers); and one prospective cohort study of pharmacists (Table F-1). Most the studies evaluated nursing and pharmacy personnel, while drug production or manufacturing employees were the least studied (only two studies). The studies originated from 10 countries: Italy (n = 5), China (n = 4), Brazil (n = 2), Croatia (n = 2), Japan (n = 2), Turkey (n = 2), Austria (n = 1), India (n = 1), Portugal (n = 1), and United States (n = 1). The studies varied in number of participants (from n = 15 to 167), and length of time in job position (2.4 months to 23 years). Some of the studies also measured other DNA damage endpoints, such as CA or MN induction (see other sections of Results and Evidence Synthesis for discussion of these other health outcomes).

Evidence Synthesis

The evidence synthesis for percent of tail DNA was based on the seven cross-sectional studies of nurses, pharmacists, and health workers handling cytostatic agents (Table F-1) (Buschini et al.

2013; Connor et al. 2010; Cornetta et al. 2008; Kopjar and Garaj-Vrhovac 2001; Moretti et al. 2013; Villarini et al. 2011; Yin et al. 2010). The results show a consistently higher rate of DNA damage measured by comet assay as measured by percent of tail DNA in exposed subjects relative to controls (Figure D-15). Five of seven studies reported that exposed subjects had a higher percent of tail DNA than controls (Cornetta et al. 2008; Kopjar and Garaj-Vrhovac 2001; Moretti et al. 2013; Villarini et al. 2011; Yin et al. 2010). The observation of no effect of exposure in a study of nurses in Italy may have been due to the lack of chilling the blood samples upon collection (Buschini et al. 2013); a lack of chilling may allow DNA repair enzymes to correct DNA damage thus biasing toward the null. A study of nurses, pharmacists, and pharmacist technicians in the United States reported a lack of effect of exposure, which the authors attributed to adequate provision of safety equipment and use of personal protective equipment by the exposed personnel (Connor et al. 2010).

The evidence synthesis for tail length was based on 11 cross-sectional studies reporting on nurses, physicians, and production workers handling cancer chemotherapy agents (Table F-1). The results show a consistently higher rate of DNA damage measured by comet assay as measured by tail length in exposed subjects relative to controls (Figure D-16). Ten of 11 studies reported significantly greater tail length (μm) in exposed subjects relative to controls (Deng et al. 2006; Deng et al. 2005; Kopjar and Garaj-Vrhovac 2001; Kopjar et al. 2009; Laffon et al. 2005; Rekhadevi et al. 2007; Sasaki et al. 2008; Yang et al. 2002a; Yin et al. 2010; Yoshida et al. 2006). One study of health workers in Italy reported no difference in tail length between exposed and control subjects (Villarini et al. 2011); however, the authors reported significantly greater percent of tail DNA in exposed subjects than controls from the same study.

The evidence synthesis for tail moment was based on seven cross-sectional studies reporting on nurses, pharmacists, physicians, and production workers working with cancer chemotherapy agents (Table F-1). The results for tail moment showed a less consistent effect of higher DNA damage measured by comet assay as were observed for percent of tail DNA or tail length, with only two studies reporting significantly greater mean tail moment compared to unexposed subjects (Kopjar and Garaj-Vrhovac 2001; Yin et al. 2010) (Figure D-17). Of the five studies reporting a lack of effect on tail moment, Connor et al. (2010) also reported no effect on percent of tail DNA or tail length, which the authors attributed to proper use of personal protective equipment and other safe handling practices. Tail moment appeared to be a less sensitive DNA damage endpoint for three other studies that reported significant effects of occupational exposure on percent of tail DNA (Villarini et al. 2011) or tail length (Deng et al. 2006; Deng et al. 2005). Ursini et al. (2006) reported that exposed nurses had similar tail moment values to unexposed nurses, which they attributed to the use of personal protective equipment and the use of specialized pharmacy to use the drugs, which meant that the nurses were not involved in drug preparation. However, the authors did not chill blood samples prior to processing, which may have contributed to the lack of difference in tail moment between exposed subjects and controls (Ursini et al. 2006). Another study reported no difference in the log-transformed values of mean tail moment between exposed nurses and unexposed nurses (Sasaki et al. 2008).

The evidence synthesis for studies reporting a DNA damage index measured by comet assay was based on one longitudinal cohort study spanning 9 months (Mader et al. 2009) and four cross-sectional studies reporting on nurses and pharmacists (Izdes et al. 2009; Maluf and Erdtmann 2000b; Rombaldi et al. 2009; Ündeğer et al. 1999) (Table F-1). The results for DNA damage measured as DNA damage index by comet assay were consistent with all five studies reporting

significantly higher number of cells with DNA damage than controls (Figure D-18). All five studies evaluated the proportion of DNA fragments in the tail; however, the number of cells evaluated, the number of categories, and the data presentation differed among the studies (see footnote of Figure D-18 for more details).

Risk-of-bias Assessment

Risk-of-bias assessment was conducted on all included studies reporting on DNA damage measured by comet assay including measurements of percent of tail DNA, tail length, tail moment, and DNA damage index (Figure D-19 and Figure D-20). Like the body of evidence for CA and MN, most studies on DNA damage measured by comet assay were rated probably low risk of bias for confounding (e.g., appropriate confounders were considered and adjusted when necessary), exposure assessment, and outcome assessment (e.g., the assessors were generally blinded to treatment).

Regarding confounding, a study reporting significantly higher tail length in exposed physicians and nurses in Croatia versus controls was rated definitely high risk of bias because there was no adjustment for sex even though all exposed subjects were females compared to 50% of control subjects, which could bias the results away from the null (Kopjar and Garaj-Vrhovac 2001). One study was rated probably high risk of bias: a cross-sectional study reporting a greater tail length in exposed nurses in China versus controls did not report the gender of the participants [presumed female] and did not adjust for age differences between controls were younger than exposed subjects (average age 18 years versus 29 years), which could have biased the results away from the null (Yang et al. 2002a).

All studies were rated probably low risk of bias for exposure characterization because exposure was based on job title in combination with work tasks (e.g., preparation and/or administration of cancer chemotherapy agents, handling patient excreta) and drug handling (e.g., frequency of drug handling, doses administered). Many studies also collected and reported on the level of safety protection available (e.g., biological safety cabinet, isolated room for drug preparation) and personal protective equipment used (e.g., gloves, masks, aprons). Urine biomonitoring was conducted in both exposed and unexposed subjects of three studies (Connor et al. 2010; Ursini et al. 2006; Villarini et al. 2011); none of the studies reported positive samples for a majority of the exposed subjects and the biomonitoring was consistent with no difference in comet assay measurements compared to unexposed subjects of these studies (Connor et al. 2010; Ursini et al. 2006). One study conducted biomonitoring in exposed subjects only and reported that cyclophosphamide was above the LOD in urine samples of 42 of 52 exposed nurses (Rekhadevi et al. 2007).

For outcome assessment, two studies reporting no difference in DNA damage measured by comet assay compared to unexposed subjects reported that blood samples were maintained at room temperature after sample collection, which resulted in definitely high risk of bias [tail moment in (Ursini et al. 2006)] or probably high risk of bias [% tail DNA in (Buschini et al. 2013)]; author responded to query for information about methods). For six studies, a rating of probably high risk of bias for blinding for lack of reporting on blinding was upgraded to probably low risk of bias due to use of automated methods for outcome assessment (Connor et al. 2010; Cornetta et al. 2008; Sasaki et al. 2008; Ursini et al. 2006; Yin et al. 2010; Yoshida et al. 2006). Seven studies did not report the methods used for the comet assay or sample processing details and, thus, were assigned probably high risk of bias (Cornetta et al. 2008; Deng

et al. 2006; Deng et al. 2005; Mader et al. 2009; Ündeğer et al. 1999; Yang et al. 2002a; Yin et al. 2010).

Confidence Ratings and Level-of-evidence Conclusions

The initial rating of moderate confidence in the body of evidence for DNA damage measured by the comet assay, including percent tail DNA, tail length and tail moment, and DNA damage index, was not upgraded or downgraded for factors affecting confidence in the body of evidence (Figure 8). The final rating of moderate confidence in the body of evidence did not change when NTP excluded data on tail moment due to known heterogeneity across laboratories in calculating the outcome measurement (OECD 2016c).

Initial Confidence for Each Body of Evidence[a] (# of Studies)	Factors Decreasing Confidence ("−" if no concern; "↓" if serious concern to downgrade confidence)					Factors Increasing Confidence ("−" if not present; "↑" if sufficient to upgrade confidence)					Final Confidence Rating
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose-Response	Residual Confounding	Consistency	Other	
% Tail DNA[b]											
Initial Moderate (7 cross-sectional)	−	−	−	−	−	−	−	−	−	−	Moderate
Tail Length[c]											
Initial Moderate (11 cross-sectional)	−	−	−	−	−	−	−	−	−	−	Moderate
Tail Moment[d]											
Initial Moderate (7 cross-sectional)	−	−	−	−	−	−	−	−	−	−	Moderate
DNA Damage, Manual Scoring and Binning[e]											
Initial Moderate (1 cohort [prospective], 4 cross-sectional)	−	−	−	−	−	−	−	−	−	−	Moderate

Figure 8. Confidence in the Body of Evidence for DNA Damage Measured by the Comet Assay

[a]Initial confidence of cross-sectional studies of genetic toxicity started as moderate due to the determination that knowledge of exposure status would not influence the results of the comet assays.
[b]% tail DNA: (Buschini et al. 2013; Connor et al. 2010; Cornetta et al. 2008; Kopjar and Garaj-Vrhovac 2001; Moretti et al. 2013; Villarini et al. 2011; Yin et al. 2010).
[c]Tail length: (Deng et al. 2006; Deng et al. 2005; Kopjar and Garaj-Vrhovac 2001; Kopjar et al. 2009; Laffon et al. 2005; Rekhadevi et al. 2007; Sasaki et al. 2008; Villarini et al. 2011; Yang et al. 2002a; Yin et al. 2010; Yoshida et al. 2006).
[d]Tail moment: (Connor et al. 2010; Deng et al. 2006; Deng et al. 2005; Kopjar and Garaj-Vrhovac 2001; Sasaki et al. 2008; Ursini et al. 2006; Yin et al. 2010).
[e]DNA damage assessed by manual scoring and binning: (Izdes et al. 2009; Mader et al. 2009; Maluf and Erdtmann 2000b; Rombaldi et al. 2009; Ündeğer et al. 1999).

Evidence of Occupational Exposure to Cancer Chemotherapy Agents

The NTP evaluation reviewed the literature reporting on environmental monitoring of the workplace (e.g., surfaces, air) and biomonitoring surveillance (e.g., urine or blood levels) of

cancer chemotherapy agents in occupationally exposed personnel to determine the prevalence of contamination of the work environment and internal doses to personnel. The studies are available in Appendix I in Supplemental Table 1 (Environmental Monitoring) and Supplemental Table 2 (Biomonitoring). The following details were collected per study: citation, publication year, study country, study setting, sampling year (date samples were collected), samples taken (type of cancer chemotherapy agent measured), sensitivity of contaminant measurements (limit of detection or limit of quantitation), and summary of results. Guidelines for safe handling of cancer chemotherapy agents were first issued in the 1980s by professional trade organizations and federal agencies of several countries, including the United States (OSHA 1986). Since that time, additional guidelines have been written and revised for handling cancer chemotherapy agents and other hazardous drugs by 13 different countries [reviewed in Bernabeu-Martinez et al. (2018)]. One of NTP's original goals for Objective 2 of the evaluation was to identify whether levels of contamination had declined in the years since implementation of the 1986 guidelines in the United States and other countries. However, NTP found this objective was challenging to address because the data were not always expressed in the same increment of measure, the same type of sample (e.g., air versus wipe sample, urine versus blood), the same chemotherapy agent (e.g., cyclophosphamide versus 5-fluorouracil), or the same type of sample location (e.g., worktop of the biological safety cabinet versus patient drug administration area). For this reason, NTP selected cyclophosphamide as a surrogate cancer chemotherapy agent and compared studies that measured the same type of sample with the same increments of measure, regardless of the country of origin of the study.

Environmental Monitoring

The NTP evaluation identified 104 studies reporting on environmental monitoring ranging in publication dates from 1983 to 2017 and years sampled from 1981 to 2016 (Supplemental Table 1 in Appendix I). The studies tested for contamination on a range of samples, including air, cleaning water, gloves, vials, and work surfaces (e.g., floor, biological safety cabinet, and storage shelf). The studies tested and reported on 20 different cancer chemotherapy agents; cyclophosphamide was the most frequently evaluated agent (83 studies). Other agents frequently evaluated in environmental monitoring studies included: ifosfamide (n = 42), 5-fluorouracil (n = 35), methotrexate (n = 27), and platinum (a marker for platinum-containing agents, including cisplatin, carboplatin, and oxaliplatin; n = 18). The remaining agents were evaluated in seven or fewer studies (Supplemental Table 1 in Appendix I). The environmental monitoring studies were conducted in 18 countries. Thirty-nine percent of the studies were conducted in the United States or Canada (41 studies; United States, n = 22, and Canada, n = 18, and one study reporting on both countries), while 52% of the studies were conducted in Europe (54 studies; including studies in Italy (n = 11), the Netherlands (n = 9), and Germany (n = 7). In addition, there were three environmental monitoring studies each from Australia and Japan, and two studies each conducted in Brazil and Iran.

A majority of the environmental monitoring studies (96%; 100/104 studies) reported that one or more samples (e.g., wipe test, air filters) tested above the LOD for any of the cancer chemotherapy agents evaluated (Supplemental Table 1 in Appendix I). To observe possible trends in contamination of the workplace by cancer chemotherapy agents over time, NTP focused on the studies testing for cyclophosphamide because this agent was measured and reported in a majority of the studies available over a wide range of sampling years (1983–2016).

Specifically, NTP evaluated the data for two areas of the drug preparation room that are frequently monitored: the workspace of the biological safety cabinet and the floor in front of the biological safety cabinet; 26 studies were available that reported the maximal level of surface contamination for these two areas. The maximum levels detected in the workspace of the biological safety cabinet ranged from $< \text{LOD}$ to 1,193 ng/cm^2 for the workspace of the biological safety cabinet (n = 22 studies) and $< \text{LOD}$ to 402.5 ng/cm^2 for the floor in front of the biological safety cabinet (24 studies) (Figure 9). The highest levels of cyclophosphamide surface contamination were reported for these two areas in 2004–2005 (maximum levels for workspace were 17.17–44.17 ng/cm^2 and floor were 26.8–100 ng/cm^2) (Acampora et al. 2005; Sessink et al. 2011; Sessink et al. 2013). The frequency of studies reporting wipe samples with maximum levels above 1.5 ng/cm^2 was lower in 2011–2016 (38%, 3/8 studies) compared to 2005–2010 (67%, 4/7 studies) based on workspace measurements. However, for the floor samples, the frequency of studies reporting wipe samples with maximum levels above 1.5 ng/cm^2 appears to have remained the same over time (2011–2016: 29%, 2/7 studies versus 2005–2010: 25%, 4/12).
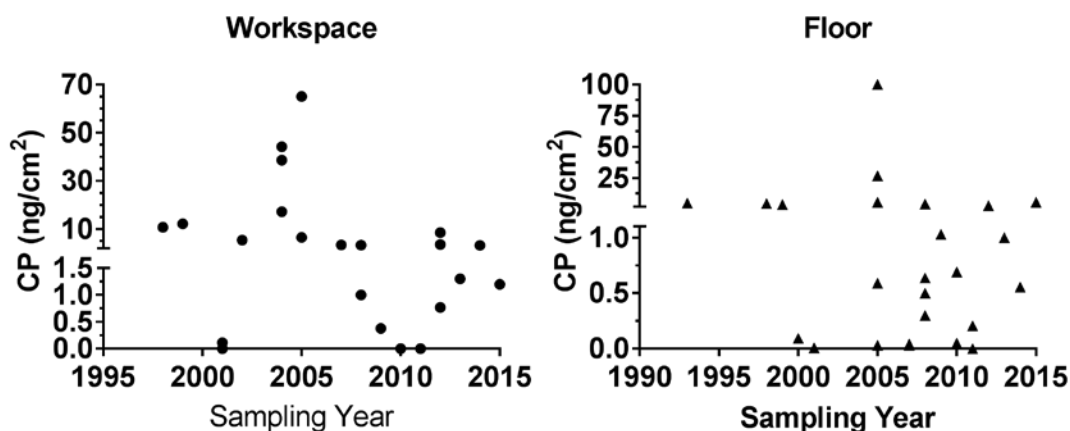
Figure 9. Maximum Levels of Cyclophosphamide Contamination Reported for the Biological Safety Cabinet Workspace and Floor in Front of the Biological Safety Cabinet from 1993 to 2016

Data included 26 studies reporting maximum levels of cyclophosphamide contamination of the workspace of biological safety cabinet (also called hood) or isolator and the floor in front of this space (n = 19): (Acampora et al. 2005; Berruyer et al. 2015; Bigelow et al. 2009; Bussières et al. 2012; Chu et al. 2012; Connor et al. 1999; Couch and dePerio 2011; Couch et al. 2012; Couch and West 2012; Crauste-Manciet et al. 2005; Hedmer et al. 2008; Janes et al. 2015; Martins et al. 2008; McDevitt et al. 1993; Merger et al. 2014; Minoia et al. 1998; Odraska et al. 2014; Odraska et al. 2011; Schmaus et al. 2002; Sessink et al. 2013; Siderov et al. 2009; Touzin et al. 2009; Vandenbroucke and Robays 2001; Wick et al. 2003) Six references reported on floor samples only (Bigelow et al. 2009; Hedmer et al. 2008; Odraska et al. 2014; Odraska et al. 2011; Schmaus et al. 2002; Siderov et al. 2009) and one reference measured biological safety cabinet samples only (Schierl et al. 2016).

Biomonitoring

The NTP evaluation identified 82 studies reporting biomonitoring of occupationally exposed workers. The studies included data collected in 1982–2016 (Supplemental Table 2 in Appendix I). Only four biomonitoring studies were conducted prior to or including 1986, when safe handling guidelines were first published (OSHA 1986). The studies reported on a total of 16 cancer chemotherapy agents or their metabolites with cyclophosphamide (54 studies) as the most frequently evaluated agent. Other agents frequently evaluated in biomonitoring studies include: ifosfamide (n = 19), platinum (as a marker of platinum-containing agents: cisplatin, carboplatin,

and oxaliplatin; n = 21), methotrexate (n = 12), alpha-fluoro-beta-alanine (a metabolite of 5-fluorouracil; n = 9), and epirubicin (n = 8). The remaining agents were evaluated in six or fewer studies: azathioprine, daunorubicin, docetaxel, doxorubicin, etoposide, gemcitabine, idarubicin, mitomycin C, paclitaxel, and pemetrexed. The biomonitoring studies were conducted in 17 countries. Most of the studies (64%, n = 54) were conducted in Europe. Only 13% were conducted in the United States (six studies) and Canada (five studies), 16 studies in Asia, and one study in Africa. Biomonitoring studies primarily evaluated urine samples, although six studies also measured blood levels only and another five studies measured both blood and urine levels of these agents.

Most studies reported the detection of one or more cancer chemotherapy agent in blood or urine of occupationally exposed individuals (89%; n = 73 of 82 total studies) (Supplemental Table 2 in Appendix I). Of the 19 studies that also evaluated control (also called unexposed) subjects, seven studies reported samples above the level of detection for both exposed and control subjects (Ensslin et al. 1994a; Fransman et al. 2007b; Konate et al. 2011; Kopp et al. 2013a; Pilger et al. 2000; Ramphal et al. 2015; Sessink et al. 1994a; Sessink et al. 1994b), which suggested that environmental contamination that may be the issue. For example, in a small study of pharmacy personnel, Ramphal et al. (2015) reported that the urine samples both exposed and unexposed pharmacy staff tested positive for cyclophosphamide on the day they received training on use of the urine sample kits in the oncology laboratory (i.e., the five unexposed pharmacy staff were exposed by entering the oncology pharmacy). In a follow-up evaluation, urine samples tested positive for cyclophosphamide in one unexposed subject who reentered the oncology laboratory, while no agent was detected in samples of four unexposed subjects who did not re-enter the area; it was determined that there was surface contamination of cyclophosphamide and methotrexate both before and after cleaning (Ramphal et al. 2015). Nurses not handling cancer chemotherapy agents, but employed in an outpatient clinic where they were administered, had detectable levels of cyclophosphamide in their urine (Fransman et al. 2007b). Of note, Hon et al. (2015) evaluated employees in five acute care sites and one cancer center in Canada and observed that workers not responsible for handling the agents in the drug administration area (e.g., volunteers, oncologist, nurse aides, and dieticians) had the highest number of positive urine samples for cyclophosphamide. The authors reported there was no correlation between urinary concentration levels and known contact with the agents; however, the urine samples with the highest levels of cancer chemotherapy agents were from employees handling the highest doses, and even higher levels of cancer chemotherapy agents were detected in urine samples from employees who did not receive training in handling these drugs versus those employees who received the training.

To observe possible trends in the number of positive subjects reported in biomonitoring efforts, NTP focused on the studies testing for cyclophosphamide because of the number of studies available (54 studies) and the wide range of years tested (1984–2015). Of the 46 studies reporting the data on a per-subject (e.g., nurse) basis, cyclophosphamide was detected in 35 studies. Twelve studies reported no detection of the agent (Figure 10), including three studies with subjects that tested positive in previous sampling years (Sabatini et al. 2012; Sottani et al. 2010; Yoshida et al. 2013). An additional six studies evaluating the data on a per-sample (not per-subject) basis also detected cyclophosphamide in more than one sample (Fransman et al. 2007a; Peelen et al. 1999; Pethran et al. 2003; Sottani et al. 2008; Turci et al. 2011; Turci et al. 2002) (data not graphed). Thus, biomonitoring studies demonstrated that workers continue to be exposed to cancer chemotherapy agents in the workplace. It is observed that the LOD of

cyclophosphamide in urine has decreased over time; the LODs for the studies in Figure 10 spanned a range from 0.1 to 1.0 ng/mL in 1992, which decreased to range from 0.009 to 0.1 ng/mL from 2011 to 2016. The prevalence of positive biomonitoring samples may be due to more sensitive analytical methods, as well as a higher volume of patients administered cancer chemotherapy agents.

Other Occupationally Exposed Populations

The potential for cancer chemotherapy exposure has increased as options for administration of treatment and the patients receiving these agents have expanded. One newer technique for administering chemotherapy directly to the target organ involves surgery. A study that evaluated platinum environmental surface levels and biomonitoring following a heated intraperitoneal perioperative chemotherapy (HIPEC) procedure using oxaliplatin detected platinum on both layers of the surgeon's gloves (external gloves: 16,284.3 to 24,857.1 ng; internal gloves: 24.3 to 83.2 ng) and a small amount on the surgeon's bare hands (2.0–2.2 ng); however, the urine samples of the surgeon and staff were negative for the agent (Konate et al. 2011). Nursing assistants and housekeeping at home care and nursing centers as well as staff at industry laundry centers maybe exposed to cancer chemotherapy agents through their duties of cleaning patients and emptying pot/urinals, and laundering exposed bed linens, respectively (Meijster et al. 2006). Although less frequently reported, laboratory animal care and veterinary staff are also potentially exposed to cancer chemotherapy agents due to companion animals administered cancer chemotherapy agents for the treatment of cancer. Sessink et al. (1993) reported detection of cyclophosphamide (700 ng) in 1 of 87 urine samples taken from four animal care workers handling mice injected with cyclophosphamide. In a study from Canada, Hall et al. (2013) estimated that 22–24% of veterinarians and 20–22% of veterinary technicians are exposed to cancer chemotherapy agents. Exposure may occur not only in preparing and administering these agents (Couch et al. 2013; Janssens et al. 2015a), but cancer chemotherapy agents have been also been detected blood samples (Knobloch et al. 2010), urine, feces, saliva, and cerumen (ear wax) of dogs several days following treatment (Janssens et al. 2015b). In addition to occupational exposure, family members and friends of patients receiving cancer chemotherapy agents may also be exposed to these agents. A cross-sectional study of family members of patients administered cyclophosphamide for breast cancer reported that 21% of the 243 urine samples (representing six of the 10 family members) tested positive for the agent (Yuki et al. 2015). The level of cyclophosphamide detected was similar in the urine samples of 4 of 6 of the family members (101.5–252 ng) compared to patients administered the drug (108.3–181.5), while urine samples from unexposed subjects were < LOD for cyclophosphamide. Individuals sharing a common bathroom or a higher amount of time in a common space with the cancer patient had the highest levels of cyclophosphamide in their urine (Yuki et al. 2015).
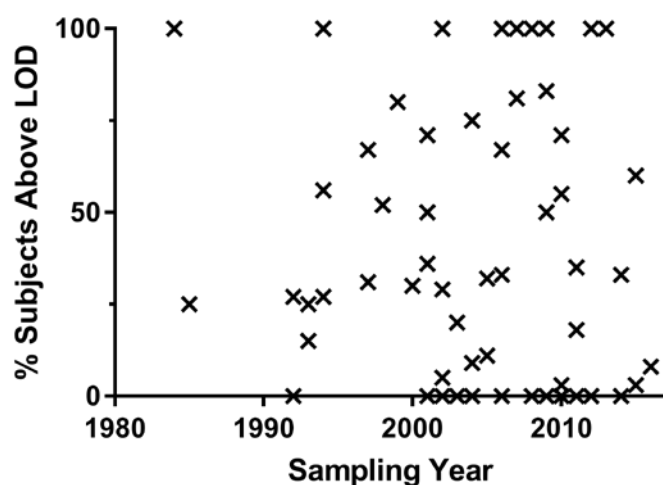
Figure 10. Percent of Workers with Cyclophosphamide Detected Above the Level of Detection in Urine Samples Displayed by the Year Samples Were Collected (1985–2016)

Includes only studies reporting the number of positive subjects or studies for which the number of positive subjects could be determined from the number of samples reported (i.e., one urine sample per subject). Data from 46 studies, including: (Bolognesi et al. 2005; Burgaz et al. 1999; Burgaz et al. 2002; Canal-Raffin et al. 2016; Connor et al. 2010; Ensslin et al. 1997; Ensslin et al. 1994b; Evelo et al. 1986; Hama et al. 2012; Hama et al. 2009; Hedmer et al. 2008; Hirst et al. 1984; Hon et al. 2015; Karahalil and Ilter Akkoyunlu 2004; Kiffmeyer et al. 2002; Korczowska and Jankowiak-Gracz 2013; Maeda et al. 2010; Minoia et al. 1998; Miyake et al. 2013; Moretti et al. 2015; Nyman et al. 2007; Poupeau et al. 2017; Ramphal et al. 2015; Ramphal et al. 2014; Rekhadevi et al. 2007; Sabatini et al. 2012; Schreiber et al. 2003; Sessink et al. 1992a; Sessink et al. 1992b; Sessink et al. 1994a; Sessink et al. 2015; Sessink et al. 1994c; Sessink et al. 1997b; Sessink et al. 1993; Sottani et al. 2010; Sottani et al. 2012; Sugiura et al. 2011a; Sugiura et al. 2011b; Tanimura et al. 2009; Turci et al. 2011; Turci et al. 2002; Vandenbroucke and Robays 2001; Villarini et al. 2011; Wick et al. 2003; Yoshida et al. 2013; Yoshida et al. 2009; Yuki et al. 2015; Ziegler et al. 2002).

Discussion

Based on a systematic review of the literature, NTP concludes that there is a moderate level of evidence that occupational exposure to cancer chemotherapy agents is associated with spontaneous abortion and genetic toxicity. The review identified several studies evaluating other health outcomes; however, there were few studies available for most organ systems and there was heterogeneity in the outcomes assessed for many of them, which limited the ability to compare results between studies. Despite the issuance of guidelines for safe handling of cancer chemotherapy, increased usage of personal protective equipment, and improved safety containment equipment, studies of environmental monitoring and biomonitoring demonstrated that workplace contamination and exposure of workers continues to occur even as recently as from 2011 to 2016.

A clear majority of the genetic toxicity studies in the NTP evaluation reported significantly higher levels of structural CA, MN induction, and DNA damage measured by the comet assay. Fourteen of the 18 studies evaluating more than one assay reported significantly greater DNA damage in exposed subjects relative to unexposed subjects. Most of the studies reporting no effect of occupational exposure also documented the availability of containment devices (e.g., ducted biological safety cabinets), isolated rooms for drug preparation and/or the high usage of personnel protective equipment (e.g., aprons, gloves, and respiratory protection) among occupationally exposed personnel. The NTP conclusion of a moderate level of evidence for genetic toxicity reflects moderate confidence in the body of evidence including consideration of study quality in terms of risk of bias and other factors that could decrease or increase confidence. The inclusion of risk-of-bias assessment in this evaluation is more extensive than previous study quality assessment methods (e.g., "quality" scoring by consideration of study features) used in three recent meta-analyses of the genetic toxicity and occupational exposure (Roussel et al. 2017; Villarini et al. 2016; Zare Sakhvidi et al. 2016). A recent meta-analysis of studies reported that occupational exposure to cancer chemotherapy agents was associated with a significantly higher occurrence of MN induction compared to unexposed subjects (Villarini et al. 2016). The authors reported an overall meta-estimate for MN frequency of 1.67 (95% CI = 1.41–1.98; analyzed as a random ratio of means) for exposed subjects compared to control subjects, and the analysis included studies measuring both the number of cells with MN as well as studies measuring the number of MN (Villarini et al. 2016). Another recent systematic review and meta-analysis of healthcare providers handling cancer chemotherapy agents reported a significantly higher DNA damage index (measured by the comet assay) compared to unexposed workers (Zare Sakhvidi et al. 2016); the authors reported an overall meta-estimate of DNA damage index of 1.93 (95% CI = 1.15–2.71; analyzed as an estimated standardized mean difference). Finally, a meta-analysis of healthcare workers occupationally exposed to cancer chemotherapy agents reported a significantly higher rate of cells with CA or number of CA per cells scored compared to unexposed subjects (Roussel et al. 2017). The overall test results for a pooled standardized mean difference were 1.006, z = 4.25, p < 0.0001 (Roussel et al. 2017). The overall results of these three meta-analyses corroborated the NTP's level-of-evidence conclusions for genetic toxicity in the current evaluation.

Many cancer chemotherapy agents are known or reasonably anticipated to be human carcinogens based on the induction of secondary cancers in patients therapeutically treated with these drugs for cancer and toxicological studies in laboratory rodents (IARC 1966; 1980; 1981; 1990; 2000;

2012; Mistry et al. 2005; NTP 2016 ; Pedersen-Bjergaard 2005). Therapy-related acute myeloid leukemia (t-AML) is the most frequently diagnosed secondary cancer and was recently reported to occur 4.70 times more frequently in patients previously administered cancer chemotherapy than in the general population of the United States in 1975–2008 (Morton et al. 2013). Secondary cancers of the bladder, lung, skin, and uterus are also reported to occur more frequently following administration of cancer chemotherapy agents to patients or laboratory animal models, including following treatment with alkylating agents, antimetabolites, and topoisomerase II inhibitors (IARC 2012). The data on cancer incidence evaluated in the NTP monograph were inadequate to reach level-of-evidence conclusions (three studies) due to the availability of only one or two studies and a low number of cases. Two risk assessments estimated the risk of leukemia, skin cancer, and bladder cancer in nurses handling cyclophosphamide based on their average measurements of dermal exposure (Fransman et al. 2014) or urine levels (Sessink et al. 1995) and cancer incidence in experimental animal studies or primary and secondary cancers in patients receiving cyclophosphamide as a treatment for cancer. Both risk assessments reported that the estimated cancer incidence based on average occupational exposure was within the prohibitory risk level (i.e., no risk higher than 100 per million a year); however, the authors point out that these assessments were based on only one cancer chemotherapy agent when many are used, and there are individuals exposed to higher than average levels, which could increase their risk of developing cancer.

Adverse reproductive outcomes were the second most frequently evaluated health outcome category associated with occupational exposure to cancer chemotherapy. There is strong biological support and concern for potential adverse reproductive health outcomes because many cancer chemotherapy agents are known teratogens or embryo toxicants as identified in toxicology studies in animals and observational studies of patients receiving these drugs for treatment of cancer and other health conditions (NTP 2016; Shepard and Lemire 2004). The NTP monograph observed a higher occurrence of spontaneous abortions in nursing and pharmacy personnel responsible for handling cancer chemotherapy agents compared to controls. One recent review and meta-analysis (Dranitsaris et al. 2005) and a systematic review (Quansah and Jaakkola 2010) of healthcare providers working with cancer chemotherapy agents reached similar conclusions that exposure was associated with spontaneous abortions. The NTP conclusions extended the evaluation of spontaneous abortion by these two reviews (Dranitsaris et al. 2005; Quansah and Jaakkola 2010) by assessing the quality of the studies (Dranitsaris et al. (2005) did not include this step), and by the addition of studies published since the previous reviews (Lawson et al. 2012; Zhang et al. 2016). While other reproductive outcomes were reported in the published literature, there was insufficient evidence to reach level-of-evidence conclusions on the body of literature for a variety of reasons. For example, while 12 studies assessed congenital malformations, only three studies limited exposure to the first trimester and the results were inconsistent. Several studies reported no association of stillbirth with occupational exposure to cancer chemotherapy agents. While the lack of an association of stillbirth with occupational exposure to cancer chemotherapy was contrary to the observed higher rate of stillbirth in women administered cancer chemotherapy during pregnancy reviewed collectively in a recent NTP monograph (NTP 2013), the results on stillbirth risk with occupational exposure to cancer chemotherapy appear to be consistent with the results of two pregnancy registry studies of women exposed to cancer chemotherapy for treatment of cancer compared to pregnancies of unexposed cancer patients (Cardonick et al. 2010; Van Calsteren et al. 2010). However, it was determined that the body of evidence was inadequate for reaching

level-of-evidence conclusions due to the inability to reach a high level of confidence needed to determine no effect, given the designs of the available studies (retrospective cohort and cross-sectional studies) and the lack of dose-response data (see OHAT *Handbook for Conducting a Literature-Based Health Assessment* [https://ntp.niehs.nih.gov/go/systematic_review]).

Impact of Exposure Protection Efforts

Several studies suggested that adherence to good practices, implementation of safety containment equipment, and other exposure mitigation efforts can be successful at reducing occupational exposure and, thus, lowering the potential for adverse health outcomes. While studies only measuring environmental monitoring and/or biomonitoring of occupational exposure to cancer chemotherapy agents following improvements to reduce exposure were not systematically reviewed in this report, the studies are briefly mentioned here because of the importance that reducing occupational exposure has in ultimately reducing adverse health outcomes. For example, a study of four hospital pharmacies in Italy from 1998 to 2007 observed decreases in positive urine samples from pharmacy staff and wipe samples of the work environment that coincided with the implementation of safe handling guidelines for handling these drugs in 1999, and the usage of personal protective equipment (e.g., chemotherapy gloves, gowns, hair covers) in the 2000s (Sottani et al. 2010). Reductions in the levels of cancer chemotherapy agents detected in exposed workers' urine samples or environmental monitoring of workspaces where cancer chemotherapy drugs are prepared and/or handled have also been observed with the implementation of a centralized system for the preparation of doses (Sabatini et al. 2012) or closed-system drug transfer devices, which limit the chance of drug spills or the escape of vapor during drug preparation and intravenous drug administration (Sessink et al. 2011; Sessink et al. 2013; Wick et al. 2003; Yoshida et al. 2009).

Of the studies reporting health outcomes that were all systematically reviewed, only one study assessed health outcomes before and after implementation of exposure control methods. The study in China reported a significant reduction in a variety of adverse health outcomes (i.e., incidence of spontaneous abortion, infertility, and hematotoxicity) in oncology nurses 2 years after the implementation of a PIVAS at the hospital, compared to the frequency of these adverse health outcomes at the time the PIVAS was first established (Zhang et al. 2016). In addition, several studies reporting no difference in the number of MN between occupationally exposed employees and controls attributed this lack of effect to the documented usage of personal protective equipment, available biological safety cabinets, and/or centralized units for drug preparation by the occupationally exposed workers (Bolognesi et al. 2005; Cavallo et al. 2005; Ensslin et al. 1997; Harris et al. 1992; Laffon et al. 2005; Pilger et al. 2000; Thiringer et al. 1991).

Limitations of the Evidence Base

Study Design Limitations

Recall bias can occur in retrospective cohort studies and case-control studies, and most of the studies reporting on reproductive outcomes or cancer in the NTP monograph were retrospective. Recall bias is most likely when both the exposure and disease status are known at time of study, and it is recommended that the study design does not explicitly reveal the purpose of questions in an interview or survey and/or uses a validated questionnaire (Andrews et al. 2002). For example,

parents of children with autism associated the condition with exposure to the MMR (mumps-measles-rubella) vaccine after this hypothesis was published in 1998; whereas, parents did not associate this exposure with MMR prior to publication of the hypothesis (Andrews et al. 2002). However, studies report that women have accurate recall of pregnancy outcomes (Axelsson 1990; Joffe et al. 1993), and nurses have accurate recall of pregnancy outcomes and health data for many outcomes (Colditz et al. 1986; Colditz et al. 1987). Thus, studies of reproductive health and major disease outcomes in medical personnel are considered of greater reliability despite the retrospective study design (Axelsson 1990). Furthermore, a study of pharmacists demonstrated accurate recall of occupational exposure to cancer chemotherapy agents using a self-reported questionnaire was corroborated by their supervisor (McDiarmid et al. 1992). Many of the studies reporting health outcomes were of the cross-sectional study design, and this study design generally cannot assure that exposure occurred prior to outcome so reverse causation is possible. Following the Hill considerations on causality (which are embedded in the OHAT adaptations of the GRADE approach to assessing confidence in the body evidence used here), there is less confidence that the relationship between exposure and outcome is causal. The initial confidence rating for cross-sectional studies is generally low confidence based on only two features: individual outcomes assessed, and that a comparison group was used. In this evaluation, the cross-sectional studies of genetic toxicity were rated moderate initial confidence, based primarily on the rapidity of the genetic toxicity mechanism (hours to days). Therefore, for genetic toxicity, NTP considered cross-sectional studies to provide sufficiently clear evidence that exposure preceded outcome, based on the fact that the studies measured rapidly developing health outcomes (hours to days versus years), the subjects worked full time the week the samples were drawn, and most subjects had worked from 1 month to a year prior to the study.

Exposure Characterization

A potential limitation of the exposure characterization of occupational exposure to cancer chemotherapy agents is the nature of the primary source of information on exposure: employment history or historical industrial hygiene data. The utility of this information is improved by use of validated questionnaires regarding work activities (e.g., drugs handled, quantities, frequency) and unusual events (i.e., accidents and needle sticks) that may influence exposure during the study period. In fact, the use of a daily diary of work activities that has been validated to estimate exposure levels has been proposed for use with genetic toxicity outcomes by the World Health Organization's International Programme on Chemical Safety (Albertini et al. 2000). The daily diary has been proposed as the most useful source to construct exposure metrics based on the level of exposure (drugs handled, frequency of handling), use of protective measures (personal protective equipment, ventilation), variances in procedures, and adverse events (Nieuwenhuijsen 2003). Biomonitoring of urine or blood samples for levels of a cancer chemotherapy agent(s) or its metabolites may be helpful to confirm that exposure occurred, but likely only provide confirmation of only the most recent exposure. Environmental monitoring of the work environment (e.g., surface wipes, air samples, dermal pads) is a useful tool to identify contaminated areas, and, thus, the potential for exposure; however, it may or may not relate to actual internal dose due to use of safety equipment (e.g., biological safety cabinets) or personal protective equipment (e.g., gloves, mask, gown). A recent review of swipe tests compared to biomonitoring results did not find a statistically significant correlation (Kibby 2017); however, the authors did observe decreases in the levels of surface contamination detected in wipe samples and urine monitoring following improvements to personal protective equipment and safe

handling techniques. Another challenge for biomonitoring and environmental monitoring assessments is the fact that most occupational exposures in the medical or veterinary setting are likely to multiple cancer chemotherapy agents, while most monitoring assessments are designed to test one or a handful of agents as surrogates of the total cancer chemotherapy exposure.

Challenges in Evaluating Reproductive Toxicity

There were many challenges in the outcome assessment of reproductive toxicity associated with occupational exposure to cancer chemotherapy. The occurrence of some pregnancy outcomes, such as major congenital malformations, is relatively rare; thus, large sample sizes are required to detect a difference between exposed and unexposed subjects. Some adverse reproductive health outcomes may be difficult to accurately detect and, thus, may not always be fully documented in the workers' medical records (e.g., early spontaneous abortion). However, several studies have determined that women have accurate recall of pregnancy outcomes, including spontaneous abortion (Axelsson 1990) and time to pregnancy (Cooney et al. 2009). Finally, occupational exposure to cancer chemotherapy agents was not a frequently reported exposure during pregnancy. For example, some studies evaluated the association of fetal loss or congenital malformations with a woman's occupation (Lorente et al. 2000; McDonald et al. 1988b), or occupational exposures to a variety of hazardous chemicals in hospitals (Hemminki et al. 1985; McAbee et al. 1993), the pharmaceutical manufacturing industry (Taskinen et al. 1986), or laboratory work (Taskinen et al. 1994). The total number of workers handling cancer chemotherapy agents in these studies was small and may not be representative of the actual prevalence of fetal loss or congenital malformations in the larger population of exposed workers.

Limitations of the Systematic Review

There were some limitations of the current systematic review. The NTP evaluation excluded studies that did not include a comparator group due to concerns that knowledge of the outcome may have influenced the association with occupational exposure to cancer chemotherapy; thus, the evaluation did not include 21 studies (e.g., case reports, case series or surveys) that reported on a variety of health outcomes, including acute effects, asthma, cancer, and reproduction. However, these studies could be useful to identify additional health outcomes that could be evaluated in future research. Secondly, the literature search may not have identified all possible studies reporting on health outcomes following occupational exposure to cancer chemotherapy, particularly if journals were not indexed for the databases that NTP searched (i.e., PubMed, Scopus, and Embase). For example, NTP identified one reference reporting on CA and MN induction in peripheral lymphocytes (Ferguson et al. 1988) and another reference reporting on MN induction in buccal cells (Odio et al. 2004) from the reference lists of recently published papers, as NTP completed its evaluation. NTP is confident it has identified the majority of papers published on these genetic toxicity outcomes and have confirmed that the results of the additional two papers reporting on CA and MN induction would not change NTP's level-of-evidence conclusions for these endpoints or genetic toxicity overall. Finally, NTP's literature search may not have captured the entire body of literature on environmental monitoring (e.g., contamination of drug vials, gloves) and biomonitoring studies because the literature search was primarily focused on identifying the health outcome studies. However, NTP is confident its review of this literature provides an accurate characterization of the levels of environmental contamination in the workplace and the prevalence of positive biomonitoring studies for a surrogate exposure (i.e., the commonly used cancer chemotherapy agent cyclophosphamide).

Research Needs

The NTP evaluation identified several data gaps and research needs to improve the scientific community's understanding of potential health risks associated with occupational exposure to cancer chemotherapy agents:

1. Expand the range of health outcomes assessed in evaluations of occupational exposure to cancer chemotherapy agents, including bone marrow function (e.g., hematotoxicity), and toxicity of the cardiovascular, kidney, and liver systems. Although some reports of these health outcomes were identified in the NTP evaluation, there was insufficient evidence to evaluate whether or not there is an association with occupational exposure to chemotherapy.

2. Expand the array of workers studied for health effects associated with occupational exposure to cancer chemotherapy agents to include support personnel (e.g., waste collectors, hospital cleaning and laundry staff), home health aides, emergency responders, and veterinary clinic staff. In addition, family caregivers could be studied as exposure to this population has been documented. There were very few studies reporting on the health outcomes or exposure levels of these worker populations, including family caregivers, in the NTP evaluation.

3. Expand the evaluation of health effects associated with occupational exposure to cancer chemotherapy agents to include emerging cancer drug therapies that target specific genes, transcription factors, or signaling molecules. Side effects have been observed in patients following administration of newer targeted drug therapies, such as monoclonal antibodies (Halsen and Kramer 2011) and B-Raf proto-oncogene inhibitors (Sibaud et al. 2013). Most studies in the NTP evaluation focused on health outcomes associated with occupational exposure primarily to antineoplastic agents.

4. Conduct more prospective cohort studies versus retrospective cohort or case-control studies to reduce the potential for recall bias in identifying occupational exposure, especially for endpoints such as cancer. Cross-sectional studies, which were among the most common study design in the NTP evaluation, also present concerns about possible reverse causation. Prospective cohort studies allow for a baseline measure of health outcomes of all subjects in the study to which subsequent health evaluations can be compared.

5. Improve exposure characterization methods:

   a. Advance analytical chemistry methods for detection of cancer chemotherapy agents to lower the LOD, allow for simultaneous detection of multiple cancer chemotherapy agent exposures (e.g., most oncology nurses and pharmacists handle multiple agents), and develop techniques to detect metabolites of the agents (e.g., most biomonitoring assays only measure the parent agent). While many of the environmental monitoring studies did evaluate more than one agent, most of the biomonitoring studies assessed only one agent. Those studies that assessed multiple agents tended to evaluate them sequentially. Very few biomonitoring studies (16 of 82 studies) tested for metabolites of cancer chemotherapy agents.

b. Continue research on ways to effectively use daily diaries that are assessed and validated to estimate exposure levels (e.g., frequency of handling, dose levels, as well as incorporation of information on use of personal protective equipment and safety containment equipment). Although many studies collected information about drugs handled, doses, and frequency of handling, these data were not generally incorporated into the association with the health outcome. In contrast, two studies of the same population that characterized exposure by daily diary allowed for an analysis that considered the individual's health outcome by the individual's drug handling activity (McDiarmid et al. 2010; McDiarmid et al. 2014).

6. Design studies to evaluate the effectiveness of different types of personal protective equipment and other exposure control strategies (e.g., closed-system drug transfer devices, centralized drug preparation units) to reduce occupational exposure (environmental monitoring and biomonitoring) and to reduce possible adverse health outcomes. The impact of exposure control strategies was evaluated in only one study reporting on health outcomes and a handful of environmental monitoring and/or biomonitoring studies reviewed in the NTP monograph.

Conclusions

The NTP evaluation concluded that there is a moderate level of evidence for spontaneous abortion and genetic toxicity associated with occupational exposure to cancer chemotherapy agents. Data on other health effects was inadequate to reach level-of-evidence conclusions due to limitations in the body of evidence (e.g., few studies, small case sizes and, in some cases, heterogeneity in the outcomes assayed). Environmental monitoring and biomonitoring studies report that workplace contamination with cancer chemotherapy agents continues to occur, although maximum levels of surface contamination detected have declined. Considering the potential for exposure, the association between exposure and DNA damage in workers, and the widespread use of cancer chemotherapy agents (e.g., veterinary use, home health care), there is a continued need to improve exposure characterization (e.g., improved analytical chemistry methods, daily diaries of drug handling) and health surveillance as well as to identify the most effective safe handling practices and exposure control equipment to reduce potential adverse health outcomes of occupationally exposed personnel.

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Appendix A. Literature Search Strategy

The strategy for this search is broad for the consideration of adverse health outcomes, including biomarkers of effect, and comprehensive for occupational exposure to cancer chemotherapy agents as an exposure or treatment in order to ensure inclusion of relevant papers.

Table A-1. Literature Search Strategy

Database	Search Terms
Embase	('Antineoplastic agent'/exp OR 'antineoplastic agent') AND ('health care personnel'/exp OR 'health care personnel') AND ('occupational exposure'/de OR 'occupational exposure' OR 'occupational hazard'/de OR 'occupational hazard' OR 'occupational safety'/de OR 'occupational safety') AND ([embase]/lim OR [embase classic]/lim)
PubMed	("Neoplasms/drug therapy"[mh] OR "antineoplastic protocols"[mh] OR "chemotherapy, adjuvant"[mh] OR "antineoplastic agents"[mh] OR "antineoplastic agents"[pharmacological action] OR chemotherapy[tiab] OR chemotherapies[tiab] OR chemotherapeutic*[tiab] OR anticancer[tiab] OR antineoplastic*[tiab] OR anti- tumor*[tiab] OR anti-tumour*[tiab] OR cytostatic[tiab] OR hazardous-drug*[tiab] OR drug*-hazardous[tiab] OR category-D[tiab] OR category-x[tiab])) OR ("4 aminofolic acid"[tiab] OR "4 epidoxorubicin"[tiab] OR "5 fluorouracil"[tiab] OR "6 mercaptopurine"[tiab] OR "6 thioguanine"[tiab] OR Abraxane[tiab] OR adrucil[tiab] OR "all-trans retinoic acid"[tiab] OR ATRA[tiab] OR altretamine[tiab] OR adriamycin[tiab] OR "actinomycin D"[tiab] OR aminopterin[tiab] OR Anastrozole[tiab] OR "ARA-C"[tiab] OR arimidex[tiab] OR aromasin[tiab] OR "behenoyl cytosine arabinoside"[tiab] OR bevacizumab[tiab] OR BHAC[tiab] OR bleomycin[tiab] OR bortezomib[tiab] OR busulfan[tiab] OR busulfex[tiab] OR carboplatin[tiab] OR capecitabine[tiab] OR carmustine[tiab] OR Cerubidine[tiab] OR chlorambucil[tiab] OR cisplatin[tiab] OR cis-platinum[tiab] OR cyclophosphamide[tiab] OR cytarabine[tiab] OR cytosar[tiab] OR "cytosine arabinoside"[tiab] OR Cytoxan[tiab] OR dacarbazine[tiab] OR dasatinib[tiab] OR daunorubicin[tiab] OR daunoxome[tiab] OR deltasone[tiab] OR docetaxel[tiab] OR doxorubicin[tiab] OR efudex[tiab] OR eldisine[tiab] OR Ellence[tiab] OR Eloxatin[tiab] OR emcyt[tiab] OR enocitabine[tiab] OR epirubicin[tiab] OR erlotinib[tiab] OR etopophos[tiab] OR etoposide[tiab] OR estramustine[tiab] OR exemestane[tiab] OR fareston[tiab] OR femara[tiab] OR fludara[tiab] OR fludarabine[tiab] OR folex[tiab] OR fulvestrant[tiab] OR Faslodex[tiab] OR gefitinib[tiab] OR gemcitabine[tiab] OR gemtuzumab[tiab] OR gemzar[tiab] OR gleevec[tiab] OR glivec[tiab] OR herceptin[tiab] OR hexamethylmelamine[tiab] OR hydroxycarbamide[tiab] OR hydroxyurea[tiab] OR idarubicin[tiab] OR IFEX[tiab] OR ifosfamide[tiab] OR imatinib[tiab] OR "interferon alpha"[tiab] OR iressa[tiab] OR irinotecan[tiab] OR ixabepilone[tiab] OR ixempra[tiab] OR lapatinib[tiab] OR letrozole[tiab] OR lomustine[tiab] OR matulane[tiab] OR mechlorethamine[tiab] OR melphalan[tiab] OR methotrexate[tiab] OR "mitomycin c"[tiab] OR mitoxantrone[tiab] OR mustargen[tiab] OR "mustine Hcl"[tiab] OR mutamycin[tiab] OR myleran[tiab] OR mylotarg[tiab] OR navelbine[tiab] OR nilotinib[tiab] OR "nitrogen mustard HCl"[tiab] OR nolvadex[tiab] OR novantrone[tiab] OR oncovin[tiab] OR oxaliplatin[tiab] OR ozogamicin[tiab] OR paclitaxel[tiab] OR paraplatin[tiab] OR pemetrexed[tiab] OR pentostatin[tiab] OR platinol[tiab] OR prednisone[tiab] OR procarbazine[tiab] OR rituxan[tiab] OR rituximab[tiab] OR sorafenib[tiab] OR sprycel[tiab] OR streptozocin[tiab] OR sunitinib[tiab] OR sunrabin[tiab] OR sutent[tiab] OR tamoxifen[tiab] OR tarceva[tiab] OR tasigna[tiab] OR taxol[tiab] OR taxotere[tiab] OR temodar[tiab] OR temozolomide[tiab] OR teniposide[tiab] OR thioplex[tiab] OR thiotepa[tiab] OR toposar[tiab] OR topotecan[tiab] OR toremifene[tiab] OR trastuzumab[tiab] OR tretinoin[tiab] OR tykerb[tiab] OR velban[tiab] OR velcade[tiab] OR vepesid[tiab] OR vesanoid[tiab] OR vinblastine[tiab] OR vincasar[tiab] OR

Database	Search Terms
	vincrex[tiab] OR vincristine[tiab] OR vindesine[tiab] OR vinorelbine[tiab] OR VM26[tiab] OR VP16[tiab] OR Vumon[tiab] OR Xeloda[tiab] OR zanosar[tiab]) AND (Environmental exposure[mh] OR Occupational exposure[mh] OR occupational diseases[mh] OR occupation*[tiab] OR workplace[tiab] OR work-related[tiab] OR exposure*[tiab] OR exposed[tiab] OR contaminat*[tiab] OR handl*[tiab]) AND Health services[mh] OR health occupations[mh] OR health personnel[mh] OR pharmacist*[tiab] OR technician*[tiab] OR nurse*[tiab] OR nursing[tiab] OR physician*[tiab] OR clinician*[tiab] OR doctor*[tiab] OR veterinarian*[tiab])) OR ((hospital[tiab] OR clinic[tiab] OR medical[tiab] OR health[tiab] OR healthcare[tiab] OR health-care[tiab] OR pharmacy[tiab] OR pharmaceutical*[tiab] OR cancer[tiab] OR oncolog*[tiab] OR veterinary[tiab]) AND (staff[tiab] OR personnel[tiab] OR worker*[tiab] OR employee*[tiab] OR technician*[tiab] OR aide*[tiab] OR assistant*[tiab] OR professional*[tiab] OR setting*[tiab] AND (Neoplasms[mh] OR neoplas*[tiab] OR cancer[tiab] OR cancerous[tiab] OR carcinogenic*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumorigen*[tiab] OR tumour*[tiab] OR leukemia*[tiab] OR lymphoma*[tiab] OR sarcoma*[tiab] OR carcinoma*[tiab] OR adenoma*[tiab] OR melanoma*[tiab] OR DNA damage[mh] OR dna-damage[tiab] OR genetic-damage[tiab] OR chromosom*[tiab] OR chromatid[tiab] OR mutagenicity tests[mh] OR mutagen*[tiab] OR genotox*[tiab] OR micronucle*[tiab]) OR (Reproduction[mh] OR reproduction[tiab] OR reproductive[tiab] OR sexual[tiab] OR intercourse[tiab] OR coitus[tiab] OR ejaculat*[tiab] OR orgasm*[tiab] OR fertiliz*[tiab] OR conception[tiab] OR gametogenesis[tiab] OR oogenesis[tiab] OR spermatogenesis[tiab] OR inseminat*[tiab] OR luteinization[tiab] OR ovulat*[tiab] OR anovulat*[tiab] OR superovulat*[tiab] OR erection*[tiab] OR Reproductive physiological phenomena[mh] OR andropause[tiab] OR menopause[tiab] OR estrous[tiab] OR fertility[tiab] OR fecund*[tiab] OR time-to-pregnancy[tiab] OR menstrua*[tiab] OR pubert*[tiab] OR adrenarche[tiab] OR menarche[tiab] OR Genital diseases, female[mh] OR endometriosis[tiab] OR infertil*[tiab] OR pelvic-inflamm*[tiab] OR genital diseases, male[mh] OR epididymitis[tiab] OR hypospadia*[tiab] OR priapism[tiab] OR prostatitis[tiab] OR cryptorchidism[tiab] OR varicocele[tiab] OR erectile-dysfunction[tiab] OR Pregnancy[mh] OR Pregnant[tiab] OR pregnancy[tiab] OR pregnancies[tiab] OR obstetric*[tiab] OR maternal*[tiab] OR mother*[tiab] OR embryonic and fetal development[mh] OR embryonic-development[tiab] OR fetal-development[tiab] OR organogenesis[tiab] OR body size[mh] OR birth-weight*[tiab] OR growth-retardation[tiab] OR small-for-gestation*[tiab] OR embryo[tiab] OR embryos[tiab] OR embryonic[tiab] OR fetus[tiab] OR foetus[tiab] OR fetal[tiab] OR foetal[tiab] OR gestation*[tiab] OR peripartum[tiab] OR postpartum[tiab] OR placent*[tiab] OR prenatal[tiab] OR perinat*[tiab] OR neonat*[tiab] OR postnat*[tiab] OR labor-onset[tiab] OR Parturition*[tiab] OR birth[tiab] OR births[tiab] OR childbirth*[tiab] OR gravidity[tiab] OR parity[tiab] OR Pregnancy complications[mh] OR pregnancy-complication*[tiab] OR complicated-pregnan*[tiab] OR labor-complication*[tiab] OR complicated-labor[tiab] OR gestational-diabetes[tiab] OR (pregnancy[tiab] AND hypertension[tiab]) OR maternal-death[tiab] OR morning-sickness[tiab] OR breech[tiab] OR ectopic[tiab] OR Pregnancy outcome[mh] OR pregnancy-outcome*[tiab] OR live-birth*[tiab] OR full-term[tiab] OR term-birth*[tiab] OR newborn*[tiab] OR baby[tiab] OR babies[tiab] OR infant*[tiab] OR premature[tiab] OR preterm[tiab] OR pre-term[tiab] OR stillbirth*[tiab] OR still-birth*[tiab] OR stillborn*[tiab] OR still-born*[tiab] OR spontaneous-abortion*[tiab] OR miscarriage*[tiab] OR infant mortality[mh] OR infant-mortality[tiab] OR embryo*-loss[tiab] OR congenital, hereditary, and neonatal diseases and abnormalities[mh] OR congenital[tiab] OR abnormal*[tiab] OR malform*[tiab] OR retard*[tiab] OR prenatal exposure delayed effects[mh] OR teratogen*[tiab] OR embryotoxic*[tiab])

Database	Search Terms
Scopus	TITLE-ABS-KEY(chemotherapy* OR anticancer OR antineoplastic* OR anti-tumor* OR anti-tumour* OR cytostatic OR hazardous-drug* OR drug*-hazardous OR category-d OR category-x OR "4 aminofolic acid" OR "4 epidoxorubicin" OR "5 fluorouracil" OR "6 mercaptopurine" OR "6 thioguanine" OR abraxane OR adrucil OR "all-trans retinoic acid" OR atra OR altretamine OR adriamycin OR "actinomycin D" OR aminopterin OR anastrozole OR "ARA-C" OR arimidex OR aromasin OR "behenoyl cytosine arabinoside" OR bevacizumab OR bhac OR bleomycin OR bortezomib OR busulfan OR busulfex OR carboplatin OR capecitabine OR carmustine OR cerubidine OR chlorambucil OR cisplatin OR cis-platinum OR cyclophosphamide OR cytarabine OR cytosar OR "cytosine arabinoside" OR cytoxan OR dacarbazine OR dasatinib OR daunorubicin OR daunoxome OR deltasone OR docetaxel OR doxorubicin OR efudex OR eldisine OR ellence OR eloxatin OR emcyt OR enocitabine OR epirubicin OR erlotinib OR etopophos OR etoposide OR estramustine OR exemestane OR fareston OR femara OR fludara OR fludarabine OR folex OR fulvestrant OR faslodex OR gefitinib OR gemcitabine OR gemtuzumab OR gemzar OR gleevec OR glivec OR herceptin OR hexamethylmelamine OR hydroxycarbamide OR hydroxyurea OR idarubicin OR ifex OR ifosfamide OR imatinib OR "interferon alpha" OR iressa OR irinotecan OR ixabepilone OR ixempra OR lapatinib OR letrozole OR lomustine OR matulane OR mechlorethamine OR melphalan OR methotrexate OR "mitomycin c" OR mitoxantrone OR mustargen OR "mustine Hcl" OR mutamycin OR myleran OR mylotarg OR navelbine OR nilotinib OR "nitrogen mustard HCl" OR nolvadex OR novantrone OR oncovin OR oxaliplatin OR ozogamicin OR paclitaxel OR paraplatin OR pemetrexed OR pentostatin OR platinol OR prednisone OR procarbazine OR rituxan OR rituximab OR sorafenib OR sprycel OR streptozocin OR sunitinib OR sunrabin OR sutent OR tamoxifen OR tarceva OR tasigna OR taxol OR taxotere OR temodar OR temozolomide OR teniposide OR thioplex OR thiotepa OR toposar OR topotecan OR toremifene OR trastuzumab OR tretinoin OR tykerb OR velban OR velcade OR vepesid OR vesanoid OR vinblastine OR vincasar OR vincrex OR vincristine OR vindesine OR vinorelbine OR vm26 OR vp16 OR vumon OR xeloda OR zanosar) AND TITLE-ABS-KEY(occupation* OR workplace OR work-related OR contaminat* OR handl*) AND TITLE-ABS-KEY((pharmacist* OR technician* OR nurse* OR nursing OR physician* OR clinician* OR doctor* OR veterinarian* OR hospital OR clinic OR medical OR health OR healthcare OR health-care OR pharmacy OR pharmaceutical* OR cancer OR oncolog* OR veterinary) AND (staff OR personnel OR worker* OR employee* OR technician* OR aide* OR assistant* OR professional* OR setting*))
TOXLINE	(chemotherapy OR chemotherapies OR chemotherapeutic OR anticancer OR "anti cancer" OR antineoplastic* OR "anti tumor" OR "anti tumorigenic" OR "anti tumour" OR "anti tumourigenic" OR cytostatic) AND (occupation* OR workplace OR work related OR contaminat* OR handl*) AND (pharmacist OR pharmacists OR technician OR nurse OR nursing OR physician OR clinician OR doctor OR veterinarian OR hospital OR clinic OR medical OR health OR healthcare OR health care OR pharmacy OR pharmaceutical OR cancer OR oncolog* OR veterinary) AND (staff OR personnel OR worker OR employee OR technician OR aide OR assistant OR professional OR setting)

Database	Search Terms
Web of Science	Topic = (Chemotherap* OR anticancer OR antineoplastic* OR anti- tumor* OR anti-tumour* OR cytostatic OR hazardous-drug* OR drug*-hazardous OR category-D OR category-x OR "4 aminofolic acid" OR "4 epidoxorubicin" OR "5 fluorouracil" OR "6 mercaptopurine" OR "6 thioguanine" OR Abraxane OR adrucil OR "all-trans retinoic acid" OR ATRA OR altretamine OR adriamycin OR "actinomycin D" OR aminopterin OR Anastrozole OR "ARA-C" OR arimidex OR aromasin OR "behenoyl cytosine arabinoside" OR bevacizumab OR BHAC OR bleomycin OR bortezomib OR busulfan OR busulfex OR carboplatin OR capecitabine OR carmustine OR Cerubidine OR chlorambucil OR cisplatin OR cis-platinum OR cyclophosphamide OR cytarabine OR cytosar OR "cytosine arabinoside" OR Cytoxan OR dacarbazine OR dasatinib OR daunorubicin OR daunoxome OR deltasone OR docetaxel OR doxorubicin OR efudex OR eldisine OR Ellence OR Eloxatin OR emcyt OR enocitabine OR epirubicin OR erlotinib OR etopophos OR etoposide OR estramustine OR exemestane OR fareston OR femara OR fludara OR fludarabine OR folex OR fulvestrant OR Faslodex OR gefitinib OR gemcitabine OR gemtuzumab OR gemzar OR gleevec OR glivec OR herceptin OR hexamethylmelamine OR hydroxycarbamide OR hydroxyurea OR idarubicin OR IFEX OR ifosfamide OR imatinib OR "interferon alpha" OR iressa OR irinotecan OR ixabepilone OR ixempra OR lapatinib OR letrozole OR lomustine OR matulane OR mechlorethamine OR melphalan OR methotrexate OR "mitomycin c" OR mitoxantrone OR mustargen OR "mustine Hcl" OR mutamycin OR myleran OR mylotarg OR navelbine OR nilotinib OR "nitrogen mustard HCl" OR nolvadex OR novantrone OR oncovin OR oxaliplatin OR ozogamicin OR paclitaxel OR paraplatin OR pemetrexed OR pentostatin OR platinol OR prednisone OR procarbazine OR rituxan OR rituximab OR sorafenib OR sprycel OR streptozocin OR sunitinib OR sunrabin OR sutent OR tamoxifen OR tarceva OR tasigna OR taxol OR taxotere OR temodar OR temozolomide OR teniposide OR thioplex OR thiotepa OR toposar OR topotecan OR toremifene OR trastuzumab OR tretinoin OR tykerb OR velban OR velcade OR vepesid OR vesanoid OR vinblastine OR vincasar OR vincrex OR vincristine OR vindesine OR vinorelbine OR VM26 OR VP16 OR Vumon OR Xeloda OR zanosar) AND Topic = ((pharmacist* OR technician* OR nurse* OR nursing OR physician* OR clinician* OR doctor* OR veterinarian* OR hospital OR clinic OR medical OR health OR healthcare OR health-care OR pharmacy OR pharmaceutical* OR cancer OR oncolog* OR veterinary) AND (staff OR personnel OR worker* OR employee* OR technician* OR aide* OR assistant* OR professional* OR setting*)) AND Topic = (occupation* OR workplace OR work-related OR contaminat* OR handl*) AND Topic = (neoplas* OR cancer OR cancerous OR carcinogenic* OR tumor OR tumors OR tumorigen* OR tumour* OR leukemia* OR lymphoma* OR sarcoma* OR carcinoma* OR adenoma* OR melanoma* OR dna-damage OR genetic-damage OR chromosom* OR chromatid OR mutagen* OR genotox* OR micronucle*) OR Topic = (reproduction OR reproductive OR sexual OR intercourse OR coitus OR ejaculat* OR orgasm* OR fertiliz* OR conception OR gametogenesis OR oogenesis OR spermatogenesis OR inseminat* OR luteinization OR ovulat* OR anovulat* OR superovulat* OR erection* OR andropause OR menopause OR estrous OR fertility OR fecund* OR time-to-pregnancy OR menstrua* OR pubert* OR adrenarche OR menarche OR endometriosis OR infertil* OR pelvic-inflamm* OR epididymitis OR hypospadia* OR priapism OR prostatitis OR cryptorchidism OR varicocele OR erectile-dysfunction OR pregnant OR pregnancy OR pregnancies OR obstetric* OR maternal* OR mother* OR embryonic-development OR fetal-development OR organogenesis OR "body size" OR birth-weight* OR growth-retardation OR small-for-gestation* OR embryo OR embryos OR embryonic OR fetus OR foetus OR fetal OR foetal OR gestation* OR peripartum OR postpartum OR placent* OR prenatal OR perinat* OR neonat* OR postnat* OR labor-onset OR Parturition* OR birth OR births OR childbirth* OR gravidity OR parity OR pregnancy-complication* OR complicated-pregnan* OR labor-complication* OR complicated-labor OR gestational-diabetes OR (pregnancy AND hypertension) OR maternal-death OR morning-sickness OR breech OR ectopic OR pregnancy-outcome* OR live-birth* OR full-term OR term-birth* OR newborn* OR baby OR babies OR infant* OR premature OR preterm OR pre-term OR stillbirth* OR still-birth* OR stillborn* OR still-born* OR spontaneous-abortion* OR miscarriage* OR infant-mortality OR embryo*-loss OR congenital OR abnormal* OR malform* OR retard* OR teratogen* OR embryotoxic*)

Appendix B. List of Included Studies Reporting Health Outcomes

Anwar WA, Salama SI, el Serafy MM, Hemida SA, Hafez AS. 1994. Chromosomal aberrations and micronucleus frequency in nurses occupationally exposed to cytotoxic drugs. Mutagenesis. 9(4):315-317. http://dx.doi.org/10.1093/mutage/9.4.315

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Zhang X, Zheng Q, Lv Y, An M, Zhang Y, Wei Y, Feng W. 2016. Evaluation of adverse health risks associated with antineoplastic drug exposure in nurses at two Chinese hospitals: The effects of implementing a pharmacy intravenous admixture service. Am J Ind Med. 59(4):264-273. http://dx.doi.org/10.1002/ajim.22553

Appendix C. Risk-of-bias Assessment for All Included Studies
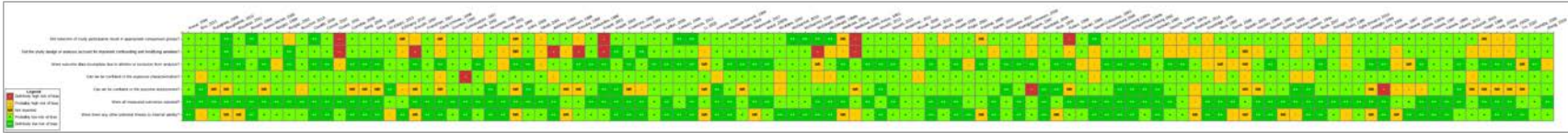
Figure C-1. Risk-of-bias Heat Map for Included Studies Reporting on Health Outcomes

Interactive figure and additional study details in HAWC (NTP, 2015a). Fransman 2007 refers to Fransman et al. (2007c).

Appendix D. Data Figures

Figures

A

Study	Description of exposed workers	Study design	statistical metric abbreviation	Exposure status	N of exposed cases	Spontaneous abortion
Fransman, 2007	Hospital nurses, The Netherlands, 1990-1997, ♀ (1,519 women; 1,259 pregnancies)	Cross-sectional	adjOR	exposed (low, ≤0.20 ug/wk)		
		Cross-sectional	adjOR	exposed (medium, >0.20-0.74 ug/wk)		
		Cross-sectional	adjOR	exposed (high, >0.74 ug/wk)		
		Cross-sectional	OR	effect measure per 1-unit increase (log-linear, exposure)		
Hemminki, 1985	Hospital nurses, 1973-1979, Finland, ♀ (169 SAB and 469 live births; only 53 pregnancies exposed to cancer chemotherapy agents)	Case-control	adjOR	exposed <once weekly		
		Case-control	adjOR	exposed ≥once weekly	12	
Lawson, 2012	Nurses' Health Study II, 1993-2002, US ♀ (775 SAB and 6,707 live births)	Cohort (Retrospective)	adjOR	exposed in 1st trimester ≥1 hour per day	48	
Peelen, 1999	Oncology nurses, The Netherlands, 1990-1997, ♀ (249 exposed and 1,010 unexposed pregnancies)	Cross-sectional	OR	exposed	18	
Selevan, 1985	Nurses, 1973-1980, Finland, ♀ (124 cases, 321 live births)	Case-control	adjOR	exposed in 1st trimester	18	
Skov, 1992	Oncology nurses, 1977-1988, Denmark, ♀ (281 exposed and 809 unexposed pregnancies)	Cohort (Retrospective)	adjOR	exposed	18	
		Cohort (Retrospective)	adjOR	exposed (not handling antineoplastic agents)	3	
		Cohort (Retrospective)	adjOR	exposed (low)	4	
		Cohort (Retrospective)	adjOR	exposed (intermediate)	3	
		Cohort (Retrospective)	adjOR	exposed (high)	5	
Stücker, 1990	Nurses in 4 hospitals, France, 1985-1986, ♀ (466 women; 139 SAB and 357 live births)	Cross-sectional	adjPR	exposed	36	
Taskinen, 1986	Pharmaceutical industry workers, 1973-1980, ♀ (44 cases,130 live births; only 6 pregnancies exposed to cancer chemotherapy agents)	Case-control	OR	exposed	3	
Taskinen, 1994	Laboratory assistants, Finland, 1970-1986, ♀ (206 cases, 329 live births; only 8 pregnancies exposed to cancer chemotherapy agents)	Case-control	adjOR	exposed	5	
Valanis, 1999	Nurses, nurse's aides, pharmacists, and pharmacy technicians, US, 1988-1989, ♂♀ (1,448 exposed and 5,297 unexposed pregnancies)	Cross-sectional	adjOR	exposed during pregnancy (no adjustment for prior exposure)	223	

Legend: ● estimate; ● estimate, significant. X-axis: 0.1 – 1 – 10 – 100, Estimate ± 95% CI

B

Study	Description of exposed workers	Study design	Exposure status	N of exposed cases	Spontaneous abortion
ElShamy 2010	Oncology nurses, Egypt, 2006, ♀ (35 exposed, 29 unexposed)	Cross-sectional	control nurses	3	
			oncology nurses	8	
Walusiak, 2003	Physicians, nurses, orderlies, Poland, ♂♀ (84 exposed, 169 unexposed)	Cross-sectional	control	9	
			exposed	7	
Zhang, 2016	Oncology nurses, China, ♀, (Pre-PIVAS: 106 unexposed, 30 exposed non-oncology, 82 exposed oncology)	Cross-sectional	Unexposed (Hospital A, before PIVAS)	10	
			Exposed (non-oncology department, Hospital A, before PIVAS)	6	
			Exposed (Oncology, Hospital A, before PIVAS)	12	
Zhang, 2016	Oncology nurses, China, ♀ (Post-PIVAS: 108 unexposed; exposed: 29 non-oncology, 87 oncology; 112 exposed oncology (Hospital B))	Cross-sectional	Unexposed (Hospital A, after PIVAS)	3	
			Exposed (non-Oncology department, Hospital A, after PIVAS)	2	
			Exposed (Oncology department, Hospital A, after PIVAS)	4	
			Exposed (Oncology department, Hospital B, no PIVAS)	25	

Legend: ▲ reference; ● estimate; ● estimate, significant; ▼ estimate, significant vs oncology nurses pre-PIVAS; ■ estimate, significant vs oncology nurses post-PIVAS. X-axis: 0 2 4 6 8 10 12 14 16 18 20 22 24 26, % pregnancies affected

Figure D-1. Spontaneous Abortion Associated with Occupational Exposure to Cancer Chemotherapy Agents Reported as (A) Odds Ratio or (B) Percent of Pregnancies Affected

Interactive figure and additional study details in HAWC (NTP, 2015a). Reference line is indicated as a vertical, blue dotted line in A. Fransman 2007 refers to Fransman et al. (2007c). Number of cases for Valanis et al. (1999) include the spouses of exposed male employees; however, the data graphed are pregnancy outcomes of exposed female employees only. Three studies are not

graphed: McDonald et al. (1988b) reported that oncology nurses handling antineoplastic drugs had similar rates of spontaneous abortion compared to control subjects (observed versus expected ratio = 0.97), Medková (1991b) reported a higher number of early spontaneous abortions in exposed medical personnel (8 of 74 pregnancies) compared to unexposed spouses of medical personnel (0 of 11 pregnancies), and Schaumburg and Olsen (1990b) observed no spontaneous abortions among eight pregnancies of exposed pharmacy assistants.
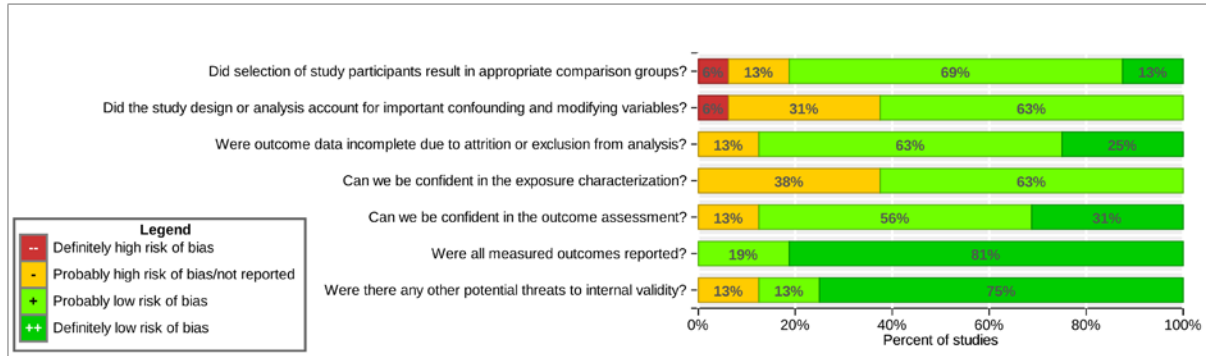
Figure D-2. Risk-of-bias Bar Graph for Studies Reporting Spontaneous Abortions

Interactive figure and additional study details in HAWC (NTP, 2015a).
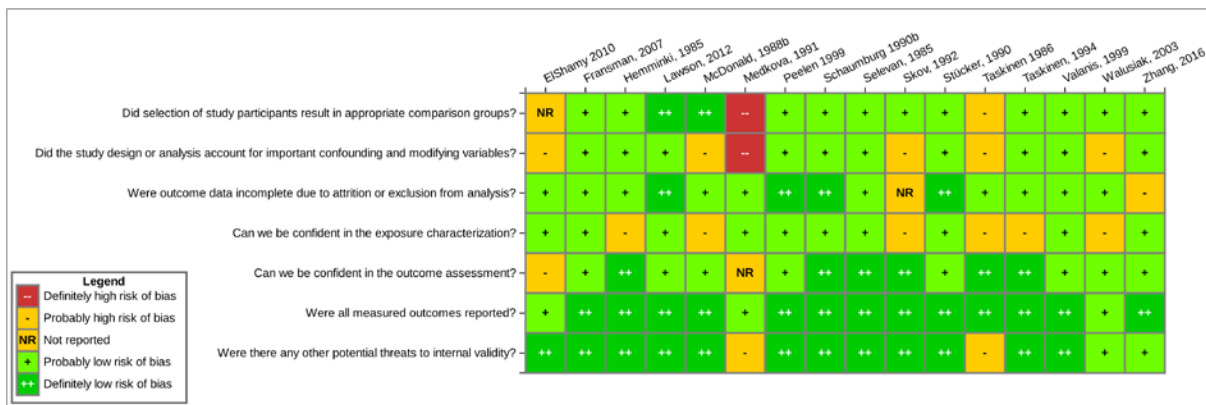
Figure D-3. Risk-of-bias Heat Map for Studies Reporting Spontaneous Abortions

Interactive figure and additional study details in HAWC (NTP, 2015a). Fransman 2007 refers to Fransman et al. (2007c).
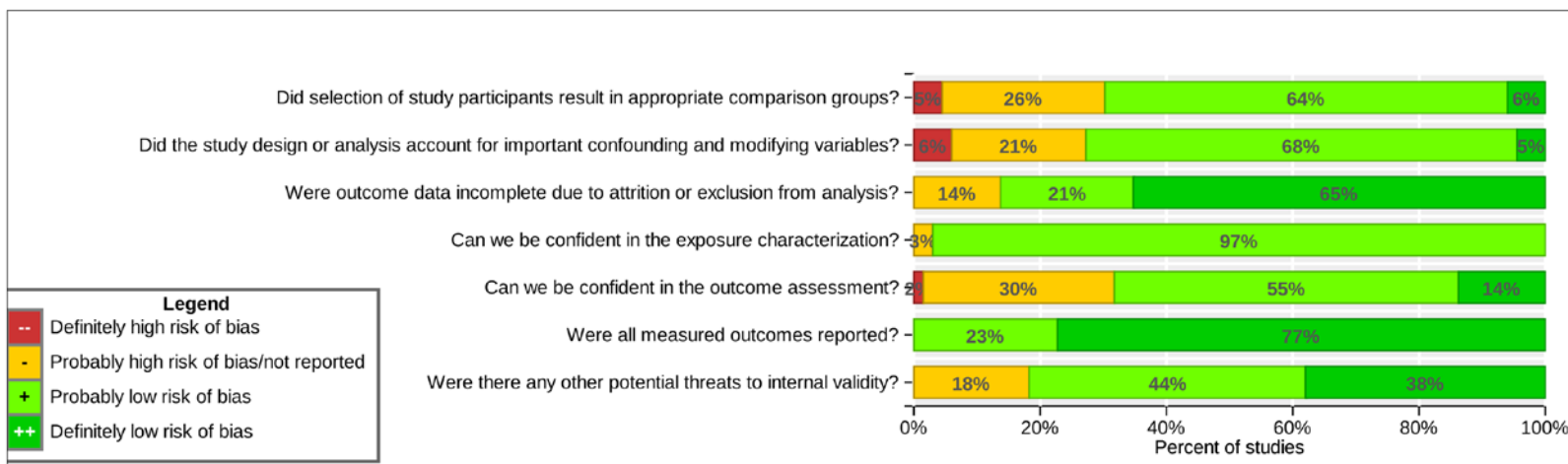
Figure D-4. Risk-of-bias Bar Graph for All Included Studies Reporting on Genetic Toxicity Outcomes of Structural Chromosomal Aberrations, Micronucleus Induction, and DNA Damage Measured by the Comet Assay

Interactive figure and additional study details in HAWC (NTP, 2015a).
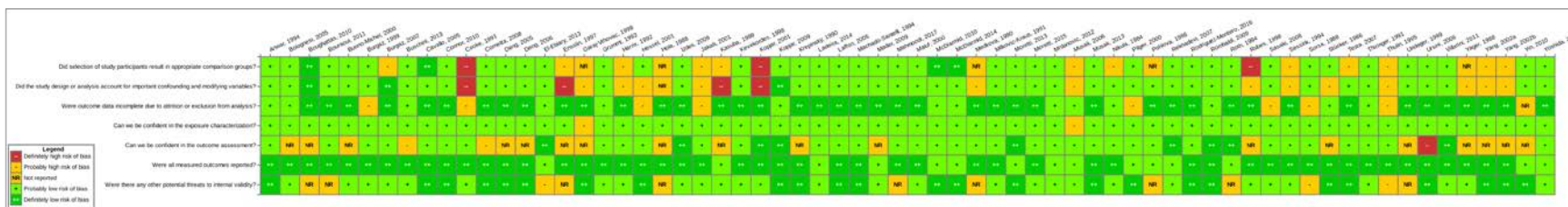
Figure D-5. Risk-of-bias Heat Map for All Included Studies Reporting on Genetic Toxicity Outcomes of Structural Chromosomal Aberrations, Micronucleus Induction, and DNA Damage Measured by the Comet Assay

Interactive figure and additional study details in HAWC (NTP, 2015a).

A
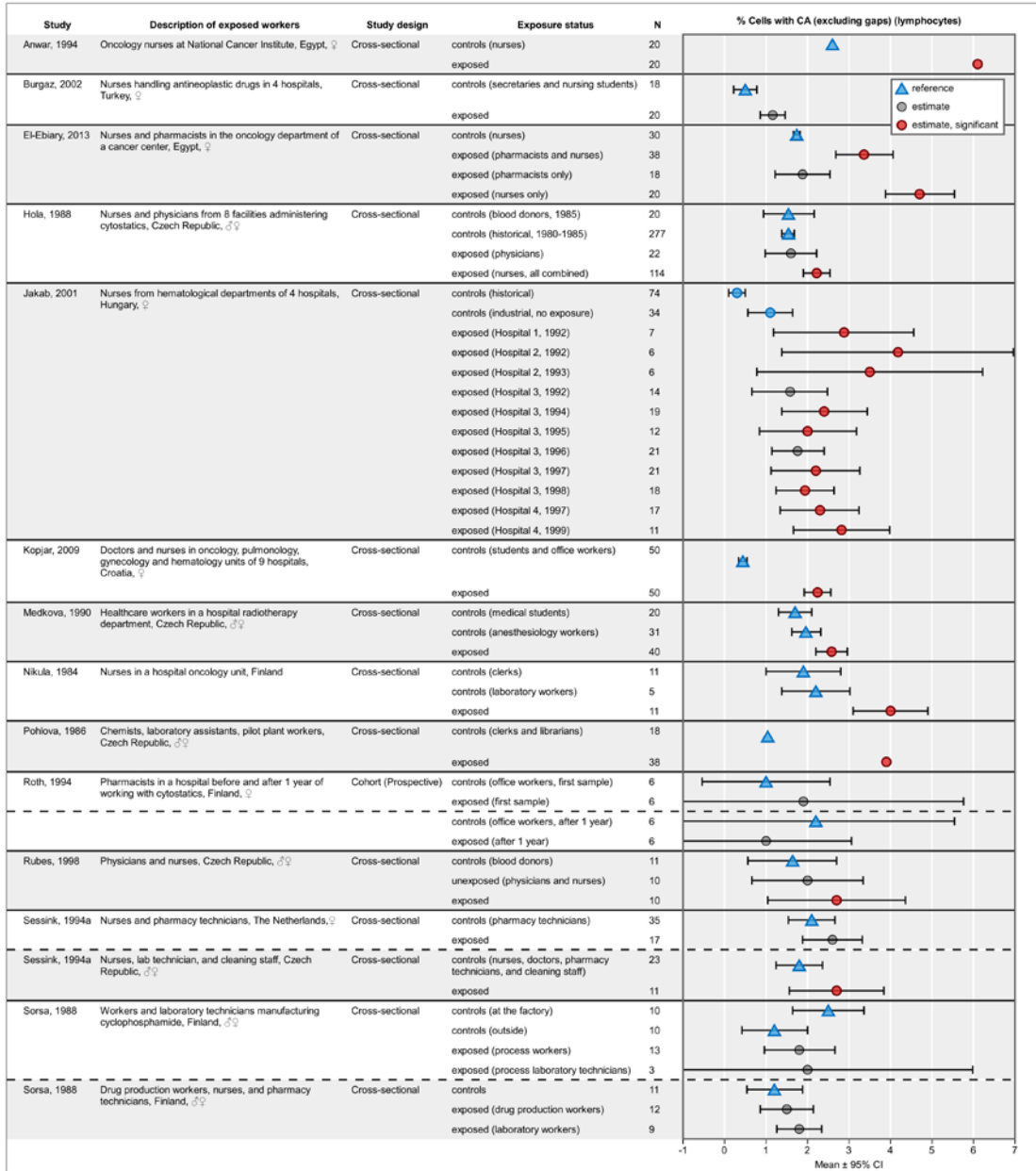
B
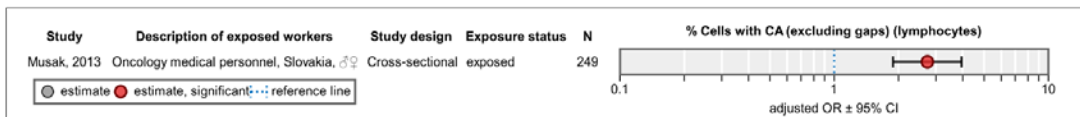
Figure D-6. Percent of Lymphocytes with Structural Chromosomal Aberrations (Excluding Gaps) Associated with Occupational Exposure to Cancer Chemotherapy Agents Presented as (A) Mean Values or (B) Adjusted Odds Ratio

Interactive figures and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population. In part B, reference line indicated by blue, dotted line.
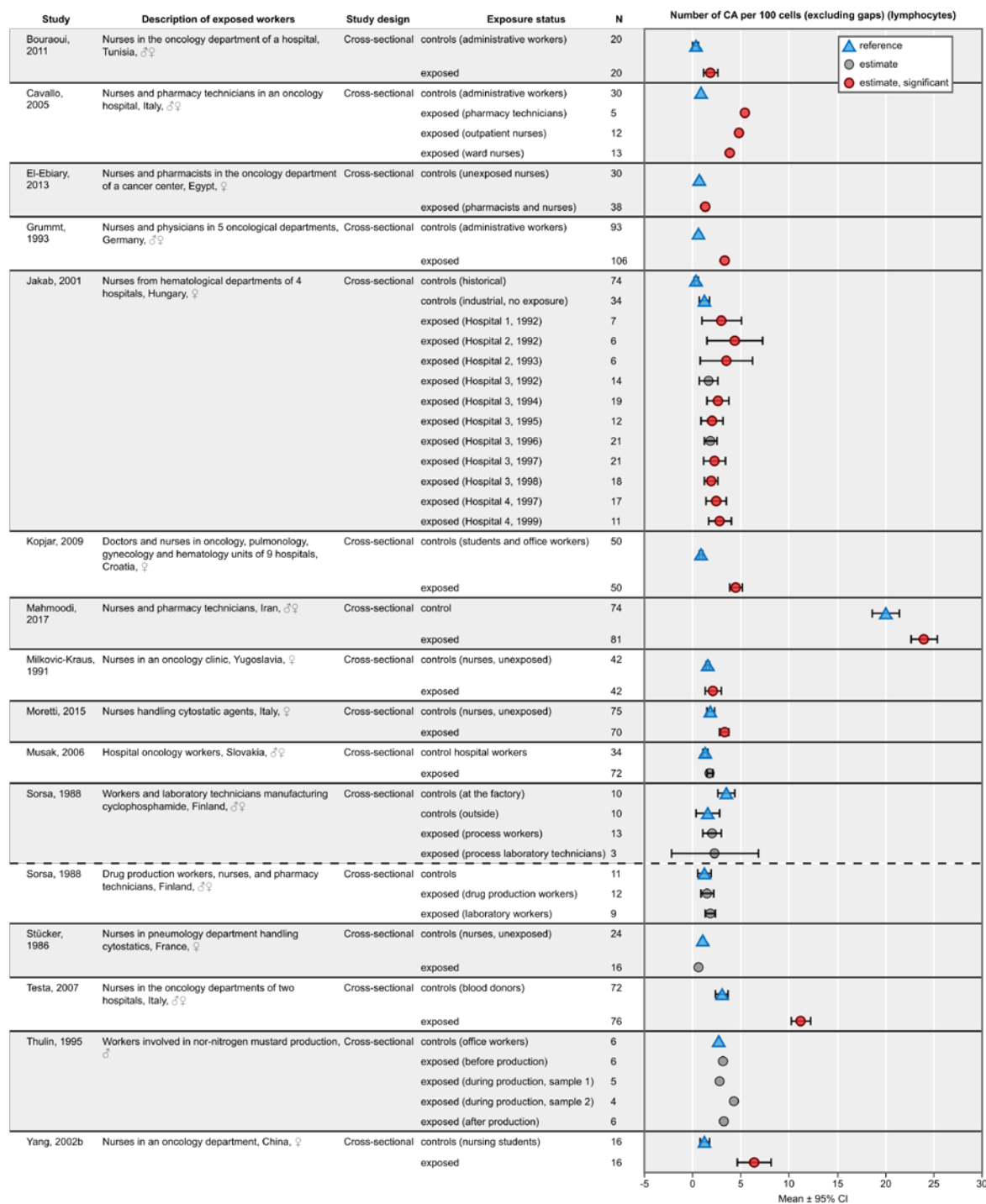
Figure D-7. Number of Chromosomal Aberrations (Excluding Gaps) per 100 Lymphocytes Scored Associated with Occupational Exposure to Cancer Chemotherapy Agents

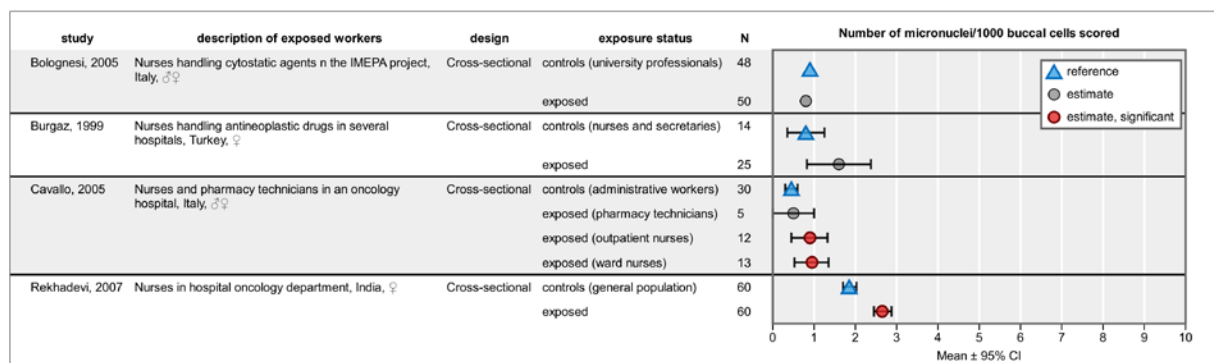Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population. Two studies reporting no difference between exposed and unexposed subjects do not appear on the figure because the authors did not report the data values in the publication (Krepinsky et al. 1990) or the reported data were log-transformed and thus could not be included on the same graph with remainder of the data (Cooke et al. 1991).
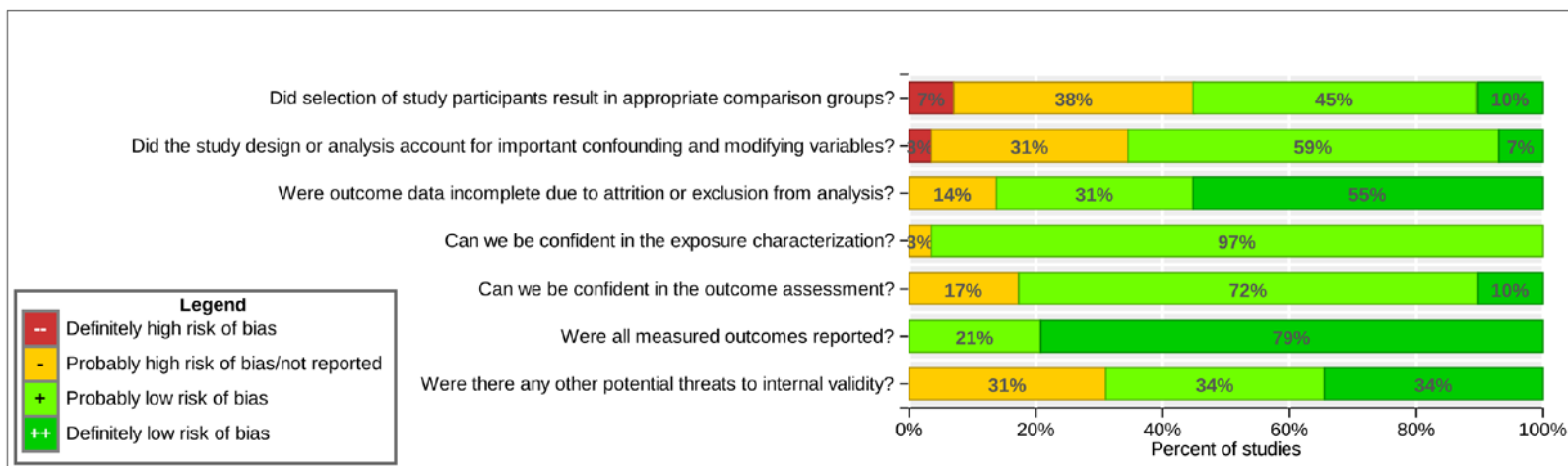
Figure D-8. Risk-of-bias Bar Graph for All Included Studies Reporting on Structural Chromosomal Aberrations

Interactive figure and additional study details in HAWC (NTP, 2015a).
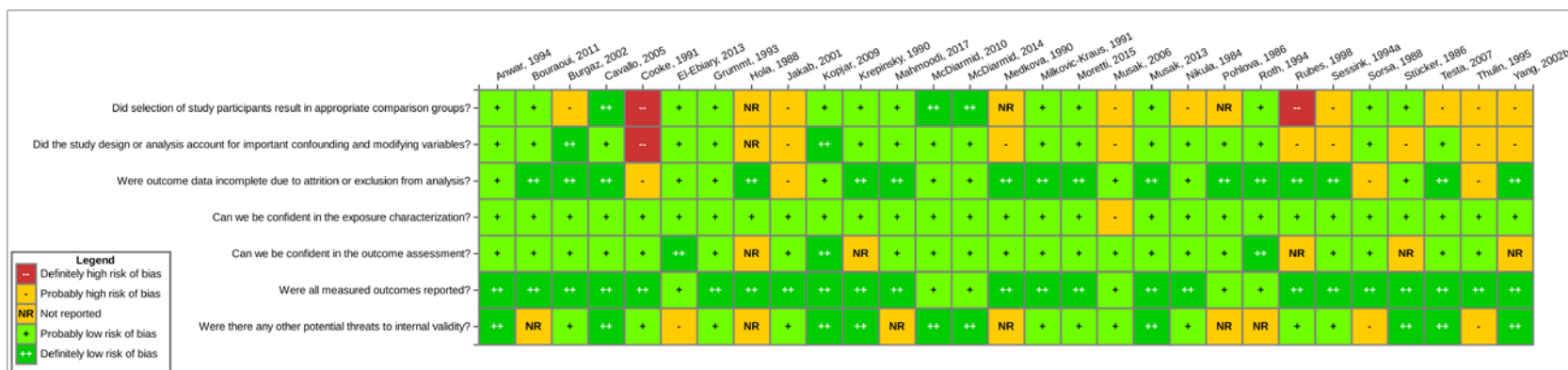
Figure D-9. Risk-of-bias Heat Map for All Included Studies Reporting on Structural Chromosomal Aberrations

Interactive figure and additional study details in HAWC (NTP, 2015a).

A
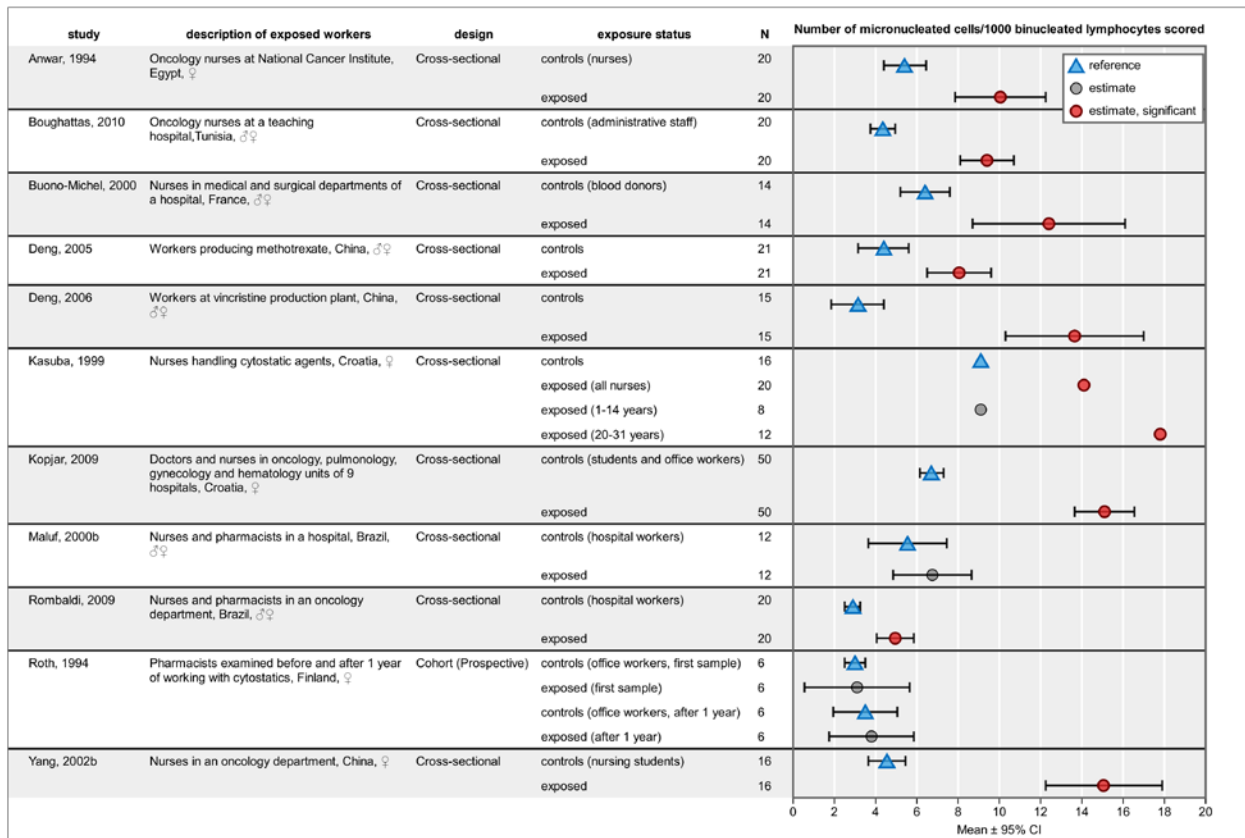
B
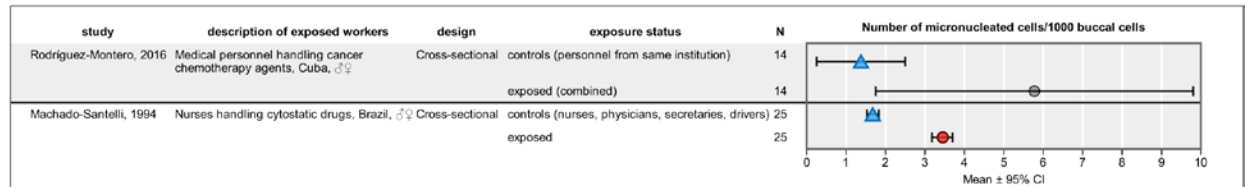
Figure D-10. Number of Cells with Micronuclei/1,000 Cells Scored Associated with Occupational Exposure to Cancer Chemotherapy Agents for (A) Binucleated Lymphocytes or (B) Buccal Cells

Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population.
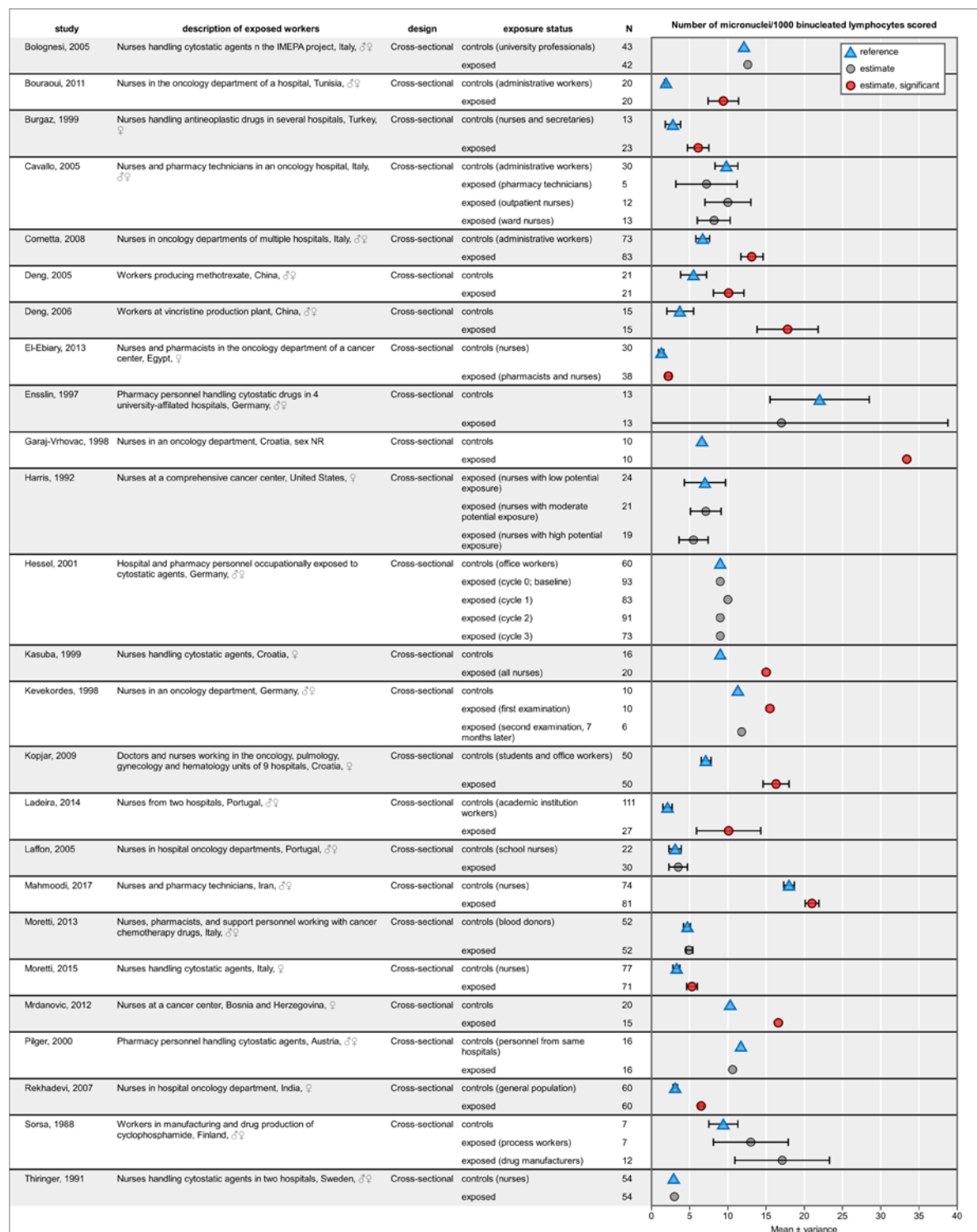
Figure D-11. Number of Micronuclei/1,000 Cells Scored Associated with Occupational Exposure to Cancer Chemotherapy Agents for Binucleated Lymphocytes

Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population. An additional study of production workers handling cyclophosphamide reported a significantly (p < 0.05) higher mean log-transformed number of MN/1,000 cells scored in an ANOVA adjusting for age differences (data not shown) (Yager et al. 1988).
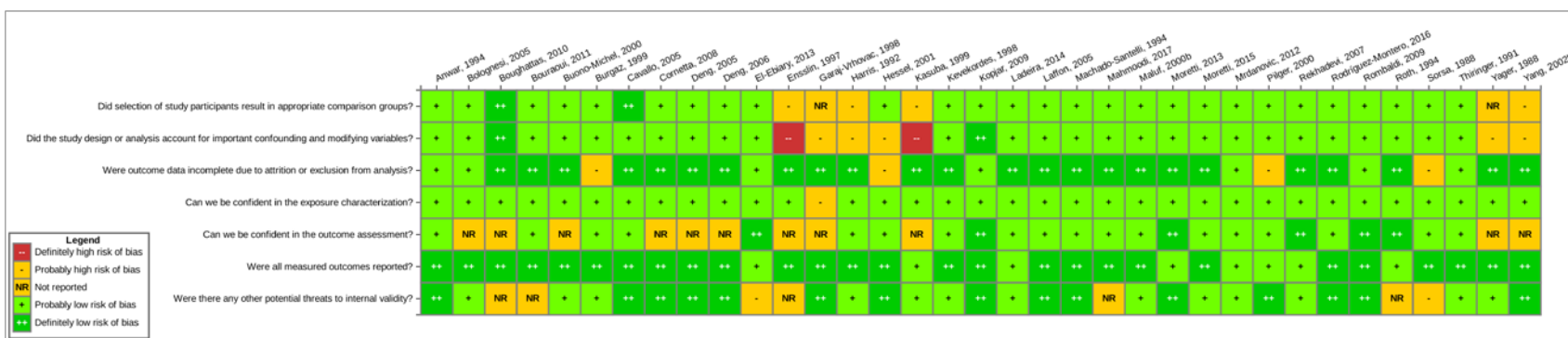
Figure D-12. Number of Micronuclei/1,000 Cells Scored Associated with Occupational Exposure to Cancer Chemotherapy Agents for Buccal Cells

Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population.
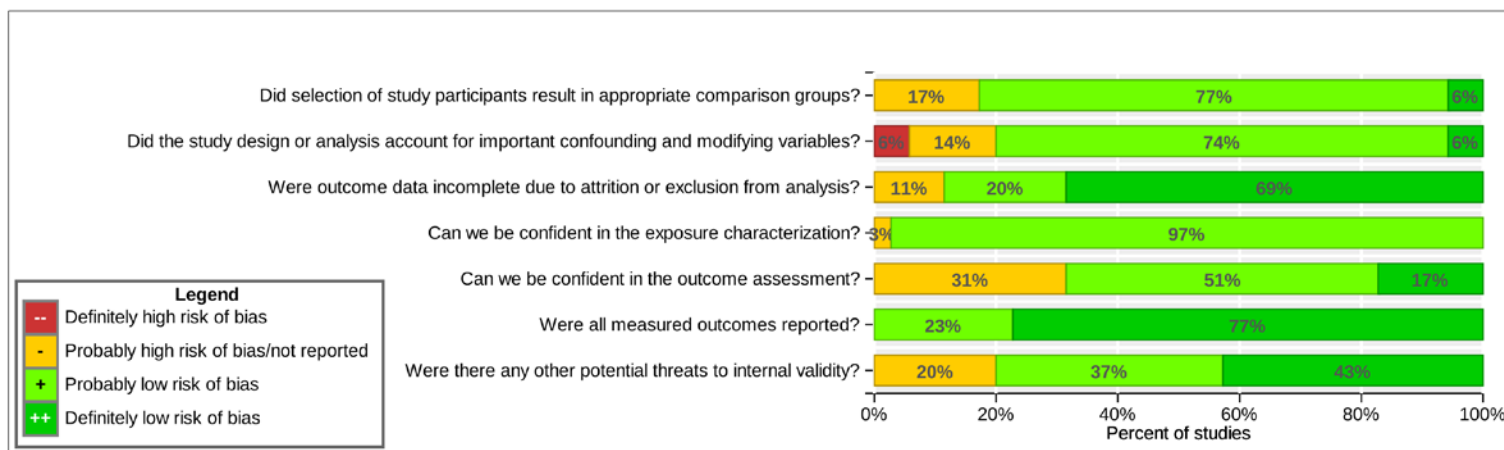
Figure D-13. Risk-of-bias Bar Graph for Included Studies Reporting on Micronucleus Induction

Interactive figure and additional study details in HAWC (NTP, 2015a).

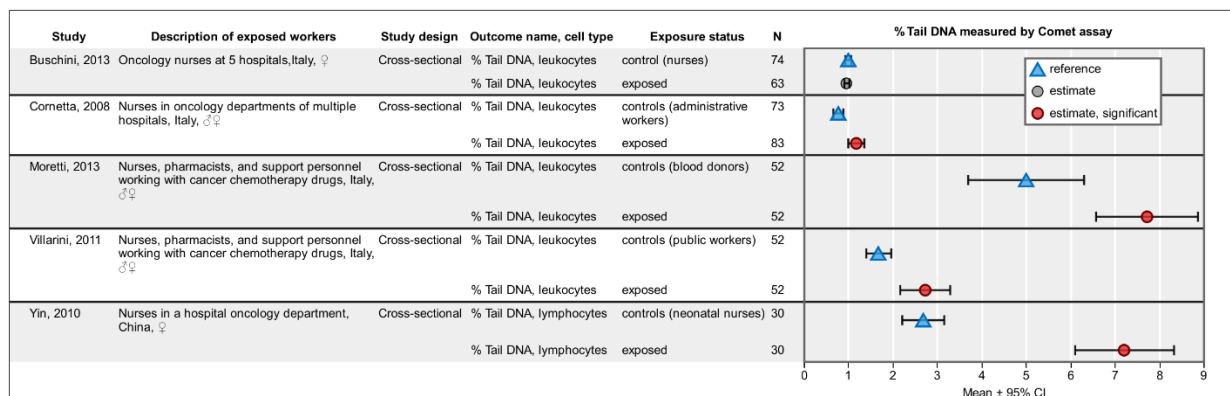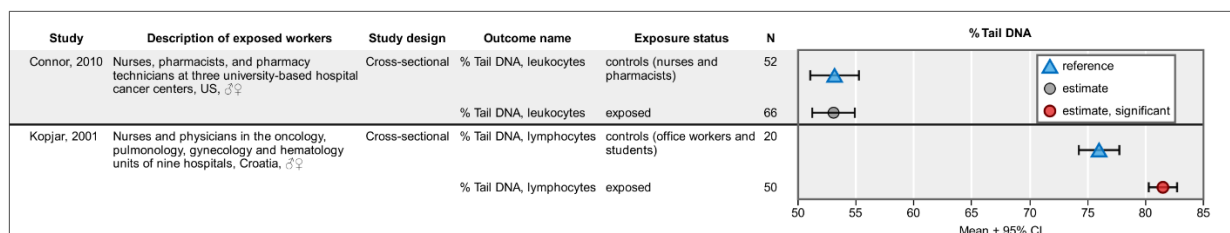**Figure D-14. Risk-of-bias Heat Map for Included Studies Reporting on Micronucleus Induction**

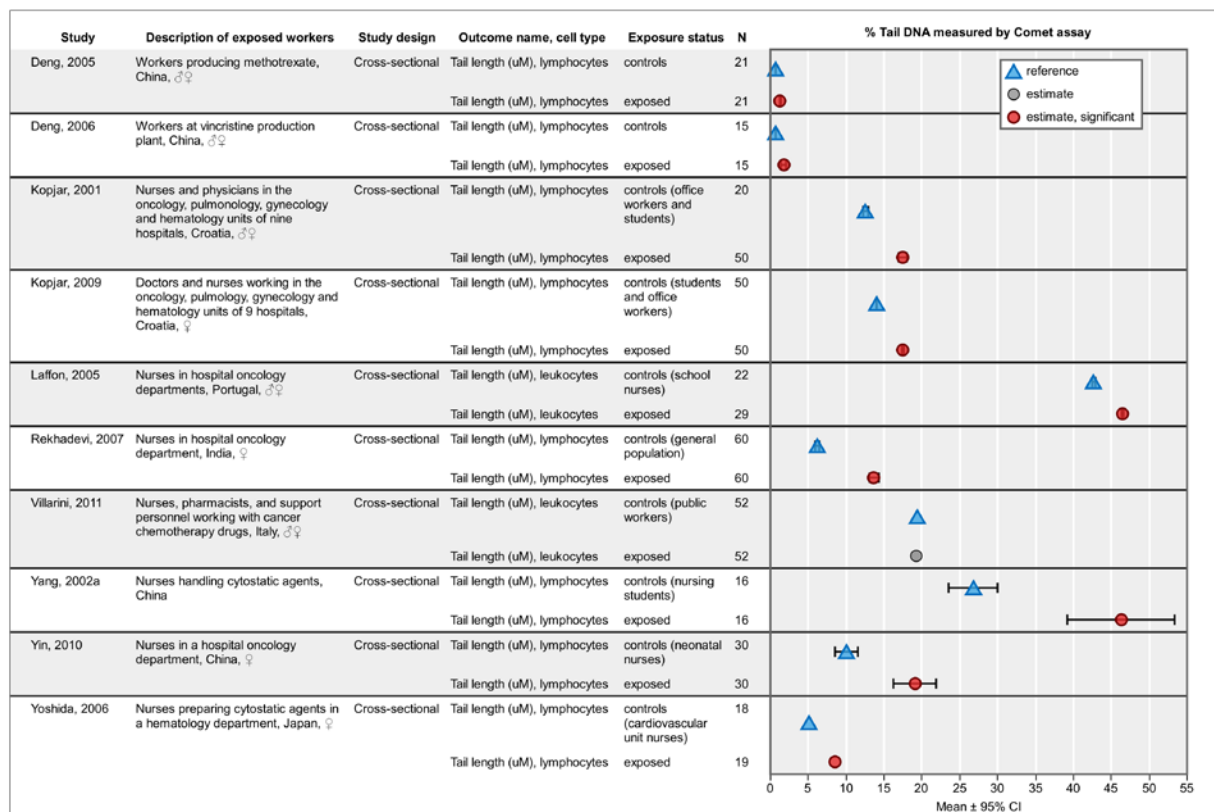Interactive figure and additional study details in HAWC (NTP, 2015a).

A

B

Figure D-15. Percent of Tail DNA Measured by the Comet Assay Associated with Occupational Exposure to Cancer Chemotherapy Agents for (A) Studies Reporting Values in the Expected Range and (B) Studies Reporting Higher than Expected Values

Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population.
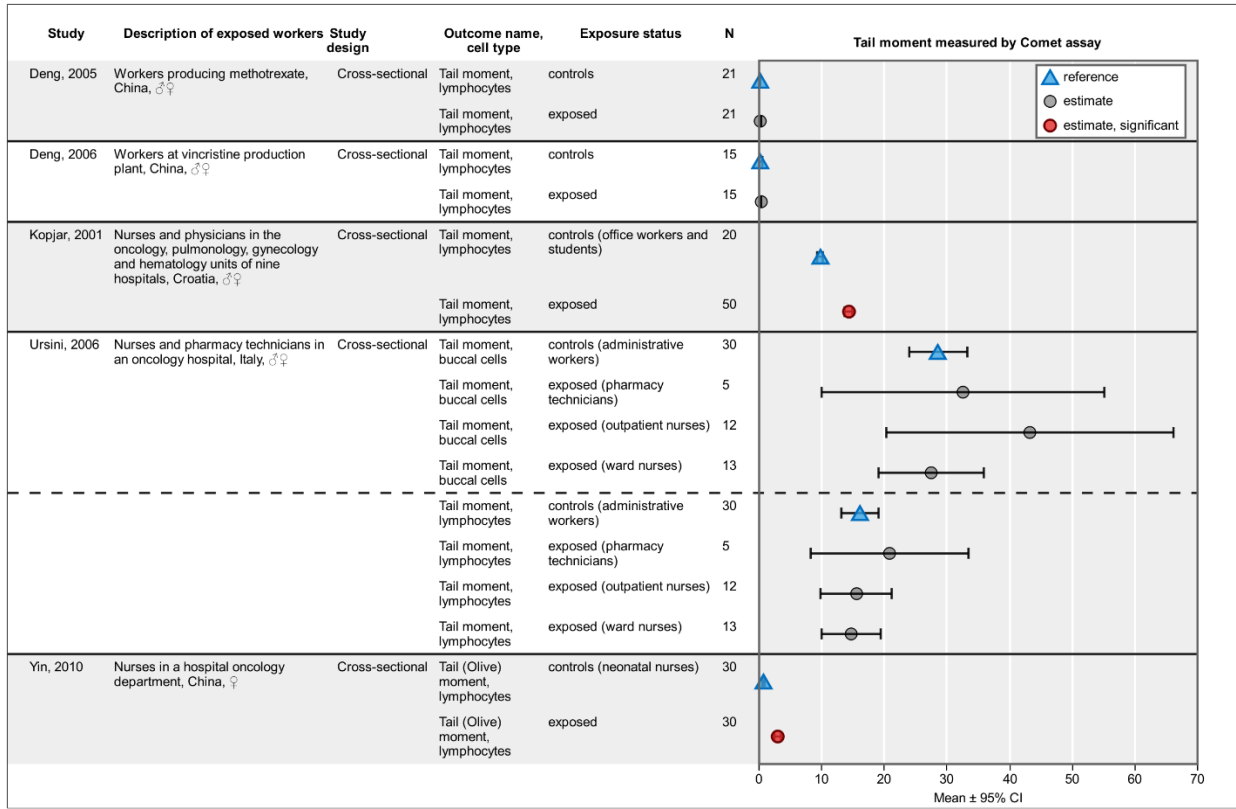
Figure D-16. Tail Length (μm) Measured by the Comet Assay Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population. An additional study reported a greater log-transformed mean tail length (μm) in exposed nurses than controls following adjustment for age, smoking, coffee-drinking habits, hemoglobin, ionizing radiation, and hospital (data not graphed) (Sasaki et al. 2008).

A

B

Figure D-17. Tail Moment Measured by the Comet Assay Associated with Occupational Exposure to Cancer Chemotherapy Agents for (A) Studies in the Expected Range and (B) Studies in Higher than the Expected Range
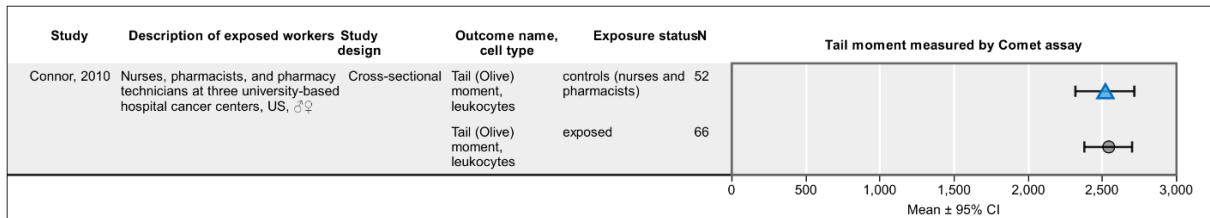
Interactive figure and additional study details in [HAWC](#) (NTP, 2015a). Controls refer to the unexposed, reference population. An additional study reported similar values of log-transformed mean tail moment in exposed nurses and controls following adjustment for age, smoking, coffee-drinking habits, hemoglobin, ionizing radiation, and hospital (data not graphed) (Sasaki et al. 2008).
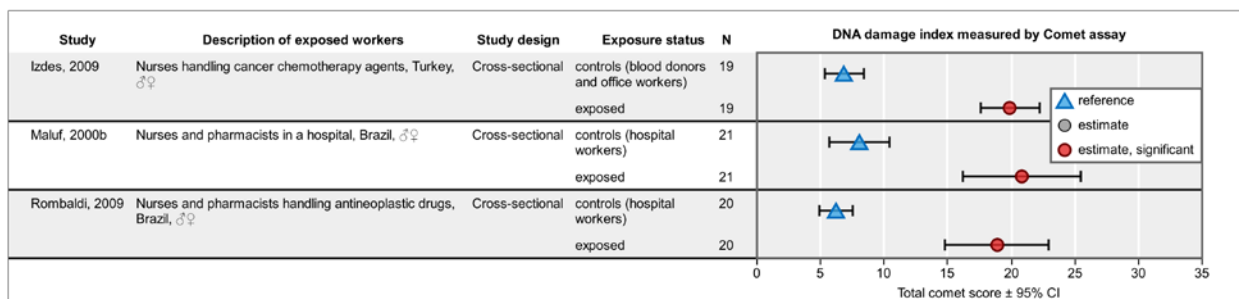
A

B
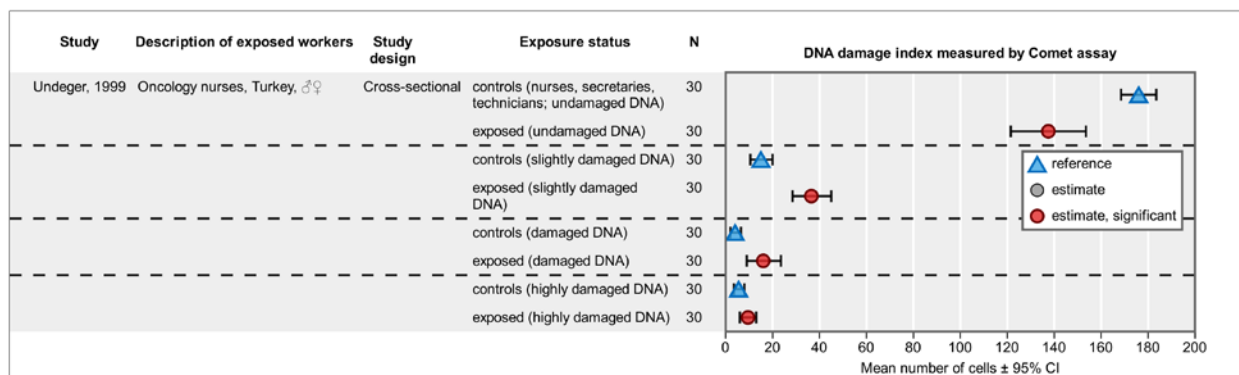
Figure D-18. DNA Damage Index Measured by the Comet Assay Associated with Occupational Exposure to Cancer Chemotherapy Agents Reported as (A) Mean Comet Score or (B) Mean Number of Cells

Interactive figure and additional study details in HAWC (NTP, 2015a). Controls refer to the unexposed, reference population. The mean comet scores (A) were calculated by binning the cells per category of DNA damage and multiplying the number of cells per category by a number per the level of DNA damage and summing up the numbers across the categories (see individual studies for more details). In addition, Mader et al. (2009) reported that a trend analysis for the entire observation period revealed a significantly greater (p = 0.02) genotoxicity in the alkaline comet assay compared to unexposed subjects; no means or standard deviations were provided (data not graphed).
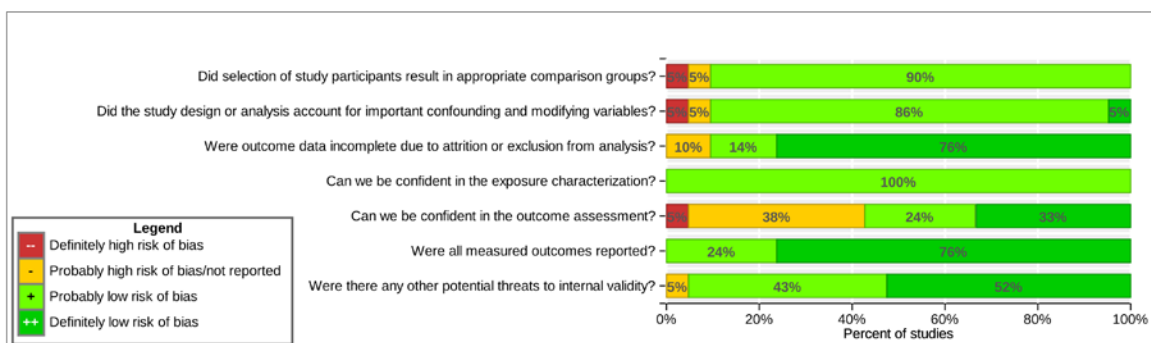
Figure D-19. Risk-of-bias Bar Graph for Included Studies Reporting DNA Damage Measured by the Comet Assay

Interactive figure and additional study details in HAWC (NTP, 2015a).
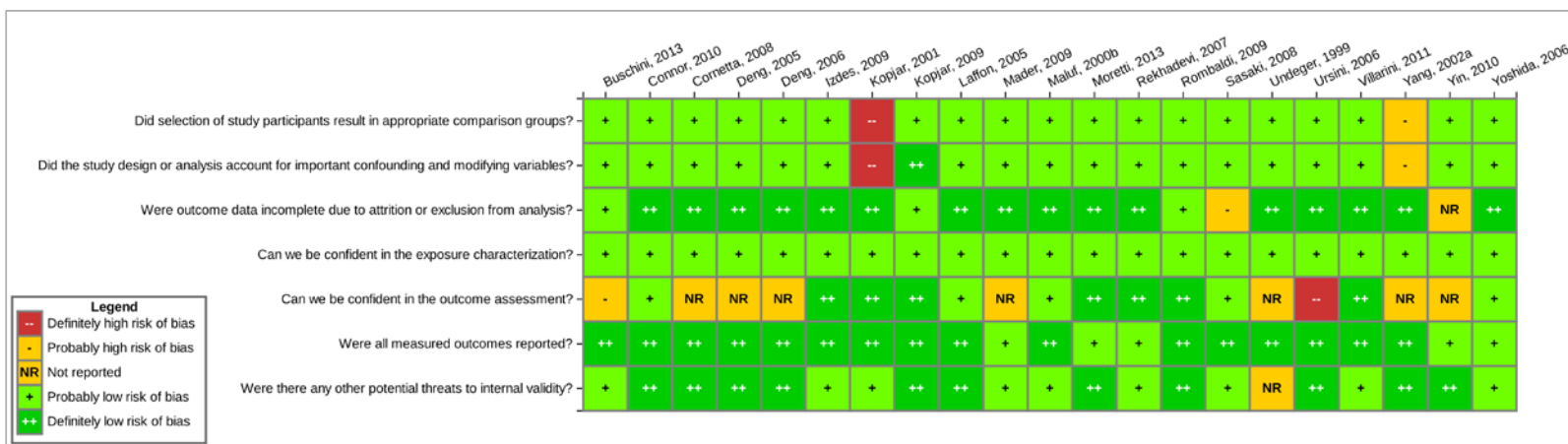
Figure D-20. Risk-of-bias Heat Map for Included Studies Reporting DNA Damage Measured by the Comet Assay

Interactive figure and additional study details in HAWC (NTP, 2015a).

Appendix E. Inadequate Evidence: Evidence Synthesis and Risk-of-bias Assessment

Table of Contents

Tables

Figures

E.1. Acute Effects

The NTP evaluation identified nine cross-sectional studies reporting on acute health effects potentially associated with occupational exposure to cancer chemotherapy (Krstev et al. 2003; Medková 1991a; Rogers and Emmett 1987; Shahrasbi et al. 2014; Valanis et al. 1987; Valanis et al. 1993a; 1993b; Walusiak et al. 2003; Zhang et al. 2016). Acute effects are defined as health effects that develop rapidly, and these effects are often transient in nature and subside when the subject is no longer exposed. Given the wide range of symptoms that could be included under this category, there was a high degree of heterogeneity in type of effects reported, which limited the ability to compare across studies.

Summary: Based on the available studies, there is *very low confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with the incidence of acute effects (Table E-1). There was a high degree of heterogeneity in the outcome assessment (i.e., symptoms evaluated), which resulted in few effects evaluated across all studies and the studies that evaluated related endpoints as a group reported mixed evidence of potential effects. For example, fewer than half of the studies that examined dermatological endpoints (e.g., skin rash, skin irritation or eczema) were significantly higher in exposed subjects versus controls (three of eight studies). Other examples of acute effects included significantly higher rates of hair loss reported in five of eight studies and significantly greater incidence of headache reported in four of six studies in exposed subjects relative to controls. The final rating of very low confidence in the body of evidence reflects downgrading for serious risk-of-bias concerns across multiple key risk-of-bias questions (e.g., majority of studies were rated probably high risk of bias for confounding, exposure characterization, and outcome assessment) (Figure E-1 and Figure E-2).

Table E-1. Studies Reporting on Acute Effects

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results
Krstev et al. (2003)	Cross-sectional (Nurses in 8 hospitals, Serbia, year NR, F)	186 exposed, 77 unexposed	Job title and self-reported questionnaire; head nurses reported on work practice and work conditions *Note: One hospital had a vertical laminar [flow] biological safety cabinet, and some concerns about its maintenance; none of the hospitals had a separate room for drug preparation; gloves were used by 81.7% of exposed nurses for drug preparation and by 60.1% for drug administration*	Self-reported questionnaire	2x2 table statistics used to compute relative risk (RR); unconditional logistic regression analysis used to adjust for confounders: age (≤35 and ≥36 years old), smoking status (smokers versus non-smokers and ex-smokers), and shift work (daily shift vs. rotating shift with night work)	Prevalence of several symptoms assessed: (*significantly higher OR compared to unexposed after adjustment for age, smoking and shiftwork) Hair loss*, skin rash*, eczema*, skin flush*, light headedness*, nausea*, dizziness*, vomiting, eye irritation, diarrhea, nasal congestion and runny nose, headache, insomnia, menstrual dysfunction, disappearance of symptoms during the weekend*, mean number of symptoms overall* and by frequency of exposure (daily ≥ weekly > monthly)*
Medková (1991a)	Cross-sectional (Physicians, nurses, auxiliary workers, Czech Republic, FM)	44 exposed, 32 unexposed partners of exposed subjects	Job title and interviewer-led questionnaire (≥5 years, n = 25; 6–10 years, n = 14; 11–15 years, n = 4; and 16–20 years, n = 1) *Note: All exposed personnel used gloves and gowns; isolated room for drug preparation only used by 25% of exposed subjects*	Interviewer-led questionnaire	NR	No difference in prevalence of dermatological afflictions (including eczema) compared to unexposed subjects

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results
Rogers and Emmett (1987)	Cross-sectional (Nurses in Oncology Nursing Society, United States, year NR, F)	59 exposed, 64 unexposed community health nurses	Job title and interviewer-led questionnaire *Note: Percent of nurses using PPE all the time was: 5% for masks, 8% for gowns, 20% for gloves; laminar flow hoods were not used*	Interviewer-led questionnaire	[Chi-squared test]	Prevalence of 21 symptoms was assessed, but authors did not report on all the outcomes; significantly higher prevalence ($p \leq 0.02$) of abdominal pain, hair loss, and headaches on a daily or weekly basis compared to unexposed; skin rash tended ($p = 0.06$) to be more frequently reported compared to unexposed nurses
Shahrasbi et al. (2014)	Cross-sectional (Nurses at 9 professional and specialized cancer hospitals, Iran, year NR, FM)	225 exposed nurses, unexposed nurses from non-oncology wards [number NR]	Job title and self-reported questionnaire *Note: Exposed nurses were working for ≥6 months in oncology ward; they used vertical flow laminar flow biological safety cabinets; PPE was available but not regularly used*	Self-reported, validated questionnaire	NR	Prevalence of several symptoms assessed: (*significantly higher compared to unexposed nurses) hair loss*, irritation of mucous membranes, eye irritation, skin irritation*, dizziness, headache, nausea and vomiting*

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results
Valanis et al. (1987)	Cross-sectional (Hospital nurses, United States, 1982–1984, sex NR)	134 exposed: 51 prepared and administered the drugs, 39 only administered the drugs, and 44 handled patient excreta; 43 unexposed nurses	Job title and self-reported, validated questionnaire (duration NR) *Note: 65% of exposed nurses used gloves during drug preparation and 45% during administration of drugs; skin contact occurred on at least half of drug-handling events for 18% of exposed nurses during drug preparation and 25% during administration of drugs; gowns, goggles and masks were rarely used*	Self-reported questionnaire	Chi-square test for prevalence of individual acute symptoms; ANOVA or t-test, as appropriate, for mean number of symptoms or total symptoms of acute symptoms grouped into one of 5 body systems	Prevalence of 27 acute effects experienced in past 3 months: (*significantly higher compared to unexposed nurses) **Cardiac related**: shortness of breath, irregular heartbeat, swelling, elevated blood pressure, chest pain; **Infection related***: chronic cough*, sore throat*, throat/sinus irritation, viral/other infection*; **Gastrointestinal***: nausea and vomiting*, diarrhea, severe constipation, colicky abdomen, abdominal pain; **General systemic***: dizziness*, headache*, insomnia, pain on urination, hair loss, nail hyperpigmentation; **Allergic***: allergic reactions, dermatitis, eye irritation*; **Miscellaneous**: fainting, anorexia, back pain, other pain; significantly higher mean total symptoms for high exposure and lack of glove use compared to unexposed nurses

| Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results
Valanis et al. (1993a)	Cross-sectional (Nurses and nurse aides in National Surgical Adjuvant Breast and Bowel Project (NSABP), USA, 1988–1990, F)	1,346 exposed (283 skin contact, 1,063 no skin contact), 738 unexposed	Job title and self-reported, validated questionnaire (duration NR) *Note: 92% of exposed nurses used gloves: during drug preparation, 82% during administration of drugs, 89% while cleaning up spills, and 75% when handling patient excreta; masks and goggles primarily during drug preparation; gowns worn only during drug preparation and cleaning up spills*	Self-reported questionnaire, effects observed during the preceding 3 months	Multiple linear regression for total number of symptoms analyzed effects of dose, duration, use of protection, and skin exposure and factors of age, smoking status, stress at work, and body mass index; likelihood ratio tests compared the goodness of fit of competing models, and large sample maximum likelihood theory computed confidence limits and p-values for specific parameter estimates; logistic regression modelled the effects of exposure and control variables	Prevalence of 27 acute effects experienced in past 3 months: (*significantly higher compared to unexposed subjects) **Cardiac:** shortness of breath, irregular heartbeat, swelling of hands and feet, chest pain, elevated blood pressure; **Infectious:** chronic cough, chronic throat irritation, cough when lying down, fever; **Gastrointestinal:** loss of appetite, nausea, vomiting, diarrhea, colicky abdomen, constipation; **General systemic:** hair loss, nail hyperpigmentation, pain on urination, decreased libido, malaise; **Allergic:** allergic reactions, eye irritation, rash; **Neurological:** headache, dizziness, fainting, insomnia; no difference in the prevalence of acute effects compared to unexposed subjects; however exposed, nurses with skin exposure tended (p = 0.07) to have more acute effects in every category than exposed nurses without skin exposure, except neurological symptoms
Valanis et al. (1993b)	Cross-sectional (Pharmacists and pharmacy technicians in NSABP, USA, 1988–1990, FM)	533 exposed, 205 unexposed	Job title and self-reported, validated questionnaire (duration NR) *Note: Exposed pharmacy personnel used gloves at least 75% of the time when handling drugs*	Self-reported questionnaire, effects observed during the preceding 3 months	Same analysis as Valanis 1993a	Prevalence of 27 acute effects experienced in past 3 months same as Valanis 1993a: significantly higher prevalence of chronic throat irritation* and diarrhea* compared to unexposed; skin contact with cancer chemotherapy agents was a significant factor for mean total symptoms or organ system subgroups

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results
Walusiak et al. (2003)	Cross-sectional (Physicians, nurses, orderlies, year NR, Poland, FM)	103 exposed, 104 unexposed	Job title and self-reported questionnaire (11.0 ± 9.3 years)	Self-reported questionnaire	Mann-Whitney U-test	Prevalence the following acute effects: (*significantly higher compared to unexposed subjects) accelerated hair loss*, changes in the fingernails (fragility, brittleness, wrinkling), dermal changes (bleed/bruising tendency), digestive tract bleeding, and skin symptoms (allergic or other etiology)
Zhang et al. (2016)	Cross-sectional (Nurses, China, 2011 pre-pharmacy intravenous admixture service (pre-PIVAS) and 2013 (post-PIVAS) in Hospital A, F)	Pre-PIVAS: 176 unexposed, 46 exposed non-oncology, 123 exposed oncology; post-PIVAS: 182 unexposed, 55 exposed non-oncology, 148 exposed oncology, and 190 exposed oncology nurses at Hospital B)	Job title and self-reported questionnaire (≥2 years in current job)	Self-reported questionnaire	[Student] t-test, Chi-square, and Wilcoxon [signed-rank sum] test	Significantly higher (p < 0.01) prevalence of severe hair loss and oral ulcers compared to unexposed nurses in pre- and post-PIVAS studies; however, the post-PIVAS prevalence of these two acute effects were significantly lower than pre-PIVAS values (p < 0.05); however, the post-PIVAS prevalence of oral ulcers was significantly higher than Hospital B without PIVAS

F = female, M = male, NR = not reported, NS = not significant, NSABP = National Surgical Adjuvant Breast and Bowel Project, OR = odds ratio, PIVAS = pharmacy intravenous admixture service.
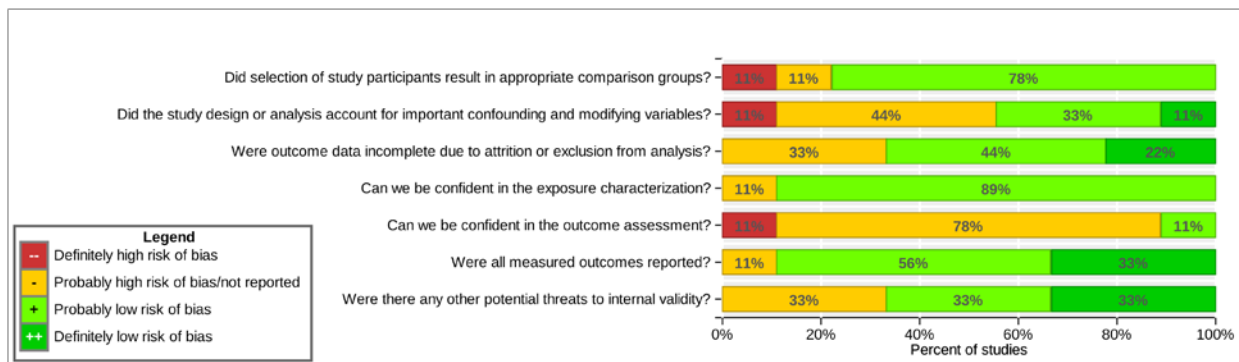
Figure E-1. Risk-of-bias Bar Graph for Studies Reporting on Acute Effects Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).
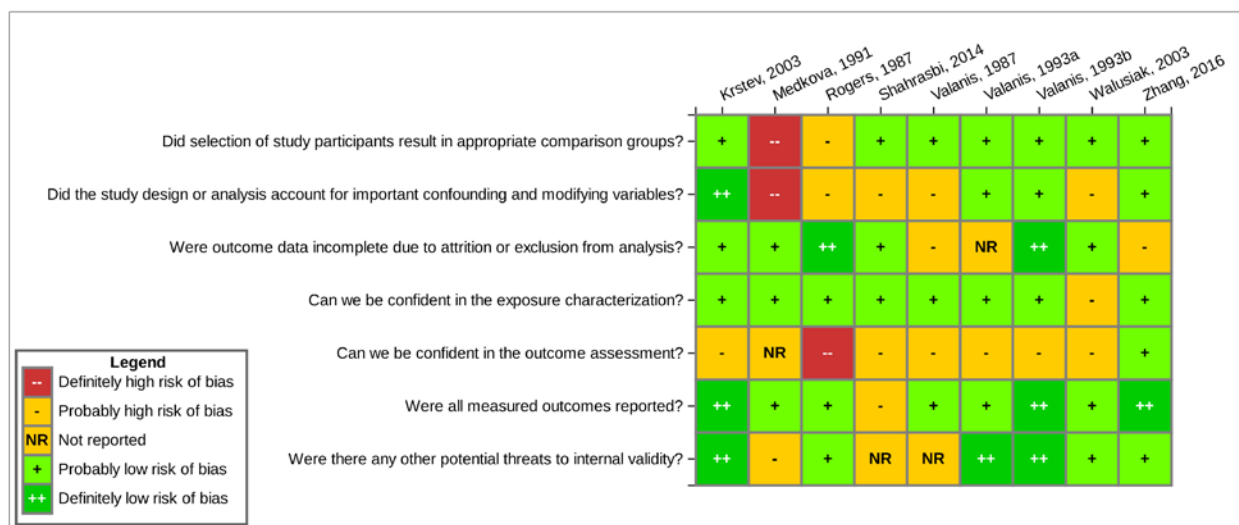
Figure E-2. Risk-of-bias Heat Map for Studies Reporting on Acute Effects Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).

E.2. Cancer

NTP identified three studies reporting on cancer incidence (Gunnarsdóttir et al. 1997; Ratner et al. 2010; Skov et al. 1992). The confidence rating on the body of evidence were based on studies reporting on the cancers most commonly associated with exposure to cancer chemotherapy agents in patients administered the drugs for treatment of cancer: leukemia and/or lymphoma (Cogliano et al. 2011; Mistry et al. 2005; Pedersen-Bjergaard 2005; Pedersen-Bjergaard et al. 2002) as well as urinary bladder (chlornaphazine, cyclophosphamide), lung (MOPP: vincristine-prednisone-nitrogen mustard-procarbazine combination therapy), and skin (azathioprine, nitrogen mustard) (Cogliano et al. 2011). In addition, an elevated risk of breast cancer has been observed in women working as nurses (Gunnarsdóttir and Rafnsson 1995; Lie et al. 2007).

Summary: Based on the available studies, there is *very low confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with cancer. There were very few studies of any one cancer site (Table E-2). For example, only one of two retrospective cohort studies of reporting on leukemia observed a significant association in nurses handling and administering cancer chemotherapy agents (Skov et al. 1992). Also, for some cancers, there were data reporting a lack of effect of exposure from study designs with lower initial confidence ratings (e.g., retrospective cohort studies), which limited the ability to reach level-of-evidence conclusions (e.g., Hodgkin lymphoma) (Ratner et al. 2010; Skov et al. 1992). The final rating of very low confidence in the body of evidence for other cancers reflects downgrading for serious risk-of-bias concerns across multiple key risk-of-bias questions (e.g., majority of studies were rated probably high risk of bias for confounding and exposure characterization) and only one to two available studies per each cancer type (Figure E-3 and Figure E-4).

Table E-2. Studies Reporting on Incidence of Cancer

| Study	Study Design (Occupation, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Measured	Analysis	Results
Gunnarsdóttir et al. (1997)	Nested case-control in a cohort of nurses (Nurses, Iceland, 1955–1979, F)	55 cases and 116 referents [number exposed to cancer chemotherapy agents NR]	National occupational records for Icelandic nurses; telephone-interviews with subjects or next of kin for deceased subjects	National cancer registry	Odds ratio adjusted for year of birth, breast cancer in first-degree relative, marital status, and nulliparity	No significant association for breast cancer (adjOR = 1.65, 95% CI = 0.53–5.17, 7 exposed cases) compared to unexposed
Ratner et al. (2010)	Cohort, retrospective (Female registered nurses from British Columbia, Canada, 1974–2000, F) Note: Subjects followed until 2000	56,213 nurses in cohort: 905 exposed (Method 1, ever working in oncology or a cancer center) or 7,635 exposed ≥15 days (Method 2, weighted duration of exposure)	Two exposure measures: Method 1: Years employed in oncology or at a cancer center (never, <5 years, ≥5 years, or ever) and Method 2: weighted duration of exposure based on job responsibilities (<15 days, ≥15 to 60 days, and >60 days, or ≥15 days; 15 days equivalent to 1 year of work in a job likely not exposed and 60 days equivalent to 1 year of work in job likely exposed to cancer chemotherapy agents)	Incidence of any cancer (combined and individual types); cases identified in the Canadian cancer registry	Poisson regression; adjusted for calendar year and age; lag of 10 years applied for cancer incidence; cancers with 3 or fewer cancers were not statistically analyzed	For Method 1, increased risk for breast cancer (aRR = 1.83; 95% CI = 1.03–3.23, 12 exposed cases) compared to never exposed and no exposed cases of leukemia, and all other cancers had >3 exposed cases for Method 1. For Method 2, there was a significant association with rectal cancer (aRR = 1.87, 95% CI 1.07–3.29, 14 exposed cases) compared to exposed <15 days, less than 3 exposed cases of Hodgkin lymphoma (HL), and no association for non-Hodgkin lymphoma (NHL) (aRR = 0.91, 95% CI = 0.42–1.96, 7 exposed cases), leukemia (aRR = 0.89, 95% CI = 0.27–2.88 3 exposed cases), bladder cancer (aRR = 1.67, 95% CI = 0.76–3.67, 7 exposed cases), lung cancer (aRR = 1.22, 95% CI = 0.65–1.94, 14 exposed cases) and melanoma (aRR = 1.28, 95% CI = 0.75–2.18, 15 exposed cases) compared to <15 days exposure

Study	Study Design (Occupation, Location, Year Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Measured	Analysis	Results
Skov et al. (1992)	Cohort, retrospective (Nurses, Denmark, 1973–1987, F) Note: Follow-up until 1987	1,282 exposed; referents were Danish national cancer rates	Employment records of 5 oncology hospitals, and data from head nurses regarding drug handling and administration of individual subjects	Medical records (Danish Cancer Registry); incidence of any cancer (combined), leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, mycosis fungoides	Standard incidence ratios	Significant association for leukemia (RR = 10.65, 95% CI = 1.29–38.5, 2 exposed cases), but not HL (RR = 8.35, 95% CI = 0.21–46.5, 1 exposed case) compared to the standard incidence ratio; one exposed nurses had both leukemia and JL was counted as 2 exposed cases

aRR = adjusted relative risk, CI = confidence interval, F = female, HL = Hodgkin lymphoma, M = male, NHL = non-Hodgkin lymphoma, No. = number, RR = relative risk.
[a]In Method 2 of Ratner et al. (2010), 15 days is equivalent to 1 year of work in a position not likely to be exposed and 60 days is equivalent to full time work in a position likely to be exposed.
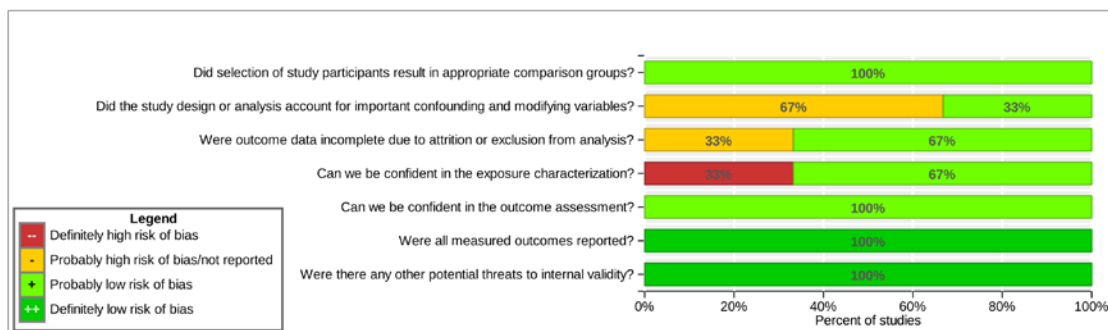
Figure E-3. Risk-of-bias Bar Graph for Studies Reporting on Cancer Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).
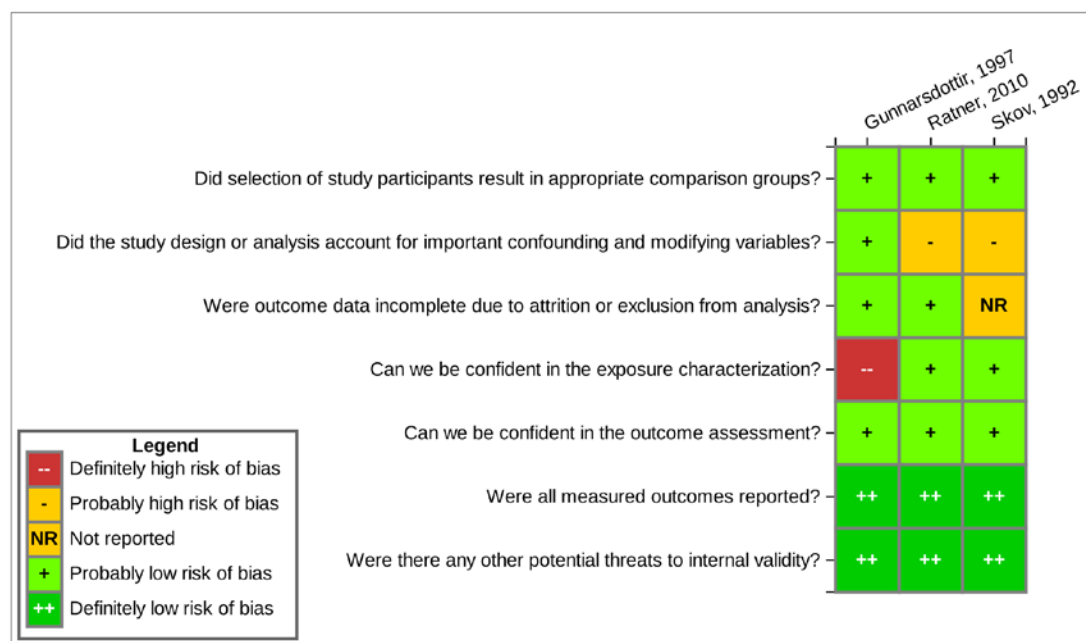
Figure E-4. Risk-of-bias Heat Map for Studies Reporting on Cancer Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).

E.3. Immune Toxicity

The NTP evaluation identified 11 cross-sectional studies reporting effects on the immune system (Biró et al. 2011; Bolognesi et al. 2005; Caciari et al. 2012; Jeebhay et al. 1993; Jochimsen et al. 1988; Li et al. 2005; Medková 1991a; Spatari et al. 2005; Valanis et al. 1987; Walusiak et al. 2003; Zhang et al. 2016). The effects included any immune-related diseases (e.g., asthma, auto-immune disease). Alterations in immune-related parameters were also reviewed, including but not limited to: white blood cell differential count, oxidative burst potential, cytokine levels, and natural killer cell function.

Summary: Based on the available studies, there is *very low confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with higher incidence of immune-related diseases or alterations of immune-related parameters. The ability to compare among studies was limited due to heterogeneity in the outcomes assessed. For example, only one study reported on an immune-related disease (asthma) and most of the studies investigating possible alterations of immune-related parameters did not measure similar endpoints (Table E-3). Of the few studies that measured a similar endpoint, there were inconsistent results (e.g., only one of five studies measuring white blood cell counts reported significantly lower counts in exposed subjects versus controls). The final rating of very low confidence in the body of evidence confidence reflects downgrading for serious risk-of-bias concerns across multiple key risk-of-bias questions (e.g., majority of studies were rated probably high risk of bias for confounding), heterogeneity in the outcomes measured, and inconsistencies in the outcomes reported (Figure E-5 and Figure E-6).

Table E-3. Studies Reporting on Immune System Toxicity

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Characterization (Duration)	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Biró et al. (2011)	Cross-sectional (Nurses, Hungary, year NR, sex NR)	308 exposed, 98 unexposed	Job title and interviewer-led questionnaire (9.0 ± 0.5 years)	Medical tests conducted using flow cytometry	Student's t-test	Significantly (p < 0.05) higher **% of B cells**, and significantly (p < 0.05) decreased **CD25+/CD4+ activated T cell**s compared to unexposed subjects; **ratio of T cells, cytotoxic T cells (Tc), helper T cells (Th), NK (natural killer) cells, and Th/Tc** were NS
Bolognesi et al. (2005)	Cross-sectional (Nurses, IMPEA project, Italy, year NR, FM)	50 exposed, 48 unexposed	Job title, [self-reported] questionnaire, and biomonitoring (10.2 years) *Note: Nurses assigned to preparation and administration of agents; adequate safety equipment and PPE were used*	Medical tests conducted using flow cytometry	Mann-Whitney U-test	No difference in **% NK cells, peripheral lymphomonocytes, regulatory T cell (CD25), and IL-6** compared to unexposed subjects
Caciari et al. (2012)	Cross-sectional (Healthcare workers (doctors, nurses, social and health assistants), Italy, year NR, FM)	57 exposed, 57 unexposed	Job title only (duration NR)	Medical tests	Student t-test, Chi-square analysis	Significantly lower **levels of monocytes** (possible myelosuppression) compared to unexposed subjects; **red blood cell populations or other white blood cell type counts** NS

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Characterization (Duration)	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Jeebhay et al. (1993)	Cross-sectional (Pharmaceutical plant workers, South Africa, year NR, M)	6 exposed to azathioprine, 17 unexposed	Job title and [self-reported] questionnaire, biomonitoring, and environmental monitoring *Note: Exposed workers in 2-week production campaign: measured at baseline, day 3, end, and 3 months after end*	Medical tests conducted by a commercial laboratory	ANOVA	Significantly fewer **reticulocytes** at the end of the production run, and significantly fewer **neutrophils** at 3 months following the production run compared to unexposed subjects; **number of platelets or white blood cell count** NS
Jochimsen et al. (1988)	Cross-sectional (Nurses, USA, year NR, sex NR)	18 exposed, 18 unexposed	Job title, work task, drug handling, and PPE usage [method NR] (4.5 years, range 1–10 years) *Note: PPE not regularly used and no hoods or vapor barriers were used*	Medical tests conducted using flow cytometry	Student's t-test	Trend, though NS, of lower **neutrophil, monocytes, platelet counts,** and **neutrophil reserve** compared to unexposed nurses

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Characterization (Duration)	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Li et al. (2005)	Cross-sectional (Nurses, China, years NR, F)	30 exposed, 30 unexposed	Job title, drug handling, and PPE usage [method NR] (14 years) *Note: Exposed nurses handled these agents ≥5 years at minimum 5 times per day without taking protective measures*	Medical tests conducted using flow cytometry	t-test	Significantly fewer **helper T cells (CD4+)** in exposed versus control nurses; **other T lymphocyte cell types (CD8+, CD4+/CD8+, CD3) or NK cells** NS
Medková (1991a)	Cross-sectional (Nurses, physicians, cleaning staff, Czech Republic, years NR, FM)	44 exposed, 32 unexposed partners of exposed subjects	Job title and interviewer-led questionnaire (≥5 years, n = 25; 6–10 years, n = 14; 11–15 years, n = 4; and 16–20 years, n = 1) *Note: All exposed personnel used gloves and gowns; isolated room for drug preparation only used by 25% of exposed subjects*	Interviewer-led questionnaire	NR	Higher **incidence of allergy** including **bronchial asthma** in exposed nurses versus controls, but statistical significance unknown
Spatari et al. (2005)	Cross-sectional (Healthcare workers, Italy, years NR, FM)	17 exposed, 17 unexposed	Job title only (13.25 ± 8.16 years)	Elisa kit	One-way ANOVA, Student-Newman Keuls test	Significantly higher **interleukin-15 levels** in exposed relative to control subjects

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Characterization (Duration)	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Valanis et al. (1987)	Cross-sectional (Pharmacists and pharmacy technicians in NSABP, USA, 1988–1990, FM)	21 exposed, 13 unexposed	Job title and self-reported, validated questionnaire (duration NR) *Note: 65% of exposed nurses used gloves during drug preparation and 45% during administration of drugs; skin contact occurred on at least half of drug-handling events for 18% of exposed nurses and 25% of nurses during administration of drugs; gowns, goggles and masks were rarely used*	Medical tests conducted in single laboratory by technician blind to exposure group	Chi-squared test	Similar total **white cell counts** between control and exposed subjects; however, an analysis of subgroups of white cell counts (<5,600, 5,600–7,000, >7,000) revealed that significantly more exposed nurses had white blood cell counts of <1,500 cells than control nurses
Walusiak et al. (2003)	Cross-sectional (Nurses, physicians, orderlies, year NR, Poland, FM)	104 exposed, 103 unexposed	Job title and self-reported questionnaire (11.0 ± 9.3 years, range 5–44 years)	Medical tests	Mann-Whitney U-test	Similar values between exposed and control subjects for all immune and hematopoietic parameters measured including: **white blood cell count, red blood cells count and platelet count**

Study	Study Design (Population, Location, Year Data Collected, Sex)	No. of Participants	Exposure Characterization (Duration)	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Zhang et al. (2016)	Cross-sectional (Nurses, China, 2011 pre-PIVAS and 2013 (post-PIVAS) in Hospital A, F)	Pre-PIVAS: 88 unexposed, 33 exposed non-oncology, 101 exposed oncology; post-PIVAS: 55 unexposed, 25 exposed non-oncology, 85 exposed oncology, and 144 exposed oncology nurses at Hospital B)	Job title and self-reported questionnaire (≥2 years in current job) *Note: All exposed nurses involved in mixing and/or administration of cancer chemotherapy agents*	Medical tests	t-test, Chi-square, and Wilcoxon	Significantly lower mean **white blood cell counts** in oncology nurses compared to controls prior to the implementation of a PIVAS; after implementation of PIVAS, the **white blood cell counts** were similar between the two groups in the same hospital. The **number of white blood cell counts, platelets, and red blood cells** counts were higher in controls and oncology numbers after PIVAS implementation than before. Finally, oncology nurses in a second hospital (Hospital B) without PIVAS had significantly lower **numbers of white bloods cells, platelets, and red blood cells** compared to the oncology nurses post-PIVAS at Hospital A

adjOR = adjusted odds ratio, CD = cluster of differentiation, F = female, M = male, NK = natural killer cells, NR = not reported, NS = not significant, NSABP = National Surgical Adjuvant Breast and Bowel Project, OR = odds ratio, PIVAS = pharmacy intravenous admixture service, Tc = cytotoxic T cells, Th = helper T cells, TNF alpha = tumor necrosis factor alpha.
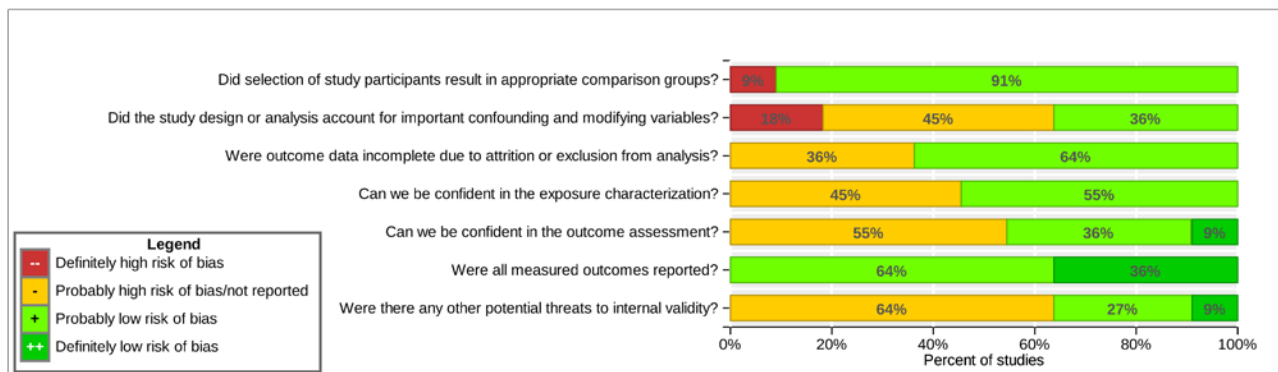
Figure E-5. Risk-of-bias Bar Graph for Studies Reporting on Immune System Effects Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).
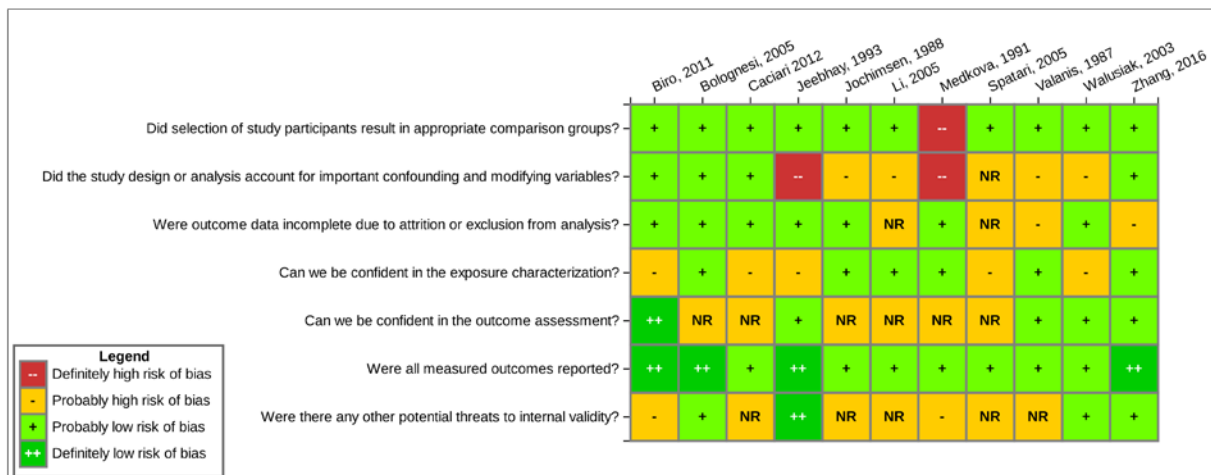
Figure E-6. Risk-of-bias Heat Map for Studies Reporting on Immune System Effects Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).

E.4. Kidney, Liver, and Cardiovascular System Toxicity

The NTP evaluation identified six cross-sectional studies total that reported on kidney toxicity (five studies), liver toxicity (four studies), and cardiovascular system toxicity (two studies) (Caciari et al. 2012; Medková 1991a; Sessink et al. 1997a; Tigha Bouaziz et al. 2016; Walusiak et al. 2003; Zhang et al. 2016). The type of data available varied from biochemical measurements (e.g., secondary health outcomes) and the incidence of morbidity, which limited the ability to compare among studies.

Summary: Based on the available studies, there is *very low confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents is associated with kidney, liver, or cardiovascular toxicity. There were very few studies per health outcome, which resulted in few effects evaluated across all studies (Table E-4). Another challenge was the lack of description provided for morbidity provided by the authors of one study (Medková 1991a). Of the four

studies reporting on kidney toxicity, one study reported a higher rate of renal disease without further description and one of three studies reporting biochemical measurements reported a higher incidence of alterations in exposed subjects versus controls. In another example, one of two studies reported cardiovascular system toxicity. The final rating of very low confidence in the body of evidence reflects downgrading for serious risk-of-bias concerns across multiple key risk-of-bias questions (e.g., majority of studies were rated probably high risk of bias for confounding and exposure characterization) (Figure E-7 and Figure E-8).

Table E-4. Studies Reporting on Kidney, Liver, or Cardiovascular System Toxicity

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Caciari et al. (2012)	Cross-sectional (Healthcare workers (doctors, nurses, social and health assistants), Italy, year NR, FM)	57 exposed, 57 unexposed	Job title only (duration NR)	Medical tests	Student t-test, Chi-square analysis	Significantly higher levels of bilirubin (possible indication of **liver damage**) compared to unexposed subjects; alanine or aspartate aminotransferase, alkaline phosphatase (measures of **liver function**) NS; blood urea nitrogen or creatinine (measures of **kidney function**) NS
Medková (1991a)	Cross-sectional (Physicians, nurses, auxiliary workers, Czech Republic, year NR, FM)	44 exposed, 32 unexposed partners of exposed subjects	Job title and interviewer-led questionnaire (≥5 years, n = 25; 6–10 years, n = 14; 11–15 years, n = 4; and 16–20 years, n = 1) *Note: Exposed personnel used gloves and gowns; isolated room for drug preparation only used by 25% of exposed subjects*	Interviewer-led questionnaire	NR	Higher occurrence of **renal disease** and **liver disease** in compared to unexposed subjects, but statistics were not provided; no difference in occurrence of **cardiovascular morbidity** (described as diseases of the heart and circulation) or hypertension
Sessink et al. (1997a)	Cross-sectional (Nurses, lab technician, and cleaning staff, t-test, year NR, FM)	11 exposed; 23 unexposed nurses, doctors, lab technicians and a cleaning woman	Job title and [self-reported] questionnaire (13, range 3–25 years) Note: *Most exposed personnel used PPE; laminar down-flow cabinets used for drug preparation*	Medical test	Student's t-test, Pearson's correlation of log-transformed data	No difference in **renal function** as measured by urinary albumin and urinary retinol-binding protein levels

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Tigha Bouaziz et al. (2016)	Cross-sectional (Nurses, Algeria, year NR, FM)	215 unexposed, 74 exposed	Job title and [self-reported] questionnaire (18.04 ± 11.11 years)	Medical tests	t-, z-, and Chi-squared tests, ANOVA, and logistic regression to adjust for age, sex, work shift, and other variables	Significantly higher occurrence **cardiovascular morbidity** associated with oncology nursing experience and higher cytostatic contact index levels (OR = 2.7, 95% CI = 1.26–6.04); significantly higher levels of creatinine, cholesterol, and triglycerides compared to unexposed nurses
Walusiak et al. (2003)	Cross-sectional (Physicians, nurses, orderlies, year NR, Poland, F)	104 exposed, 103 unexposed	Job title and self-reported questionnaire (11.0 ± 9.3 years)	Self-report questionnaire	Mann-Whitney U-test	No difference in biochemical measures of **liver function** (aspartate and alanine transaminases, bilirubin, glutamyltransferase) or **kidney function** (creatinine, urea)
Zhang et al. (2016)	Cross-sectional (Nurses, China, 2011 pre-PIVAS and 2013 (post-PIVAS) in Hospital A, F)	Pre-PIVAS: 138 unexposed, 39 exposed non-oncology, 118 exposed oncology; Post-PIVAS: 185 unexposed, 55 exposed non-oncology, 137 exposed oncology, and 163 exposed oncology nurses at Hospital B)	Job title and self-reported questionnaire (≥2 years in current job)	Self-report questionnaire	[Student] t-test, Chi-square, and Wilcoxon for outcomes [authors did not specify which method]	Significantly (p < 0.05) altered levels of biochemical measurements of **liver function** (alanine transaminase, serum aspartate transaminase) and **kidney function** (creatinine, blood urea nitrogen) compared to unexposed nurses in Hospital A regardless of PIVAS implementation

ANOVA = analysis of variance, CI = confidence interval, F = female, M = male, No. = number, NR = not reported, NS = not significant, OR = odds ratio, PIVAS = pharmacy intravenous admixture service.
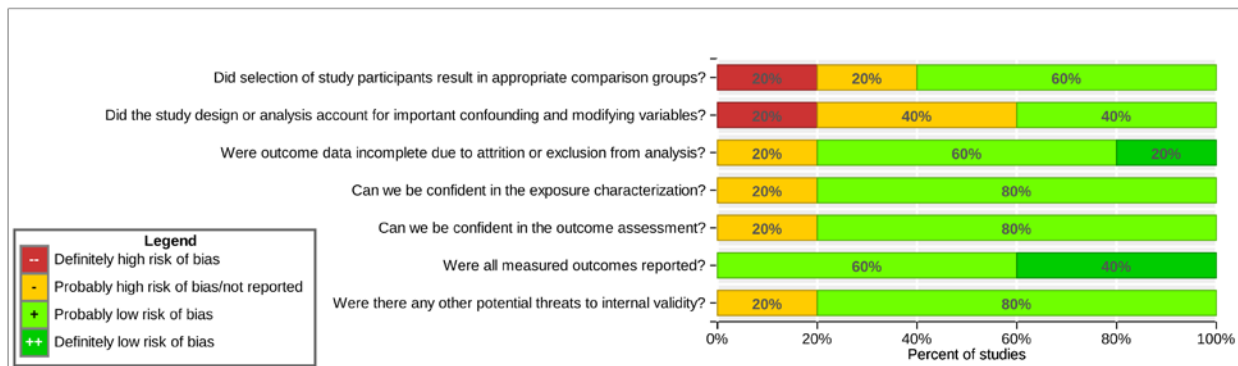
Figure E-7. Risk-of-bias Bar Graph for Studies Reporting on Kidney, Liver, or Cardiovascular System Toxicity Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).
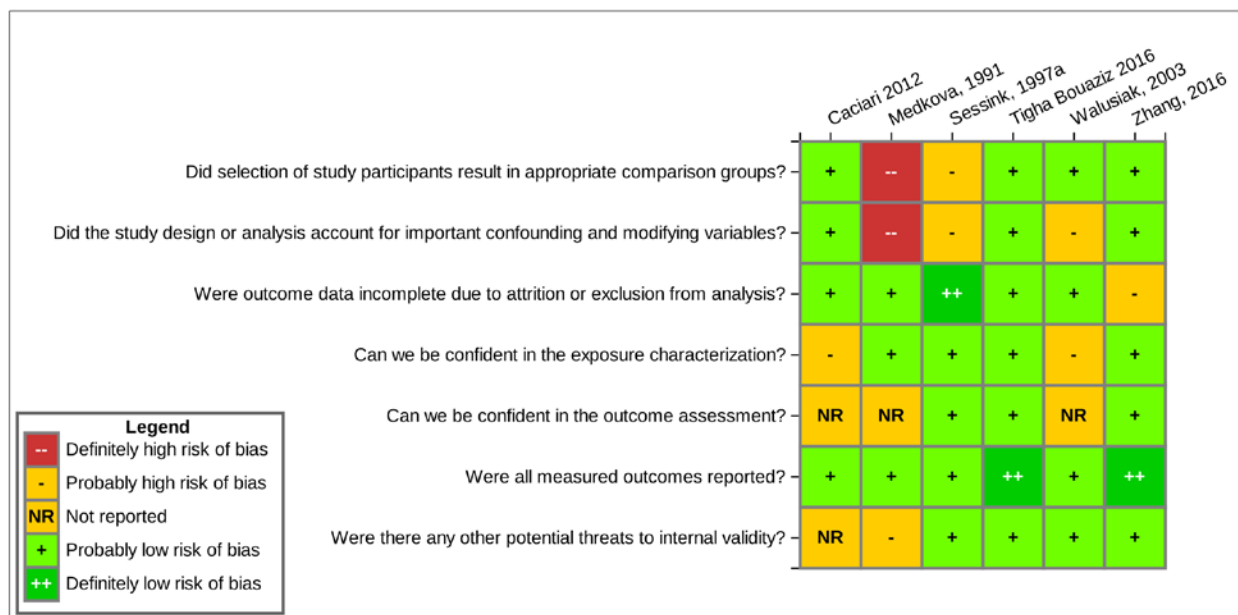
Figure E-8. Risk-of-bias Heat Map for Studies Reporting on Kidney, Liver, or Cardiovascular System Toxicity Associated with Occupational Exposure to Cancer Chemotherapy Agents

Interactive figure and additional study details in HAWC (NTP, 2015a).

E.5. Reproductive Toxicity, Other Than Spontaneous Abortion

In addition to spontaneous abortion, the NTP evaluation identified 24 studies of 19 unique populations reporting on reproductive and developmental toxicity, including pregnancy outcomes and female reproductive function (Bouyer et al. 1998; Elshamy et al. 2010; Fransman et al. 2007c; Hemminki et al. 1985; Krstev et al. 2003; Lawson et al. 2009; Lorente et al. 2000; McAbee et al. 1993; McDonald et al. 1988a; 1988b; Medková 1991a; Peelen et al. 1999; Ratner et al. 2010; Saurel-Cubizolles et al. 1993; Schaumburg and Olsen 1989; 1990a; 1991; Shortridge et al. 1995; Skov et al. 1992; Stücker et al. 1993; Valanis et al. 1997; Valanis et al. 1999; Walusiak et al. 2003; Zhang et al. 2016). The pregnancy outcomes included endpoints such as

congenital malformations (12 studies), stillbirth (seven studies), preterm birth (seven studies), low birth weight or small for gestational age (eight studies), and ectopic pregnancy (three studies). Other studies reported on reproductive function, including time to pregnancy (three studies), infertility (three studies), and menstrual irregularities (three studies).

Summary*:* Based on the available data, there is *very low confidence in the body of evidence* that occupational exposure to cancer chemotherapy agents during pregnancy is associated with reproductive and developmental toxicity for endpoints other than spontaneous abortion.

Very few exposed cases were observed for some endpoints (e.g., congenital malformations), while there were very few studies were available for other endpoints (e.g., infertility) (Table E-5). There were 12 studies (of 11 unique populations) available that evaluated congenital malformations, including 11 studies evaluating any malformation (Elshamy et al. 2010; Fransman et al. 2007c; Hemminki et al. 1985; McAbee et al. 1993; McDonald et al. 1988a; Medková 1991a; Peelen et al. 1999; Ratner et al. 2010; Schaumburg and Olsen 1990a; Skov et al. 1992; Walusiak et al. 2003) and one study specifically evaluating oral clefts (Lorente et al. 2000). However, the results were inconsistent between studies with six of nine studies (one case-control study and five cross-sectional studies) reporting significantly higher rates of congenital malformations from exposed pregnancies, while three retrospective cohort studies, two with a larger number of exposed pregnancies, did not observe a significant increase. Only three studies limited the exposure characterization to the first trimester, and the results remained inconsistent when considering only the highest quality studies. Stillbirth did not appear to be associated with occupational exposure to cancer chemotherapy based on five available studies (one retrospective cohort study and six cross-sectional studies; six unique populations). However, the level of evidence for no effect conclusion requires a final rating of high confidence in the body of evidence (Rooney et al. 2014) and these studies did not achieve higher than a moderate confidence in the body of literature based on their study design. The final rating of very low confidence in the body of evidence for the reproductive and developmental toxicity effects, other than spontaneous abortion, reflected downgrading for inconsistency in the results for congenital malformations. No downgrading or upgrading for key risk-of-bias questions were identified for the other non-spontaneous abortion endpoints and few available studies were available for some endpoints, which also led to a final rating of very low confidence (Figure E-9 and Figure E-10).

Table E-5. Studies Reporting on Reproductive and Developmental Toxicity, Other Than Spontaneous Abortions

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Bouyer et al. (1998)	Case-control (Hospital personnel, France, 1995, F) *Note: Follow-up study to Saurel-Cubizolles 1993*	140 cases, 279 control pregnancies (exposure to cancer chemotherapy: 37 pregnancies with past exposure and 43 with exposure in 3 months prior to conception)	Self-reported questionnaire on past and present occupational exposure to cancer chemotherapy agents, solvents, disinfectants, anesthetic agents, and ionizing radiation *Note: Authors excluded subjects self-reporting to be seldom exposed or using a protective device*	NR [presumably medical records]	Multivariate analysis using unconditional logistic regression	No association with **ectopic pregnancy** and past exposure (adjOR = 1.56, 95% CI = 0.65–3.72, 15 exposed cases) or 3-month prior exposure (adjOR = 0.95, 95% CI = 0.39–2.31, 10 exposed cases) compared to controls

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Elshamy et al. (2010)	Cross-sectional (Nurses, Egypt, 2006, F)	35 exposed, 29 unexposed	Job title, length of employment, self-administered questionnaire about drug handling, frequency of handling, number of accidents with cancer chemotherapy in past year, personal protective equipment usage, and level of training. *Note: Only 42.9% of nurses reported using gloves when handling patient waste, and 45.7% of nurses admitted to eating in the drug preparation area*	Self-reported questionnaire; no definitions were provided	Chi-square test with continuity correction, if indicated	Significantly higher (p<0.05) percentage of exposed than unexposed nurses experienced **infertility/subfertility** (11.4% vs. 3.4%), **premature labor** (11.4% vs. 3.4%), **fetal loss [presumed stillbirth]** (8.6% vs. 3.4%), **congenital malformations** (8.6 vs. 3.4), and **developmental and behavioral abnormalities of offspring** (5.7% vs. 0%), and higher but NS **menstrual changes** and **low birth weight**

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Fransman et al. (2007c)	Cross-sectional (Nurses, the Netherlands, 1990–1997, F) *Note: Same data as Peelen 1997*	Exposed pregnancies: 279 background, 146 low, 145 medium, 134 high; 555 unexposed pregnancies	Estimated dermal exposure based on job title, self-reported questionnaire, and glove usage in first trimester of pregnancy (or during time trying to get pregnant), combined with data on CP glove contamination conducted in 1996–1997 and glove and hand contamination in 2003–2007; categorized as: unexposed, background, low (≤0.20 μg CP/wk), medium (>0.20–0.74 μg CP/wk) or high exposure (>0.74 μg CP/wk)	Self-reported questionnaire	Logistic regression analysis; adjusted a prior for age at conception, parity, smoking, alcohol consumption, coffee intake during 1st trimester of pregnancy, vitamin/folic acid use during pregnancy as well as work factors (e.g., co-exposures during 1st trimester)	Significantly longer **time to pregnancy** in highly exposed nurses compared to unexposed nurses (aHR = 0.8, 95% CI = 0.6–0.9) and there was a log-linear increase in **low birth weight** per unit exposure (OR = 1.11, 95% CI = 1.01–1.21) and **premature birth** per unit exposure (OR = 1.08, 95% CI = 1.00–1.17); data on **stillbirth**; **congenital anomalies**, and **alterations in sex ratio** (% boys) NS

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Hemminki et al. (1985)	Case-control (Nurses, 1973-1979, Finland, F)	38 cases and 99 normal infants (16 pregnancies exposed to cancer chemotherapy agents)	Central Registry of Health Care Personnel and a questionnaire to head nurses regarding each subjects' occupational exposures, including anesthetic gases, sterilizing agents, disinfectants, cancer chemotherapy drugs, and x-ray radiation, shift work and telephone duty *Note: Exposed nurses were from non-oncology departments where exposure was relatively uncommon*	Medical records	Odds ratios and logistic model of conditional likelihood function adjusted for shift work and co-exposures (e.g., ionizing radiation)	Significantly higher odds of **congenital malformations** compared to unexposed pregnancies (adjOR = 4.7, 95% CI = 1.2–18.1, 8 cases)
Krstev et al. (2003)	Cross-sectional (Nurses in 8 hospitals, Serbia, year NR, F)	186 exposed, 77 unexposed	Job title and self-reported questionnaire; head nurses reported on work practice and work conditions *Note: 60.1 to 81.7% of exposed nurses used gloves for drug administration or preparation; only one hospital had a vertical laminar [flow] biological safety cabinet, and some concerns about its maintenance*	Self-reported questionnaire	Relative risks using two by two table statistics. Unconditional logistic regression measured effect of age, smoking and shift work	No difference in the occurrence of **menstrual dysfunction** compared to unexposed nurses

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Lawson et al. (2009)	Cohort, retrospective (Nurses' Health Study II, USA, 1993–2001, F)	270 exposed, 6,688 unexposed pregnancies, and 19 pregnancies missing exposure data	Self-reported questionnaire on first trimester exposure to anesthesia, cancer chemotherapy agents, anti-viral drugs, sterilizing agents, and X-ray radiation	Self-report questionnaire on most recent pregnancy since 1993	Logistic regression adjusted for age; multivariate analysis included all 5 work exposures, parity, shift work, and hours worked adjusted for age and parity	No association with **preterm birth** (only 22 exposed preterm cases)
Lorente et al. (2000)	Case-control (Working women, Europe, 1989–1992, F)	Cases (infants): 64 cleft lip with or without cleft palate and 36 cleft palate only, 751 controls (no. of infants exposed to cancer chemotherapy agents not reported)	Interviewer-led questionnaire and industrial hygienist defined the exposure by route of exposure, level of exposure, frequency, and reliability of the assessment *Note: Authors reported that all exposure to antineoplastic drugs was low-level, low-frequency, and certain exposure*	National malformation registry	Odds ratio adjusted for study center, maternal age, mother's socioeconomic status, urbanization, and country of origin; backward stepwise logistic regression to determine exposures independently associated with oral clefts	**Cleft palate** was not significantly elevated in cases exposed to cancer chemotherapy (adjOR = 5.1, 95% CI = 0.8–34, 2 exposed cases)
McAbee et al. (1993)	Cross-sectional (Nurses, USA, year NR, F)	663 women and 1,133 pregnancies (318 women exposed to cancer chemotherapy agents, no. of exposed pregnancies NR)	Job title and self-reported questionnaire about occupational exposure to ionizing radiation, cancer chemotherapy agents, solvents, and video display terminals	Self-report questionnaire	Mantel-Haenszel test for linear associations	Authors report a higher prevalence of **congenital malformations** in nurses exposed to cancer chemotherapy than unexposed nurses (10 exposed cases, p = 0.02)

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Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
McDonald et al. (1988a)	Cross-sectional (Working women, Canada, 1982–1984, F) *Note: Same population as McDonald 1988b*	47, 913 pregnancies of working women (152 pregnancies exposed to cancer chemotherapy agents)	Interviewer-led questionnaire; jobs were assigned a code without knowledge of outcome; estimate made from published and unpublished studies, and occupational surveillance *Note: Medical questionnaire also asked nurses or physicians if they administered cancer chemotherapy agents in the month after the first missed menstrual period*	Interviewer-led questionnaire verified by medical records of previous pregnancy outcome	Poisson regression evaluated observed versus expected cases; age, gravidity, history of previous abortion, ethnic group, educational level as well as smoking habit and alcohol consumption	Significantly higher occurrence of **congenital malformations** from exposed pregnancies (8 exposed cases observed versus 4 cases expected)
McDonald et al. (1988b)	Cross-sectional (Working women, 1982–1984, Canada, F) *Note: Same population as McDonald 1988a*	22,713 (63 pregnancies exposed to cancer chemotherapy agents)	Interviewer-led questionnaire; jobs were assigned a code without knowledge of outcome; estimate made from published and unpublished studies, and occupational surveillance	Interviewer-led questionnaire of pregnancy outcome prior to most recent live birth	Poisson regression evaluated observed versus expected cases; age, gravidity, history of previous abortion, ethnic group, educational level, and smoking habit and alcohol consumption	None of the 63 exposed pregnancies ended in **stillbirth** (expected rate = 0.48)
Medková (1991a)	Cross-sectional (Physicians, nurses, auxiliary workers, Czech Republic, year NR, FM)	50 exposed infants, 11 unexposed infants (to partners of exposed subjects)	Job title and interviewer-led questionnaire *Note: Isolated room for drug preparation only used by 25% of exposed subjects; glove and gowns used*	Interviewer-led questionnaire	NR	Two **congenital malformations** were reported in exposed infants compared to none in the unexposed infants

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Peelen et al. (1999)	Cross-sectional (Nurses, the Netherlands, 1990–1997, F) *Note: Same data as Fransman et al. 2007c*	Exposed: 249 pregnancies and 229 live births; unexposed: 1,010 pregnancies and 956 live births	Job title, self-reported questionnaire, biomonitoring, and environmental monitoring	Self-reported questionnaire on most recent pregnancies; [same as Fransman et al. 2007c]	[Logistic regression]; adjusted for age, coffee consumption, smoking, alcohol consumption, pregnancy, physical strain, and co-exposures (e.g., ionizing radiation, disinfectants), as needed	Significantly higher odds of congenital malformations (OR = 5.1, 95% CI 1.1–23.6; >7 exposed cases), and **low birth weight** in infants of exposed nurses preparing the agents (adjOR = 16.7, 95% CI = 3.4–81.6) and **low birth weight** in infants of exposed nurses involved in cleaning activities associated with the agents (adjOR = 2.9, 95% CI = 1.2–7.2) compared with unexposed nurses; **time to pregnancy, stillbirth, premature birth** NS

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Ratner et al. (2010)	Cohort, retrospective (Female registered nurses from British Columbia, Canada, 1974–2000, F) *Note: Subjects followed until 2000*	22,491 infants total: 190 exposed (Method 1, ever working in oncology or a cancer center) or 1,062 exposed ≥15 days during 1st trimester or 2,650 during 10 years prior to pregnancy (Method 2, weighted duration of exposure)	Two exposure measures: Method 1: Years employed in oncology or at a cancer center (never, <5 years, ≥5 years, or ever) and Method 2: weighted duration of exposure based on job responsibilities (<15 days, ≥15 to 60 days, and >60 days, or ≥15 days; 15 days equivalent to 1 year of work in a job likely not exposed and 60 days equivalent to 1 year of work in job likely exposed to cancer chemotherapy agents)	Provincial cancer registry	Logistic regression; adjusted for age of mother at birth, year of birth, and sex of child	Not significant, but higher, odds of **congenital malformations** (Method 1, adjOR = 1.42, 95% CI = 0.86–2.36, 17 exposed cases), **premature birth** (Method 1, adjOR = 1.88, 95% CI = 0.80–4.41, 6 exposed cases), and **low birth weight** (Method 1, adjOR = 1.41, 95% CI = 0.44–4.54, 3 exposed cases) following exposure at any time during pregnancy; using Method 2, **congenital malformations** (e.g., cleft palate/lip, adjOR = 1.84, 95% CI = 0.75–4.49, 6 exposed cases), **premature birth**, **low birth weight**, and **stillbirth** were NS
Saurel-Cubizolles et al. (1993)	Cross-sectional (Medical personnel except physicians, France, 1987–1988, F)	82 exposed, 599 unexposed pregnancies	Job title and interviewer-led questionnaire asked about exposure to anesthetic gases, formol, ionizing radiation, or antineoplastic drugs during the first trimester of pregnancy	Interviewer-led questionnaire	Chi-square analysis and logistic regression	Significantly greater odds of **ectopic pregnancy** in medical personnel exposed during first trimester to cancer chemotherapy agents (adjOR = 11.4, 95% CI = 2.7–47.6, 6 exposed cases) compared to unexposed subjects

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Schaumburg and Olsen (1989)	Cohort, retrospective (Pharmacy assistants, Denmark, 1979–1984, F) *Note: Same population as Schaumburg and Olsen 1990a; 1991*	4.924 women; 1,124 unexposed; only 8 exposed to cancer chemotherapy agents	Membership in national union of pharmacy assistants and self-reported questionnaire asked about work during pregnancy, type of pharmacy, work tasks, exposure to drugs and chemicals	Medical records	Stratified analyses with the Mantel-Haenszel test statistics and an unconditional logistic regression model; adjusted for parity, year of graduation, smoking, and alcohol consumption	**Time to pregnancy** was not prolonged for the 8 exposed subjects; all women became pregnancy in 0–6 months
Schaumburg and Olsen (1990a)	Cohort, retrospective (Pharmacy assistants, Denmark, 1979–1984, F) *Note: Same population as Schaumburg and Olsen 1989; 1991*	1,182 births; 718 unexposed pregnancies; only 8 pregnancies exposed to cancer chemotherapy agents	Membership in national union of pharmacy assistants and self-reported questionnaire asked about work during pregnancy, type of pharmacy, work tasks, exposure to drugs and chemicals	Medical records and Central Bureau of Statistics	Unconditional logistic regression model; adjusted for maternal age, parity, smoking	No **congenital malformations** were observed in offspring of 8 exposed pregnancies
Schaumburg and Olsen (1991)	Cohort, retrospective (Pharmacy assistants, Denmark, 1979–1984, F) *Note: Same population as Schaumburg and Olsen 1989; 1990a*	1,182 births; 709 unexposed pregnancies; only 8 pregnancies exposed to cancer chemotherapy agents	Membership in national union of pharmacy assistants and self-reported questionnaire asked about work during pregnancy, type of pharmacy, work tasks, exposure to drugs and chemicals	Medical records and Central Bureau of Statistics	Analysis of variance and unconditional logistic regression model; adjusted for maternal age, parity, smoking, and alcohol consumption	Non-significant decreases in **birth weight** in offspring of exposed subjects; no increased risk of **premature birth** (OR = 6.50, 95% CI = 0.9–31.6: 2 of 8 exposed births were premature)

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Shortridge et al. (1995)	Prospective cohort (Nurses in Oncology Nursing Society, USA, F)	596 exposed, 497 unexposed women	Self-administered, validated questionnaire	Self-reported questionnaire	Logistic regression; evaluated age, interaction of age and exposure, and stress	Significant logistic regression results for **menstrual dysfunction** included: age groups >30 years old (p = 0.002), the interaction of age group and exposure (p = 0.03), and job stress (p = 0.045); **menstrual dysfunction** was significantly higher in nurses ages ≥30 years old (OR = 1.6, 95% CI = 1.3–1.9) and >46 years old (OR = 1.4, 95% CI = 1.1–1.8)
Skov et al. (1992)	Cohort, retrospective (Nurses, Denmark, 1973–1988, F)	213 exposed, 604 unexposed pregnancies	Employment records of 5 oncology hospitals, and data from head nurses regarding drug handling and administration of individual subjects of individual subjects	Medical records	Logistic regression analysis; adjustment for maternal age	No higher odds of **congenital malformations** (adjOR = 0.99, 95% CI = 0.5–1.96) or **low birth weight** (adjOR = 1.06, 95% CI = 0.42–2.67), and no higher odds of altered **sex ratio** (% male) (OR = 1.12, 95% CI = 0.79–1.61) compared to unexposed infants; no difference in gestational age at birth
Stücker et al. (1993)	Cross-sectional (Nurses, France, 1985–1986, F)	107 exposed, 292 unexposed pregnancies	Job position and interviewer-led questionnaire *Note: At time of study, no special protective equipment was in operation and use of PPE was not uniform*	Interviewer-led questionnaire	Logistic regression analysis; evaluated effect of gestational age, infant sex, age of mother at birth, parity, BMI maternal smoking during pregnancy	No association of **birth weight** with exposure to cancer chemotherapy agents during pregnancy

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| Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Valanis et al. (1997)	Case-control (Nurses, nurse's aides, pharmacists, and pharmacy technicians, USA, 1988–1989, FM) *Note: Same population as Valanis 1999*	405 cases and 1,125 controls (355 exposed women due to prior handling of cancer chemotherapy agents)	Self-reported, validated questionnaire	Self-reported questionnaire	Two-way ANOVA and conditional logistic regression	Significant association of **infertility** with prior handling of cancer chemotherapy agents regardless of skin contact compared to unexposed subjects (OR = 1.5, 95% CI 1.2–2, 206 exposed cases)
Valanis et al. (1999)	Cross-sectional (Nurses, nurse's aides, pharmacists, and pharmacy technicians, USA, 1988–1989, FM) *Note: Same population as Valanis 1997*	1,448 exposed, 5,297 unexposed pregnancies (6,041 pregnancies of female personnel and 704 from spouse of male personnel)	Self-reported, validated questionnaire; subjects exposed to cancer chemotherapy agents 2 years prior or during pregnancy	Self-report questionnaire	Logistic regression analyses for (1) independence model and (2) generalized estimating equations model; all models adjusted for age and gravidity at time of pregnancy, maternal smoking during pregnancy	No difference in **stillbirth** in subjects exposed during pregnancy (no adjustment for prior exposure) compared to unexposed subjects (adjOR = 1.1, 95% CI = 0.5–2.2)
Walusiak et al. (2003)	Cross-sectional (Physicians, nurses, orderlies, year NR, Poland, F)	84 exposed, 169 unexposed pregnancies	Job title and self-reported questionnaire	Self-report questionnaire	Mann-Whitney U-test	Significantly higher occurrence of **congenital malformations** in exposed (4.8%) versus unexposed pregnancies (0.6%); [but incidence did not appear to be higher that US general population value of 3.0% (Correa et al. 2007)]; data on **ectopic pregnancy**, **premature birth**, and **birth weight** NS

Study	Study Design (Occupation, Location, Years Data Collected, Sex)	No. of Participants, Pregnancies, or Infants, as Noted	Exposure Measure	Outcome Assessment	Analysis	Results (Outcomes Measured in Bold)
Zhang et al. (2016)	Cross-sectional (Nurses, China, 2011 pre-PIVAS and 2013 (post-PIVAS) in Hospital A, F)	Pre-PIVAS: 106 unexposed, 30 exposed non-oncology, 82 exposed oncology; Post-PIVAS: 108 unexposed, 29 exposed non-oncology, 87 exposed oncology, and 112 exposed oncology nurses at Hospital B)	Job title and self-reported questionnaire *Note: All exposed nurses involved in mixing and/or administration of cancer chemotherapy agents*	Self-report questionnaire	[Student] t-test, Chi-square, and Wilcoxon for outcomes [authors did not specify which method]	Significantly higher rate of **infertility** among exposed oncology nurses versus unexposed nurses in Hospital A both before (p<0.01; 26.8 versus 9.4%) and after implementation of the PIVAS (p<0.05; 13.8% versus 3.7%); significant (p<0.05) decrease in infertility (13.8% versus 26.8%) and increase in **full-term births** (reduction in **premature births**) (33.3% versus 15.9%) in exposed oncology nurses after implementation of PIVAS compared to pre-PIVAS; significantly higher rates of **infertility** (p<0.01; 30.4% versus 13.8%) and lower **full-term births** (p<0.05; 19.6% versus 33.3%) were observed in Hospital B (no PIVAS) compared to post-PIVAS Hospital A

aHR = adjusted hazard ratio, adjOR = adjusted odds ratio, aRR = adjusted relative risk, CI = confidence interval, F = female, M = male, NK = natural killer cells, No. = number, NR = not reported, NS = not significant OR = odds ratio, PIVAS = pharmacy intravenous admixture service, USA = United States of America.
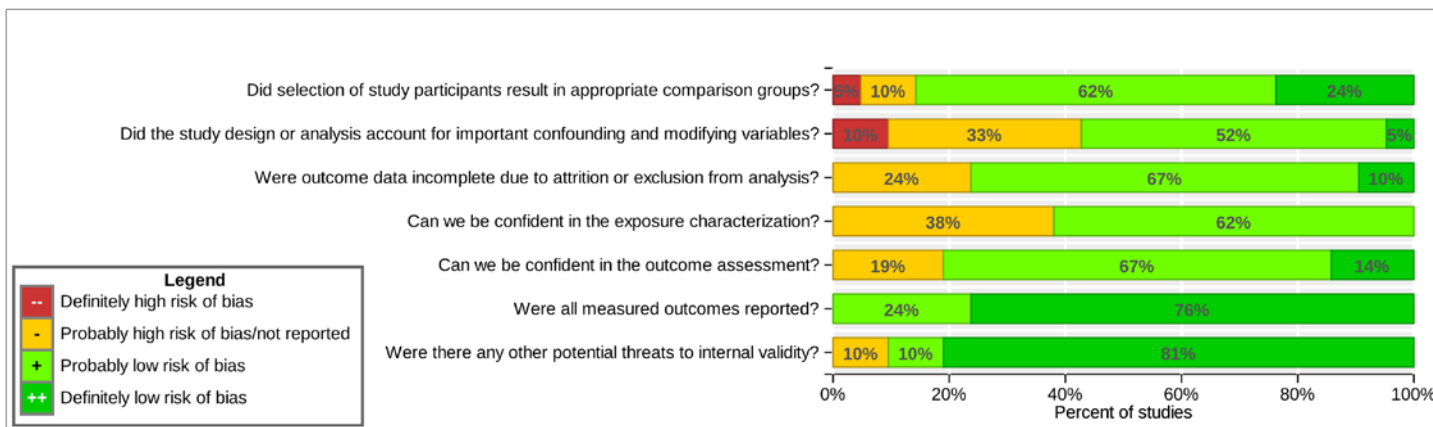
Figure E-9. Risk-of-bias Bar Graph for Studies Reporting on Reproductive and Developmental Toxicity, Other Than Spontaneous Abortion, Associated with Occupational Exposure to Cancer Chemotherapy

Interactive figure and additional study details in HAWC (NTP, 2015a).
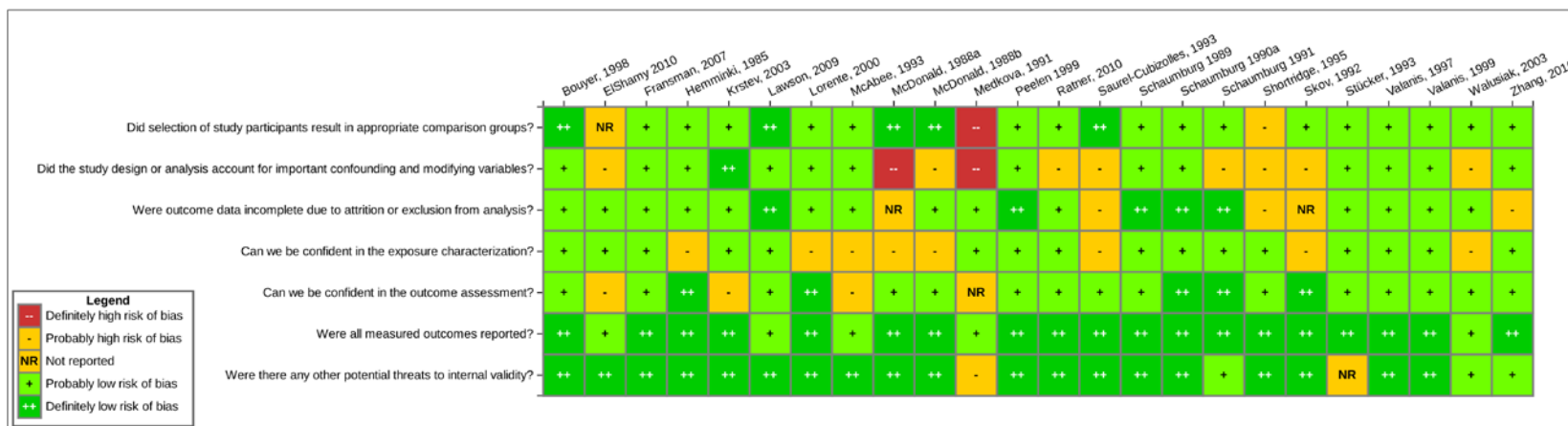
Figure E-10. Risk-of-bias Heat Map for Studies Reporting on Reproductive and Developmental Toxicity, Other Than Spontaneous Abortion, Associated with Occupational Exposure to Cancer Chemotherapy

Interactive figure and additional study details in HAWC (NTP, 2015a). Fransman 2007 refers to Fransman et al. (2007c).

Appendix F. Studies Reporting on Genetic Toxicity

Table F-1. Studies Reporting on Genetic Toxicity, Including Chromosomal Aberrations, Micronucleus Induction, and DNA Damage Measured by Comet Assay

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Anwar et al. (1994)	Cross-sectional (Nurses, National Cancer Institute, Egypt, F)	20 exposed, 20 unexposed nurses	Job title and interviewer-led questionnaire (79.9 ± 46.2 months) *Note: Nurses routinely operated under inadequate protection*	% cells with CA/100 cells and no. of MN/1,000 cells (lymphocytes)	Chi-squared test	Significantly higher **% cells with CA** and n**o. of cells with MN** compared to control nurses
Bolognesi et al. (2005)	Cross-sectional (Nurses, IMPEA project, Italy, FM)	For lymphocytes: 42 exposed, 43 unexposed university professionals; for buccal cells, 50 exposed and 50 unexposed	Job title, [self-reported] questionnaire, and biomonitoring (10.2 years) *Note: Adequate safety equipment and PPE were used*	No. of MN/1,000 cells (lymphocytes or buccal)	Mann-Whitney U-test	No difference in **no. of MN** (lymphocyte or buccal) compared to control subjects
Boughattas et al. (2010)	Cross-sectional (Nurses, Tunisia, FM) *Note: Same population as Bouraoui 2011*	20 exposed, 20 unexposed administrative staff	Job title and self-reported questionnaire (range 1–16 years) *Note: 80% of nurses used PPE; ward nurses usually used a laminar flow cabinet to prepare doses, while outpatient nurses usually prepared drugs at patient's side or in the hallway*	No. of cells with MN/1,000 cells (lymphocytes)	Pearson' Chi-squared test; ANOVA and Student's t-test used to test effect of age, sex, exposure duration, smoking, PPE, cytostatic contact index (CCI), family history of cancer	Significantly higher **no. of cells with MN** in exposed nurses; significant effect of CCI on outcome and other variables were NS

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Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Bouraoui et al. (2011)	Cross-sectional (Nurses, Tunisia, FM) *Note: Same population as Boughattas 2010*	20 exposed, 20 unexposed administrative staff	Job title and self-reported questionnaire (range <5–10 years) *Note: 75% of nurses used gloves, 10% used gowns, 15% used masks, and 5% did not use PPE*	No. of CA/100 cells and no. of MN/1,000 cells (lymphocytes)	Student's-t-test; multivariate regression on effect of age, sex exposure duration, smoking, PPE, and proliferation rate index on CA	Significantly higher **no. of CA** and **no. of MN** compared to unexposed administrative staff; no effect of variables on CA
Buono-Michel et al. (2000)	Cross-sectional (Nurses, France, FM)	14 exposed, 14 unexposed blood donors	Job title and self-reported questionnaire (range 1–28 years) *Note: No hood or dedicated ventilation available in drug preparation area; most nurses wore gloves and accidental exposure occurred to 7 nurses*	No. of cells with MN/1,000 cells (lymphocytes)	Mann-Whitney U-test; ANOVA tested effects of age, family history of cancer; correlation analysis tested for effect of smoking and exposure duration	Significantly higher **no. of cells with MN** compared to unexposed blood donors; no correlation or effect of variables on MN
Burgaz et al. (1999)	Cross-sectional (Nurses, Turkey, F) *Note: Overlapping population with Burgaz 2002*	Lymphocytes: 23 exposed, 13 unexposed nurses and office staff; for buccal cells, 25 and 14, respectively	Job title, interviewer-led questionnaire, and biomonitoring (5 ± 4.45 years) *Note: Nurses involved in preparation and administration of the agents for at least 1 year, 4–5 times per day, no safety hoods were used, and inconsistent PPE use*	No. of MN/1,000 cells (lymphocytes or buccal cells)	Student's t-test or Mann-Whitney U-test; Pearson and Spearman Rank test examined influence of age, smoking, exposure duration, frequency of handling	Significantly higher **no. of MN in lymphocytes** and higher, but NS, **no. of MN in buccal cells** compared to unexposed subjects; no significant effect of variables on outcome

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Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Burgaz et al. (2002)	Cross-sectional (Nurses, Turkey, F) *Note: Overlapping population with Burgaz 1999*	20 exposed, 18 unexposed secretaries and nursing students	Job title, [self-reported] questionnaire, and biomonitoring (8.15 ± 4.70 years) *Note: Nurses involved in preparation and administration of the agents for at least 1 year with minimal protection*	% cells with CA/200 cells (lymphocytes)	Student's t-test or Mann-Whitney U-test; multivariate ANOVA examining effect of exposure, smoking, and age; correlation analysis on urinary CP, frequency of handling, and PPE	Higher, but NS, **% cells with CA** compared to unexposed subjects; exposure a significant factor in ANOVA; no relationships observed in correlation analysis
Buschini et al. (2013)	Cross-sectional (Hospital nurses, Italy, F) *Note: Same population as Moretti 2015*	63 exposed, 74 unexposed nurses	Job title and [self-reported] questionnaire (110 ± 86 months)	% Tail DNA (leukocytes)	Wilcoxson rank sum test	No difference in % tail DNA

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Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Cavallo et al. (2005)	Cross-sectional (Ward and outpatient nurses, and pharmacy technicians, Italy, FM) *Note: Same population as Ursini 2006*	30 exposed: 13 ward nurses, 12 outpatient nurses, 5 pharmacy technicians, and 30 unexposed administrative staff	Job title, [self-reported] questionnaire, and biomonitoring (6.2 ± 2.9 years, ward nurses; 7.0 ± 2.0 years, pharmacists; 8.1 ± 6.0 years, outpatient nurses) *Note: All exposed personnel used adequate PPE, including gloves, caps, overalls, and goggles*	No. of CA/100 cells (lymphocytes) and no. of MN/1,000 cells (lymphocytes or buccal cells)	ANOVA for CA, and Z normal test for MN	Significantly higher **no. of CA** compared to unexposed subjects; significantly higher **no. of MN in buccal cells** in ward and outpatient nurses compared to unexposed subjects; **no. of MN in lymphocytes** NS
Connor et al. (2010)	Cross-sectional (Nurses, pharmacists, and pharmacy technicians, USA, FM) *Note: Same population as McDiarmid 2010 and 2014*	66 exposed, 52 unexposed nurses and pharmacy personnel	Job title, [self-reported] questionnaire, 6–week diary of drug-handling events, biomonitoring, and environmental monitoring (>6 months) *Note: Exposed personnel followed safe handling practices as per NIOSH, and used biological safety cabinets for drug preparation*	% Tail DNA and tail moment	Linear models adjusted for covariates; covariates included: study site location, age, glove usage, personal medication use	No difference in **% tail DNA** or **tail moment**; covariate NS
Cornetta et al. (2008)	Cross-sectional (Nurses, Italy, FM) *Note: Population overlaps with Testa 2007*	83 exposed, 73 unexposed administrative staff	Job title and interviewer-led questionnaire (12.2 ± 7.3 years) *Note: Exposed nurses used adequate PPE and vertical laminar flow cabinet*	No. of MN/1,000 cells (lymphocytes) and % tail DNA	Mann-Whitney U-test and unpaired t-test; multivariate regression examined influence of age, sex, smoking, exposure duration, and genotype	Significantly higher **no. of MN** and **% tail DNA** compared to unexposed subjects; age and sex were significant variables for **no. of MN**

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Cooke et al. (1991)	Cross-sectional (Nurses, pharmacists and pharmacy technicians, United Kingdom, sex NR)	61 exposed, 12 unexposed office workers	Job title and [self-reported] questionnaire (mc > 6 months) *Note: Exposed pharmacists used biological safety cabinets*	No. of CA/100 cells (lymphocytes)	Chi-squared test for individuals with ≤0.9 versus ≥1.0 CA per 100 cells; ANOVA of transformed data	No difference in **no. of CA** compared to unexposed controls
Deng et al. (2005)	Cross-sectional (Methotrexate production workers, China, FM)	21 exposed, 21 unexposed [no description]	Job title, demographics, and job tasks reported [method NR] (range 1–14 years) *Note: Inadequate ventilation equipment; 20 of 21 workers used PPE*	No. of cells with MN and no. of MN/1,000 cells, tail length and tail moment (lymphocytes)	Student's t-test; Kendall's test evaluated correlation of exposure duration	Significantly higher **no. of cells with MN**, **no. of MN**, and significantly greater **tail length** compared to controls; significant correlation with exposure duration for **no. of cells with MN**, **no. of MN**; **tail moment** NS
Deng et al. (2006)	Cross-sectional (Vincristine production workers, China, FM)	15 exposed, 15 unexposed [no description]	Job title, work tasks and safety equipment availability [method NR] (range 1–20 years) *Note: Inadequate ventilation equipment; all 15 workers used PPE*	No. of cells with MN and no. of MN/1,000 cells (lymphocytes), tail length and tail moment	Student's t-test (tail moment only), Wilcoxon's rank sum; Kendall's test evaluated correlation of exposure duration	Significantly higher **no. of cells with MN**, **no. of MN**, and **tail length**; **tail moment** NS
El-Ebiary et al. (2013)	Cross-sectional (Nurses and pharmacists, Egypt, F)	38 exposed, 30 unexposed nurses	Job title and [self-reported] questionnaire (8.18 ± 4.55 years) *Note: Nurse used gloves, but not other PPE; pharmacists used adequate PPE and worked with biological safety cabinets*	% cells with CA and no. of CA/200 cells, no of MN/1,000 cells (lymphocytes)	Student's t-test; correlation analysis by Pearson's test for age and exposure duration	Significantly higher **% cells with CA**, **no. of CA**, and **no. of MN** compared to unexposed nurses; significant Pearson's coefficient for duration of exposure for CA

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Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Ensslin et al. (1997)	Cross-sectional (Pharmacy personnel, Germany, FM)	13 exposed, 13 unexposed [no description]	Job title, work tasks and drugs handled [method NR], and biomonitoring (31.6 ± 13.5 months) *Note: Pharmacists used vertical laminar flow hood; gloves and gown always worn*	No. of MN/1,000 cells (lymphocytes)	Wilcoxon rank test	No difference in **no. of MN** compared to unexposed subjects
Garaj-Vrhovac and Kopjar (1998)	Cross-sectional (Nurses, Croatia, sex NR) *Note: Same population as Kasuba 1999*	10 exposed, 10 unexposed [no description]	Job title only (17.3 years)	No. of MN/500 cells (lymphocytes)	Chi-squared test	Significantly higher **no. of MN** compared to unexposed subjects
Grummt et al. (1993)	Cross-sectional (Nurses and physicians, Germany, FM)	106 exposed, 93 unexposed [no description]	Job title and self-reported questionnaire (range 1–39 years) *Note: Exposed personnel prepared, administered and handled drugs with a biological safety cabinet*	No. of CA/100 cells	Mann-Whitney U-test, including analyses of data by smoking status, age, and exposure duration	Significantly higher **no. of CA** compared to unexposed subjects
Harris et al. (1992)	Cross-sectional (Nurses, USA, F)	24 low exposure, 21 moderate exposure, and 19 high exposure	Job title and interviewer-led questionnaire (duration NR)	No. of MN/1,000 cells (lymphocytes)	Kruskal-Wallis one-way ANOVA, evaluated effect of age, ionizing radiation, chemicals or drugs, exposure duration, smoking, PPE	No difference in **no. of MN** compared to lower exposed nurses; significantly higher **no. of MN** was observed in low and moderate exposure nurses using gloves <100% of the time compared to nurses using gloves 100% of the time

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Hessel et al. (2001)	Cross-sectional (Nurses, pharmacy personnel, one physician, and one orderly, Germany, FM)	113 exposed (tested end of 1 work week for 3 cycles: 83 for cycle 1, 91 for cycle 2, 73 for cycle 3), 93 baseline (3-week absence from exposure), and 60 unexposed office workers	Job title, self-reported questionnaire, and biomonitoring (53 months, range 1–144 months)	No. of MN/1,000 cells (lymphocytes) – tested beginning work shift and 3 work cycles	Mann-Whitney U and Student's t-test; Friedman's ANOVA to test outcome over study period; multiple linear regression to test the effect of age, ionizing radiation, and exposure status	No difference in **no. of MN** compared to unexposed subjects on cycle 1 or over the entire study; ionizing radiation exposure was a significant factor in MN at baseline; for cycle 1 (highest exposure cycle), age was a significant factor, but not ionizing radiation or exposure status
Hola et al. (1988)	Cross-sectional (Nurses and physicians, Czech Republic, FM)	136 exposed (114 nurses and 22 physicians), 20 unexposed blood donors, 277 historical unexposed controls	Job title, number of drug administrations, and use of safety cabinet [method NR] (9.3 ± 0.7 years, nurses and 10.3 ± 1.4 years, physicians)	% cells with CA/100 cells scored (lymphocytes)	Student's t-test	Significantly higher **% cells with CA** in exposed nurses working in pulmonary department compared to unexposed blood donors; **% cells with CA** in exposed physicians NS
Izdes et al. (2009)	Cross-sectional (Nurses, Turkey, FM)	19 exposed, 19 unexposed office workers	Job title and self-reported questionnaire (11.3 ± 4.2 years) *Note: Vertical flow safety cabinet, gloves and mask used during preparation of drugs*	DNA damage index (0 = none, 1 = low, 2 = high migration)	Mann-Whitney U-test with Bonferroni correction; Pearson's or Spearman's correlation test for exposure duration (years of employment)	Significantly greater **DNA damage index** compared to unexposed office workers; no correlation with years of employment

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Jakab et al. (2001)	Cross-sectional (Nurses, Hungary, F)	95 exposed from 4 hospitals, 34 unexposed industrial workers, 74 historical unexposed controls	Job title and interviewer-led questionnaire (mean range 4.0–6.5 years across 4 hospitals) *Note: Hospital 1 had no safety equipment, Hospital 2 had insufficient safety equipment, and Hospital 3 and 4 had sufficient equipment*	% of cells with CA and no. of CA/100 cells	Student's t-test and Mann-Whitney U-test	Significantly higher **% cells with CA** and **no. of CA** in exposed nurses from all 4 hospitals compared to unexposed industrial workers
Kašuba et al. (1999)	Cross-sectional (Nurses, Croatia, F) *Note: Same population as Garaj-Vrhovac and Kopjar 1998*	20 exposed, 16 unexposed [no description]	Job title, work tasks, and drugs handled [method NR] (range 1–31 years)	No. of cells with MN and no. of MN/1,000 cells (lymphocytes)	Chi-squared test	Significantly higher **no. of cells with MN** and **no. of MN** in exposed nurses, with significant increases in nurses with duration of exposure 20-31 years, but not 11–14 years compared to compared to unexposed subjects
Kevekordes et al. (1998)	Cross-sectional (Nurses, Germany, FM)	10 exposed (n = 10 in first examination 2 months after installation of [vertical] laminar flow safety hood and n = 6 retested 9 months after installation), 10 unexposed [no description]	Job title and self-reported questionnaire (duration NR) *Note: Exposed nurses reported following recommended safety precautions; PPE was used*	No. of MN/1000 cells (lymphocytes)	Mann-Whitney U-test	Significantly higher **no. of MN** compared to unexposed subjects in first examination (2 months after installation of safety hood); second examination (9 months following installation of safety hood) revealed no difference in MN compared to first examination values for exposed or unexposed subjects

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Kopjar and Garaj-Vrhovac (2001)	Cross-sectional (Nurses and physicians, Croatia, FM) *Note: Overlapping population with Kopjar 2009*	50 exposed, 20 unexposed students and office workers	Job title and self-reported questionnaire (12.9 years, range 1–30 years) *Note: PPE usage differed among exposed subjects; n = 20 used gloves only, n = 8 used gloves and masks, n = 19 used gloves and safety cabinet with vertical air flow, and n = 3 used gloves, masks, and safety cabinet with vertical air flow*	% Tail DNA, tail length, and tail moment (lymphocytes)	Mann-Whitney U-test	Significantly greater **% tail DNA, tail length** and **tail moment** compared to unexposed subjects; significantly greater DNA damage seen in exposed nurses using only gloves versus exposed nurses using glove and *safety cabinet with vertical air flow*, or using glove, mask, and *safety cabinet with vertical air flow*
Kopjar et al. (2009)	Cross-sectional (Nurses and physicians, Croatia, F) *Note: Overlapping population with Kopjar and Garaj-Vrhorac 2001*	50 exposed, 50 unexposed students and office workers	Job title and self-reported questionnaire (12.9 years, range 1–30 years) *Note: 38% of exposed subjects used gloves and vertical laminar flow; 16% used gloves and mask, while only 6% simultaneously used gloves, mask, and vertical laminar flow cabinet*	% cells with CA and no. of CA/200 cells, no. of cells with MN and no. of MN/1,000 cells and tail moment (lymphocytes)	Mann-Whitney U-test; Spearman Rank Order Correlations age, smoking, exposure duration, PPE; Kruskal-Wallis ANOVA by ranks	Significantly higher **% cells with CA, no. of CA, no. of cells with MN, no. of MN**, and **tail length** compared to unexposed subjects; highest level of tail length observed in exposed subjects who only used latex gloves; age and exposure duration influenced MN; longer exposure duration was accompanied with a shift toward higher values for tail length, % cells with CA and number of cells with MN

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Krepinsky et al. (1990)	Cross-sectional (Nurses, Canada, F)	10 exposed, 10 unexposed nurses	Job title, types and frequency of drug handling, and safety equipment used [method NR] (duration NR) *Note: Exposed nurses prepared drugs in separate rooms without safety hoods or special ventilation; safety education provided, but PPE usage not monitored*	No. of CA/300 cells (lymphocytes) measured at end of work cycle and after 2–6 days off work	Chi-squared test	No difference in **no. of CA** compared to unexposed nurses at end of work cycle or after time off work; **no. of CA** was higher, but NS, compared to unexposed nurses (combining end of work and after work samples)
Ladeira et al. (2014)	Cross-sectional (Nurses, Portugal, FM)	27 exposed, 111 unexposed university employees	Job title, self-reported questionnaire, and environmental monitoring (6.01 years, range 0.17–30 years)	No. of MN/1,000 cells (lymphocytes)	Mann-Whitney U-test, multiple linear regression of exposure, age, sex, smoking and alcohol consumption	Significantly higher **no. of MN** compared to unexposed subjects; exposure and age were significant variables
Laffon et al. (2005)	Cross-sectional Nurses, Portugal, FM)	30 exposed, 22 unexposed nurses from schools	Job title and interviewer-led questionnaire (6.40 ± 6.22 years) *Note: Exposed nurses used laminar airflow hoods and wore laboratory coat, mask, and gloves while preparing, mixing, and administering these drugs*	No. of MN/1,000 cells (lymphocytes) and tail length (leukocytes)	ANOVA with Student's t-test; overall F-test assessed effect of exposure duration, age, sex, smoking and genotypes	Significantly greater **tail length** compared to unexposed subjects; exposure duration was a significant factor; no difference in **no. of MN** compared to unexposed subjects

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Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Machado-Santelli et al. (1994)	Cross-sectional (Nurses, Brazil, FM)	25 exposed, 25 unexposed nurses, physician, secretaries, and drivers	Job title and self-reported questionnaire (range 1–6 years) *Note: Only one nurse used a safety hood, 21 nurses used gloves, 19 nurses used masks, and 2 nurses did not use PPE*	No. of cells with MN/1,000 cells (buccal cells)	Chi-squared test	Significantly higher **no. of cells with MN** compared to unexposed subjects
Mader et al. (2009)	Cohort, longitudinal (Nurses, Austria, F) *Note: Same population as Pilger 2000*	15 subjects served as their own controls: exposed (1, 3, 6, and 9 months on job, referent, after a 3-week vacation)	Job title, self-reported questionnaire, and environmental monitoring (range 1–17 years)	DNA damage index (0 = <5%, 1 = 5–20%, 2 = >20–40%, 3 = >40–95%, 4 = >95%)	Kruskal-Wallis test followed by a post-hoc Dunn's multiple comparisons; trend analysis by linear regression	Significantly higher **DNA damage** compared to referent using trend analysis (p = 0.02); no correlation with years of exposure
Mahmoodi et al. (2017)	Cross-sectional (Nurses and pharmacy technicians, Iran, FM)	71 exposed nurses, 10 exposed pharmacy technicians, 74 unexposed nurses	Job title and self-reported questionnaire (duration >6 months and worked the week prior to assessment)	No. of CA/100 cells and no. of MN/1,000 cells (lymphocytes)	Student's t-test	Significantly higher **no. of CA** and **no. of MN** compared to unexposed nurses

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Maluf and Erdtmann (2000b)	Cross-sectional (Nurses and pharmacists, Brazil, FM)	First study: 10 exposed and 10 unexposed workers; follow-up study: 12 exposed and 12 unexposed; 34 historical unexposed controls	Job title and self-reported questionnaire (range 1–6 years)	No. of MN/2,000 cells and DNA damage index (0 = <5%, 1 = 5–20%, 2 = >20–40%, 3 = >40–95%, 4 = >95%) (lymphocytes)	Mann-Whitney U-test; Spearman rank test for correlations for age and smoking	In first study, significantly **higher no. of MN** compared to concurrent unexposed workers; in follow-up study, no difference in **no. of MN** and significantly higher **DNA damage index** (only measured in follow-up study) compared to both unexposed groups; no correlation with age or smoking
McDiarmid et al. (2010)	Cross-sectional (Nurses, pharmacists, and pharmacy technicians, USA, FM) *Note: Same population as Connor 2010 and McDiarmid 2014*	63 exposed, 46 unexposed nursing and pharmacy personnel	Job title, interviewer-led questionnaire, and 6–week diary of drug-handling events (duration >6 months and worked 24 hours in week prior to assessment) *Note: Exposed personnel followed safe handling practices, including drug preparation in a biological safety cabinet, use of gloves, work practices to reduce drug aerosolization*	No. of CA/200 cells scored and IRR of CA on chromosomes 5, 7, and 11 (lymphocytes)	Poisson regression (categorical analysis) and Poisson distribution and log link function (continuous variable for frequency of drug handling)	Significantly higher **no. of CA** and **IRR of CA on chromosome 5** of highest exposed nurses compared to unexposed subjects; significantly higher **IRR of CA on chromosome 5** with increasing handling events of all cancer chemotherapy or alkylating agents only; IRR of CA on chromosome 7 or 11 NS

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McDiarmid et al. (2014)	Cross-sectional (Nurses, pharmacists, and pharmacy technicians, USA, FM) *Note: Same population as Connor 2010 and McDiarmid 2010*	63 exposed, 46 unexposed nursing and pharmacy personnel	Job title, interviewer-led questionnaire, and 6-week diary of drug-handling events (duration >6 months and worked 24 hours in week prior to assessment) *Note: Exposed personnel followed safe handling practices, including drug preparation in a biological safety cabinet, use of gloves, work practices to reduce drug aerosolization*	IRR of CA on chromosomes 5, 7, and 11 for non-alkylating agent exposure/200 cells scored (lymphocytes)	Poisson regression (categorical analysis) and Poisson distribution and log link function (continuous variable for frequency of drug handling)	Significantly **higher IRR of CA on chromosome 5** with increasing handling events of non-alkylating cancer chemotherapy agents; IRR of CA on chromosome 7 or 11 NS
Medková (1990)	Cross-sectional (Physicians, nurses, auxiliary workers, Czech Republic, FM)	40 exposed from Department of Radiotherapy, 51 unexposed (20 medical studies and 31 workers from Department of Anesthesiology and Resuscitation)	Job title and [self-reported] questionnaire (range 0–15 years)	% cells with CA/100 cells scored (lymphocytes)	Student's t-test	Significantly higher **% of cells with CA** compared to unexposed subjects
Milković-Kraus and Horvat (1991)	Cross-sectional (Nurses, Yugoslavia, F)	42 exposed, 42 unexposed nurses	Job title and [self-reported] questionnaire (duration NR) *Note: None of nurses routinely used PPE*	No. of CA/200 cells (lymphocytes)	Sign test for paired samples; linear regression analysis for possible age-dependent increase of observed variables	Significantly higher **no. of CA** compared to unexposed nurses; age was not a significant factor

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Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Moretti et al. (2013)	Cross-sectional (Nurses, pharmacists, and support personnel, Italy, FM) *Note: Same population as Villarini 2011*	52 exposed, 52 unexposed blood donors	Job position and [self-reported] questionnaire (<10 years, 65%; >10 years, 35%) *Note: 3 nurses used gloves only, 41 used gloves and mask, and 8 used no protection*	No. of MN/1,000 cells and % tail DNA (lymphocytes)	Mann-Whitney U-test followed by Whitney U-test and Bonferroni correction; multiple linear regression tested effects of exposure, sex, age, smoking, type of occupation, exposure duration, and PPE	Significantly higher **% tail DNA** compared to unexposed blood donors; >10 years of employer had significantly higher levels of % tail DNA than less years employed; **no. of MN** NS
Moretti et al. (2015)	Cross-sectional (Nurses, Italy, F) *Note: Same population as Buschini 2013*	71 exposed, 77 unexposed nurses (70 exposed and 75 unexposed for no. of CA/100 cells)	Job title, self-reported questionnaire, biomonitoring, and environmental monitoring (9.20 ± 7.18 years)	No. of CA/100 cells and no. of MN/1,000 cells (lymphocytes)	Mann-Whitney U-test; followed by Mann-Whitney U-test post-hoc analysis with Bonferroni correction; multiple linear regression tested effects of exposure, age, type of occupation, exposure duration, PPE and urinary CP	Significantly higher **no. of CA** and **no. of MN** compared to unexposed nurses; variance was mainly explained by the subjects' type of occupation (another measure of exposure)
Mrđanović et al. (2012)	Cross-sectional (Nurses, Bosnia and Herzegovina, F)	15 exposed, 20 unexposed workers [no description provided]	Job title and self-reported questionnaire (range 1–20 years) *Note: Nurses used gloves, masks, and protective clothes*	No. of MN/1,000 cells (lymphocytes)	Mann-Whitney U-test and ANOVA	Significantly higher **no. of MN** in exposed nurses
Mušák et al. (2006)	Cross-sectional (Healthcare workers, Slovakia, FM) *Note: Same population as Mušák 2013*	72 exposed, 34 unexposed hospital workers	Job title (8.09 ± 7.30 years)	No. of CA/100 cells (lymphocytes)	Mann-Whitney U-test	Higher, but NS (p = 0.07), **no. of CA** compared to unexposed workers
Mušák et al. (2013)	Cross-sectional (Nurses and physicians, Slovakia, FM) *Note: Same population as Mušák 2006*	249 exposed, 250 unexposed hospital workers	Job title and self-reported questionnaire (8.5 ± 8.6 years)	% cells with >1 CA (lymphocytes)	Mann-Whitney U-test and Kruskal-Wallis test and logistic regression tested effect of exposure, age, sex, and smoking	Significantly higher **% cells with >1 CA** compared to unexposed workers; exposure was only significant variable

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Nikula et al. (1984)	Cross-sectional (Nurses, Finland, [F])	11 exposed, 16 unexposed (11 hospital clerks and 5 laboratory workers)	Job title and interviewer-led questionnaire (range 2.5–10 years) *Note: After 1980, improvements were made to work practices and safety equipment (e.g., biological safety cabinet and isolated room for drug handling); nurses wear gloves and masks*	% cells with CA (lymphocytes)	Mann-Whitney U-test	Significantly higher **% cells with CA** compared to either unexposed hospital clerks or unexposed laboratory workers
Pilger et al. (2000)	Cross-sectional (Pharmacy personnel, Austria, FM) *Note: Same populations as Mader 2009*	16 exposed, 16 unexposed workers from same hospital who were tested at 5 time points	Job title, self-reported questionnaire, and biomonitoring (duration NR) *Note: Hospitals had central workplaces containing cabinets with vertical laminar flow and personnel wear glove, overalls, caps, and goggles*	No. of MN/2,000 cells (lymphocytes)	ANOVA with stochastic components to compare data on the same subjects over 5 sampling periods	No difference in the **no. of MN** compared to unexposed subjects
Pohlová et al. (1986)	Cross-sectional (Chemists, laboratory assistants, pilot plant workers, Czech Republic, FM)	38 exposed (8 pilot workers and 30 chemists and laboratory assistants), 18 unexposed librarians and clerks	Job title and self-administered questionnaire (range >1–<6 years)	% cells with CA (lymphocytes)	Student's t-test	Significantly higher **% of cells with CA** compared to unexposed workers

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Rekhadevi et al. (2007)	Cross-sectional (Nurses, India, F)	60 exposed, 60 unexposed from general population	Job title, interviewer-led questionnaire, and biomonitoring (range 6–23 years)	No. of MN/1,000 cells (lymphocytes or buccal cells), and tail length (lymphocytes)	Student's t-test; multiple linear regression for age, exposure duration, daily exposure	Significantly higher **no. of MN** (buccal or lymphocytes) and **tail length** compared to unexposed subjects; age and exposure duration were significant for MN and tail length; significantly higher tail length for nurses with ≥10 years exposure compared to <10 years exposure
Rodríguez-Montero et al. (2016)	Cross-sectional (Medical Oncology Service workers, Cuba, FM)	14 exposed: 10 workers preparing doses in the Central Unit of Cytostatic Mixes (CUCM) and 4 workers of the Ambulatory Chemotherapy Room (ACR), 14 unexposed workers at same medical institution	Job title, job tasks, duration, and frequency of handling drugs [method NR] (mean range 12.8–129.6 months) *Note: Drugs were prepared in CUCM with correct use of primary protective barriers; good laboratory practice is employed in both the CUCM and the ACR*	No. of cells with MN/1,000 cell (buccal cells)	Mann-Whitney U-test	No difference in **no. of MN** compared to unexposed subjects

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Rombaldi et al. (2009)	Cross-sectional (Nurses and pharmacists, Brazil, FM)	20 exposed, 20 unexposed office workers	Job position and self-reported questionnaire (range 0.5–10 years) *Note: All nurses and pharmacists used PPE, such as protective clothes, eyes glasses, gloves, masks; both hospitals had vertical laminar flow hoods*	No. of cells with MN/1,000 cells and DNA damage index (0 = <5%, 1 = 5–20%, 2 = >20–40%, 3 = >40–95%, 4 = >95%) (lymphocytes)	Student's t-test; ANOVA with post-hoc Tukey's t-test for multiple comparisons during the week; Pearson coefficient for age and exposure duration	Significantly higher **no. of cells with MN** and **DNA damage index** compared to unexposed subjects**;** age was a significant factor for MN; positive correlation between DNA damage index and sampling day such that the it was significantly greater on Wednesday or Thursday relative to Monday (the first day sampled); alcohol consumption also a significant factor for DNA damage index

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Roth et al. (1994)	Cohort, prospective (Pharmacists, Finland, F)	6 exposed: tested at start of job and after 1 year of work, 6 unexposed office workers	Job title, previous and current drug handling, use of PPE [method NR] (duration not applicable) *Note: Pharmacists used overall, masks, and gloves; drug handling conducted in vertical laminar flow safety cabinet in a special negative-pressured laboratory, apart from other working facilities*	% cells with CA and no. of cells with MN/1,000 cells scored (lymphocytes)	Logistic-binomial regression (30 trials); model considered exposure, age, and sample batch	No difference in **% cells with CA** or **no. of cells with MN** after 1 year of work compared to unexposed subjects
Rubeš et al. (1998)	Cross-sectional (Nurses and physicians, Czech Republic, FM)	10 exposed, 10 unexposed nurses and doctors, 11 unexposed blood donors	Job title and drug handling (types, frequency, and duration) [method NR] (4–27 years)	% cells with CA (lymphocytes)	Mann-Whitney U-test	Significantly higher **% cells with CA** compared to unexposed blood donors, but not to unexposed nurses and physicians; significantly higher **% cells with CA** in all medical personal compared to unexposed blood donors; exposure duration or smoking status NS

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Sasaki et al. (2008)	Cross-sectional (Nurses, Japan, F)	121 exposed (only 57 prepared and administered agents), 46 unexposed hospital clerks	Job title and self-reported questionnaire (≤6 months)	Tail length and tail moment (lymphocytes)	ANCOVA tested for influence of exposure, sex, age, smoking habits, occupation, exposure duration, and PPE; logarithmic-transformation because data were not normally distributed	Following log-transformation, significantly greater **tail length** in all 121 nurses and in the 57 actively exposed nurses compared to unexposed clerks; however, no difference in **tail length** of 64 nurses not actively exposed compared to unexposed clerks or the 57 exposed nurses; **tail moment** NS

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Sessink et al. (1994a)	Cross-sectional (Nurses and pharmacy technicians, the Netherlands, F)	17 exposed, 35 unexposed pharmacy technicians	Job title, [self-reported] questionnaire, and biomonitoring (7 years, range 4–14 years) *Note: Most workers wore PPE; drugs were prepared in laminar down-flow hoods*	% cells with CA (lymphocytes)	Two-way ANOVA evaluated exposure and smoking	No difference in **% cells with CA** compared to unexposed subject
	Cross-sectional (Nurses, laboratory technicians, cleaning staff, Czech Republic, FM)	11 exposed, 23 unexposed physicians, nurses, lab technicians and a cleaning woman	Job title, [self-reported] questionnaire, and biomonitoring (13 years, range 3–25 years) *Note: Most workers wore PPE; drugs were prepared in laminar down-flow hood*	% cells with CA (lymphocytes)	Two-way ANOVA evaluated exposure and smoking	Significantly higher **% cells with CA** compared to unexposed workers; additive effects between exposure and smoking
Sorsa et al. (1988)	Cross-sectional (Drug manufacturing workers and laboratory technicians working with cyclophosphamide (CP), Finland, FM)	36 exposed (13 manufacturing workers, 3 laboratory technicians), 20 unexposed (10 unexposed factory employees, 10 controls from outside the factory)	Job title, work tasks, use of PPE [method NR], and air monitoring (range 1.5–16 years based on subjects with MN data) *Note: PPE and best available safety techniques were used; during the preparation of CP powder, manufacturing and production workers wore gas-protective suits*	% cells with CA and no. of CA/100 cells (lymphocytes)	NR	No difference in **% cells with CA** or **no. of CA** between exposed subjects and controls
	Cross-sectional (Drug production and laboratory workers working with cyclophosphamide, Finland, FM)	21 exposed (12 drug production workers, 9 laboratory workers), 11 unexposed factory employees		% cells with CA and no. of CA/100 cells (lymphocytes)	NR	No difference in **% cells with CA** or **no. of CA** between exposed subjects and controls

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
	Cross-sectional (Same group of drug manufacturing and production workers working with cyclophosphamide, Finland, FM)	19 exposed (7 process workers, 12 drug manufacturing workers), 7 unexposed factory employees		No. of MN/1,000 cells (lymphocytes)	NR	No difference in the **no. of MN** compared to unexposed employees; significant correlation with age
Stücker et al. (1986)	Cross-sectional (Nurses in pneumology, France, F)	16 exposed, 24 unexposed hospital staff from same department	Job title and [self-reported questionnaire] (3.5 years) *Note: PPE not consistently used, no vertical laminar flow cabinet or isolated room for drug preparation was available*	No. of CA/100 cells (lymphocytes)	Chi-squared test	No difference in **no. of CA** compared to unexposed hospital staff; correlation with age and adjustment for radiodiagnostic exposure NS; authors state that nurses had moderate exposure (11 perfusion per week)
Testa et al. (2007)	Cross-sectional (Nurses, Italy, FM)	76 exposed, 72 unexposed blood donors	Job title and interviewer-led questionnaire (12.2 ± 7.7 years) *Note: Exposed nurses were involved in preparation and administration of drugs; they used PPE (gloves, overalls, and goggles) and chemical and biohazard laminar flow [safety cabinets]*	No. of CA/100 cells (lymphocytes)	Mann-Whitney U-test	Significantly higher **no. of CA** compared to unexposed blood donors

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Thiringer et al. (1991)	Cross-sectional (Nurses, Sweden, FM)	54 exposed nurses in Hematology and Oncology, 54 unexposed nurses	Job title and self-reported questionnaire (duration NR) *Note: 91% of exposed nurses always used the safety hood; all but one nurse always used gloves; use of masks was less consistent*	No. of MN/1,000 cells (lymphocytes)	Wilcoxon signed-rank test	No difference in the **no. of MN** compared to unexposed nurses
Thulin et al. (1995)	Cross-sectional (nor-Nitrogen mustard production workers, [Sweden], M)	6 exposed, 6 unexposed office workers Exposed subjects were sampled before production, 1 and 2 weeks during production, and 4 weeks after end of production	Job title, PPE usage, and environmental monitoring (4 years) *Note: Production unit was in a building adjacent to the office with free access between the two spaces; all workers wore PPE with personal fresh-air devices during production*	No. of CA/100 cells (lymphocytes)	Student's t-test and Wilcoxon's test	No difference in **no. of CA** compared to unexposed controls at any sampling time; **no. of CA** in unexposed office workers were higher than concurrent unexposed subjects or historical unexposed data
Ündeğer et al. (1999)	Cross-sectional (Nurses, Turkey, FM)	30 exposed, 30 unexposed nurses, secretaries, and technicians	Job title and self-reported questionnaire (range 0.5–13 years) *Note: 26 exposed nurses used safety ventilation cabinets; 13 used gloves, masks, and gowns; 17 did not use gloves*	DNA damage index (2.5 = <5%, 12.5 = 5–20%, 30 = >20–40%, 67.5 = >40–95%, 97.5 = >95%)	Student's t-test; linear regression for effects of exposure duration	Significantly greater **DNA damage index** of >5% damage compared to unexposed subjects; no correlation with age, exposure duration; exposed nurses without safety equipment had significantly higher **DNA damage index** than those with safety equipment

Systematic Review of Occupational Exposure to Cancer Chemotherapy Agents

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Ursini et al. (2006)	Cross-sectional (Nurses and pharmacy technicians, Italy, FM) *Note: Same population as Cavallo 2005*	30 exposed (5 pharmacy technicians, 15 day nurses, 10 ward nurses), 30 unexposed administrative staff	Job title, self-reported questionnaire, biomonitoring, and environmental monitoring (6.2 ± 2.9 years, ward nurses; 7.0 ± 2.0 years, pharmacists; 8.1 ± 6.0 years, outpatient nurses) *Note: Exposed personnel wore PPE, including gloves, caps, overalls, and goggles; specialized pharmacy prepared the doses*	Tail moment (lymphocytes or buccal cells)	Student's t-test; ANOVA to test effects of age and exposure duration	No difference in **tail moment** (in either cell population) compared to unexposed subjects
Villarini et al. (2011)	Cross-sectional (Pharmacy technicians, nurses, and nurses' aides, Italy, FM) *Note: Same population as Moretti 2013*	52 exposed subjects involved in preparation, administration, transportation, and disposal, 52 unexposed public workers from same localities as exposed	Job title, interviewer-led questionnaire, biomonitoring, and environmental monitoring (<10 years, n = 13; 11–20 years, n = 14, and >20 years, n = 4) *Note: Exposed workers involved in preparation, transportation, administration, and disposal of cancer chemotherapy agents*	% Tail DNA and tail length (leukocytes)	Mann-Whitney U-test; sub-group analysis by Kruskal-Wallis H-test; multivariate regression analysis to examine effect of exposure status, gender, age, smoking, occupation, PPE, job seniority, and genetic polymorphisms	Significantly greater **% tail DNA** in exposed subjects; **tail length** NS; occupation was a significant covariate
Yager et al. (1988)	Cross-sectional (Chemical process workers, manufacturing workers, and nurses, Finland, FM) *Note: Overlapping population with Sorsa 1988*	27 exposed (7 chemical process workers, 12 manufacturing workers, and 8 oncology nurses), 9 unexposed subjects [no description provided]	Job title and work history [method NR] (range 2–25 years)	No. of MN/1,000 cells (lymphocytes)	ANOVA; log-transformation of data and adjustment for influence of age	ANOVA variables for exposure and age were significant); log-transformed data adjusted for age revealed significantly higher **no. of MN** compared to unexposed subjects

Study	Study Design (Occupation, Location, Sex)	No. of Participants	Exposure Measure (Duration)	Outcome Measured	Analysis	Results
Yang et al. (2002a)	Cross-sectional (Nurses, China, [F]) *Note: Same population as Yang 2002b*	16 exposed, 16 nursing students	Job title and drug handling (types and frequency) (5.6 years, range 1–16 years)	Tail length	[Mann-Whitney] U-test	Significantly greater **tail length** in exposed subjects than controls
Yang et al. (2002b)	Cross-sectional (Nurses, China, F) *Note: Same population as Yang 2002a*	16 exposed, 16 nursing students	Job title and frequency of drug handling (5.5 years)	No. of CA/100 cells and no. of MN/1,000 cells (lymphocytes)	[Mann-Whitney U-test]	Significantly higher **no. of CA** and **no. of MN** compared to unexposed nursing students
Yin et al. (2010)	Cross-sectional (Oncology Nurses, China, F)	30 exposed, 30 unexposed nurses	Job title, work tasks, drug handling, PPE usage [method NR] (9.8 ± 5.9 years) *Note: PPE and biosafety cabinets were used during preparation of doses*	% Tail DNA, tail length, and tail moment	Logarithmic-transformation followed by multiple linear regression	Significantly greater **% tail DNA**, **tail length**, and **tail moment** compared to unexposed nurses
Yoshida et al. (2006)	Cross-sectional (Nurses from hematology department, Japan, F)	19 exposed nurses, 18 unexposed nurses from Department of Cardiovascular Disease	Job title and self-reported questionnaire (5.7 years, range 0.2–25.2 years)	Tail length (lymphocytes)	Mann-Whitney U-test	Significantly greater **tail length** compared to unexposed nurses; age and duration of exposure were significant variables

ANCOVA = analysis of covariance, ANOVA = analysis of variance, CA = chromosomal aberrations, CCI = cytotoxic contact index, CP = cyclophosphamide, DNA = deoxyribonucleic acid, F = female, IRR = incident rate ratios, M = male, MN = micronucleus or micronuclei, n or No. = number, NR = not reported, NS = not significant OR = odds ratio, PPE = personal protective equipment, USA = United States of America.

Appendix G. List of Included Studies Reporting on Environmental Monitoring or Biomonitoring

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Appendix H. Protocol History

The original and revised protocols are available in Appendix I.

Table H-1. Protocol History and Revisions

Date	Activity or Revision
May 28, 2015	Draft evaluation protocol reviewed: sent to experts for comment/review
October 9, 2015	Evaluation protocol posted on Office of Health Assessment and Translation website
December 7, 2018	Revised protocol posted to reflect principal updates made during evaluation with justifications noted (date implemented):
	1. Decision to evaluate evidence of all health effects, including reproductive and developmental toxicity, to make the evaluation comprehensive and ensure that the most recent papers on reproductive system effects were included (January 2016).
	2. Consideration of acute effects as well as genetic toxicity as primary health outcomes, not secondary health outcomes. Genetic toxicity moved to primary health outcome because of the established association of chromosome aberrations and micronucleus induction with future cancer incidence. These changes were made based on consultation with a technical advisor and federal experts following review of a preliminary draft on the monograph (November 2016).
	3. Adjustment of exposure characterization risk-of-bias assessment to include job position with work tasks and details about drug handling (e.g., types of cancer chemotherapy agents, frequency of drugs handled) via questionnaire or self-reported daily diary with validation as probably low risk of bias. These changes were made based on consultation with a technical advisor and federal experts following review of a preliminary draft on the monograph (November 2016).
	4. Adjustment of initial confidence rating in the body of evidence of cross-sectional studies of genetic toxicity from low initial confidence to moderate initial confidence because the three genetic toxicity outcomes are rapidly developing (e.g., hours to days) and the period of occupational exposure began prior to development of the outcome (January 2017).
	5. Removal of the hazard identification step due to lack of a formal way to integrate authoritative reviews into the integration of evidence streams step (January 2017). Note, given that level of evidence was moderate and no hazard conclusions reached, a formal public comment period was not included

Appendix I. Supplemental Files

The following supplemental files are available at https://doi.org/10.22427/NTP-DATA-MONOGRAPH5.

I.1. Protocol Information

Protocol
Protocol.pdf

Revised Protocol
Revised_Protocol.pdf

I.2. Monitoring References

Supplemental Table 1. Environmental Monitoring References
Supplemental Table_1 Environmental Monitoring references_final.xlsx

Supplemental Table 2. Biomonitoring References
Supplemental Table_2 Biomonitoring references_final.xlsx