

# **NTP Evaluation Concept:** **Adverse Health Effects Associated With Occupational Exposure To** **Cancer Chemotherapy Agents**

## **Project Leader**

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## **Background and Rationale**

The Office of Health Assessment and Translation (OHAT) of the Division of the National Toxicology Program (NTP) proposes to conduct a systematic review of the scientific evidence for health effects associated with occupational exposure to cancer chemotherapy agents. Cancer chemotherapy agents are cytotoxic drugs, and many of these agents are known mutagens and/or developmental toxicants. The evaluation of adverse health effects in workers occupationally exposed to cancer chemotherapy agents was identified as a research need in the NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy (<http://ntp.niehs.nih.gov/go/36495>).

Occupational exposure to cancer chemotherapy agents may occur in medical, veterinary, and manufacturing settings among personnel involved in production, preparation and administration of these agents, as well as other workers involved with the care of patients administered chemotherapy. Potential routes of occupational exposure may 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 specific combination therapy and it may occur over a longer period of time. Furthermore, occupational exposures usually are unrecognized due to lack of systematic environmental monitoring and biomonitoring programs.

There is documented contamination of healthcare work environments with cytotoxic cancer chemotherapy agents. Evidence for 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 elevated levels of biomarkers of exposure such as chromosome aberrations, sister chromatid exchanges, and DNA damage in workers handling these agents, as well as direct identification of chemotherapy agents or their metabolites in workers' urine. The monitoring of workplace contamination was implemented following the establishment of guidelines for safe handling of hazardous drugs in the 1980s and 1990s by national health care worker agencies in multiple countries, including the Occupational Safety and Health Administration in the United States (OSHA, 1999). Beginning in the 1990s, numerous publications have documented surface contamination of safety cabinets, countertops, floors, and equipment with chemotherapy agents. While improved handling procedures and engineering controls have reduced contamination, Connor et al. (2012) reported that surface contamination persists in pharmacy and nursing areas of some hospital-based cancer centers. In addition, potential occupational exposure to cancer chemotherapy agents has increased with: (1) greater usage of

chemotherapy for non-cancer disease conditions and (2) the development of new surgical techniques involving intraperitoneal administration of chemotherapy.

To help refine the focus of the evaluation, OHAT undertook an exploratory search of the literature where citations were reviewed from a preliminary search to estimate the likely number of relevant studies and types of health outcomes being investigated (but no results are summarized). In the exploratory literature search, OHAT identified 59 studies that assessed the association between occupational exposure to cancer chemotherapy agents and health, with the majority of studies reporting on pregnancy outcomes and reproductive function (Supplemental Figure 1). We consider this to be a manageable number of studies and do not consider it necessary to limit the scope to a particular type of health outcome. In addition, the OHAT literature search identified 66 biomonitoring studies of blood or urine concentrations, and 108 studies reporting biomarkers of exposure. We are aware of two other systematic reviews that have been conducted on this topic. One review was conducted in 2005 (Dranitsaris *et al.*, 2005) and although the health outcomes were broad (cancer, pregnancy outcomes, and acute toxic effects) it focused on nurses, pharmacists, or pharmacy technicians/assistants and did not include the full range of possibly exposed occupations. In addition, we identified 18 studies published in 2005 to 2013 since the review by Dranitsaris *et al.* (2005). A more recent systematic review of occupational exposures in adverse pregnancy outcomes in nurses included consideration of exposure to chemotherapy agents; however, other occupations and health outcomes were not considered (Quansah and Jaakkola, 2010). Thus, a broad evaluation to consider a wide range of occupations and health outcomes would seem appropriate.

The proposed evaluation will assist the National Institute for Occupational Safety and Health's (NIOSH) efforts to evaluate the effects of occupational exposure to cancer chemotherapy agents. In addition to conducting research on occupational exposures, scientists at NIOSH maintain a webpage of the literature on adverse health effects associated with occupational exposure to hazardous drugs (<http://www.cdc.gov/niosh/topics/antineoplastic/#c>) and are currently completing a narrative review on adverse reproductive effects due to occupational exposure to hazardous drugs. The proposed OHAT evaluation will assist NIOSH's efforts by evaluating the literature on health effects in relationship to occupational exposure using systematic review methodology with steps to evaluate individual study quality and establish confidence in the body of evidence (<http://ntp.niehs.nih.gov/go/38673>). Data management will be conducted in a manner that permits public sharing of the exploratory literature search results as well as the sharing of data extracted from included studies in a database format when the monograph is finalized following peer-review. The sharing of extracted data in a database format should facilitate future updates to this evaluation conducted by NTP or other organizations.

### **Key Issues**

There is need for a critical review of the health effects observed in employees occupationally exposed to cancer chemotherapy agents. Some challenges for assessing the effects of occupational exposure to cancer chemotherapy agents include: (1) the temporal nature of exposure, (2) differences in the composition of the exposures (i.e., combination therapy versus

single agents), and (3) difficulty in estimating the internal exposure based on environmental contamination. It is difficult to determine internal dose from environmental contamination; however, biomonitoring studies of the more commonly used cytotoxic drugs can provide background information about the levels of the parent drug or metabolites in blood and urine of the occupationally exposed workers. The literature on biomarkers of exposure is more developed (approximately 108 studies) and may be considered supportive evidence for the proposed evaluation. OHAT will continue to refine the breadth of the proposed evaluation with the evaluation design team.

### **Specific Aims**

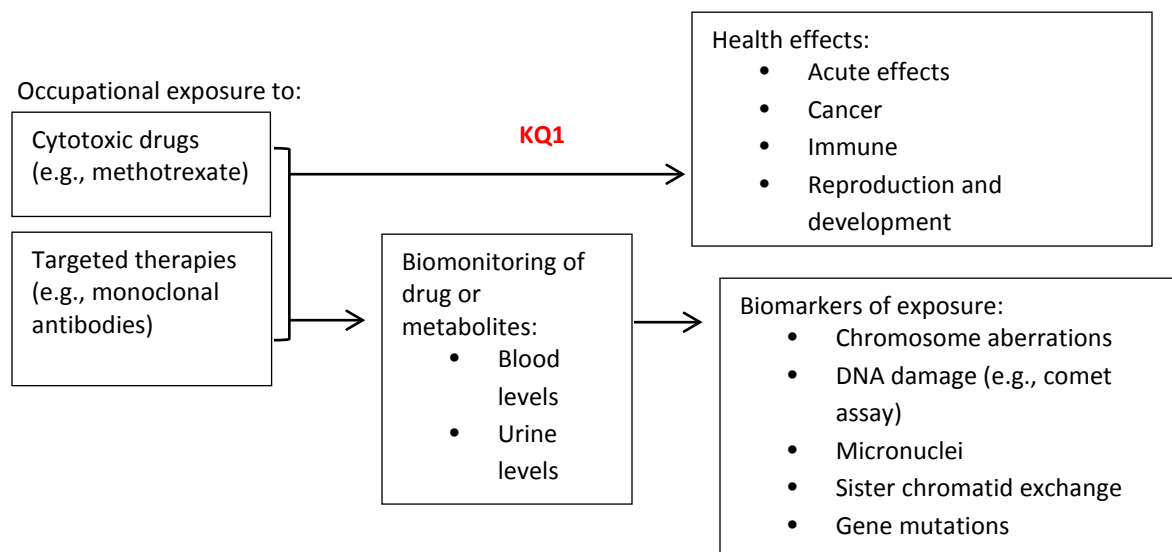
The overall objective of this evaluation is to reach hazard identification conclusions (“known,” “presumed,” “suspected,” or “not classifiable”) for identified health outcomes by integration of evidence from human observational studies. A state of the science paper will be written if sufficient data are not available to reach hazard identification conclusions for this evaluation.

The key question for the proposed evaluation is:

- What is our confidence in the body of evidence for an association between occupational exposure to cancer chemotherapy agents and adverse health effects based on the results of observational studies in humans?

**Figure 1** conveys the relationship between the key question and the types of evidence included in the evaluation.

Figure 1. Analytical framework



## **Proposed Approach**

In addition to the preliminary literature screening, OHAT has solicited input from scientists at other federal agencies who work on chemotherapy agents and occupational exposure issues including scientists at the Food and Drug Administration (FDA), National Cancer Institute, NIOSH as well as NIEHS/NTP. OHAT will further refine the scope of the proposed evaluation following an initial characterization of the relevant studies.

The proposed OHAT evaluation will use systematic review methodology with steps to evaluate individual study quality and establish confidence in the body of evidence (<http://ntp.niehs.nih.gov/go/38673>). Data management will be conducted in a manner that permits public sharing of the exploratory literature search results as well as data extracted from studies in a database format when the monograph is finalized following peer-review. Sharing of data in this format should facilitate future updates to this evaluation conducted by NTP or other organizations. After additional steps to refine the project and develop a protocol, the protocol will be posted and other key milestones in the evaluation will be announced on the NTP listserv (e.g., posting list of included studies).

## **Significance**

The proposed NTP evaluation will build upon and extend the NIOSH efforts to understand the health effects of occupational exposure to cancer chemotherapy. Based on a sufficient literature base, the proposed evaluation will reach hazard conclusions for the relationship of adverse health outcomes with occupational exposure to cancer chemotherapy. Data management will be conducted in a manner that permits public sharing of the exploratory literature search results as well as sharing the data extracted from included studies in a database format.

## **References**

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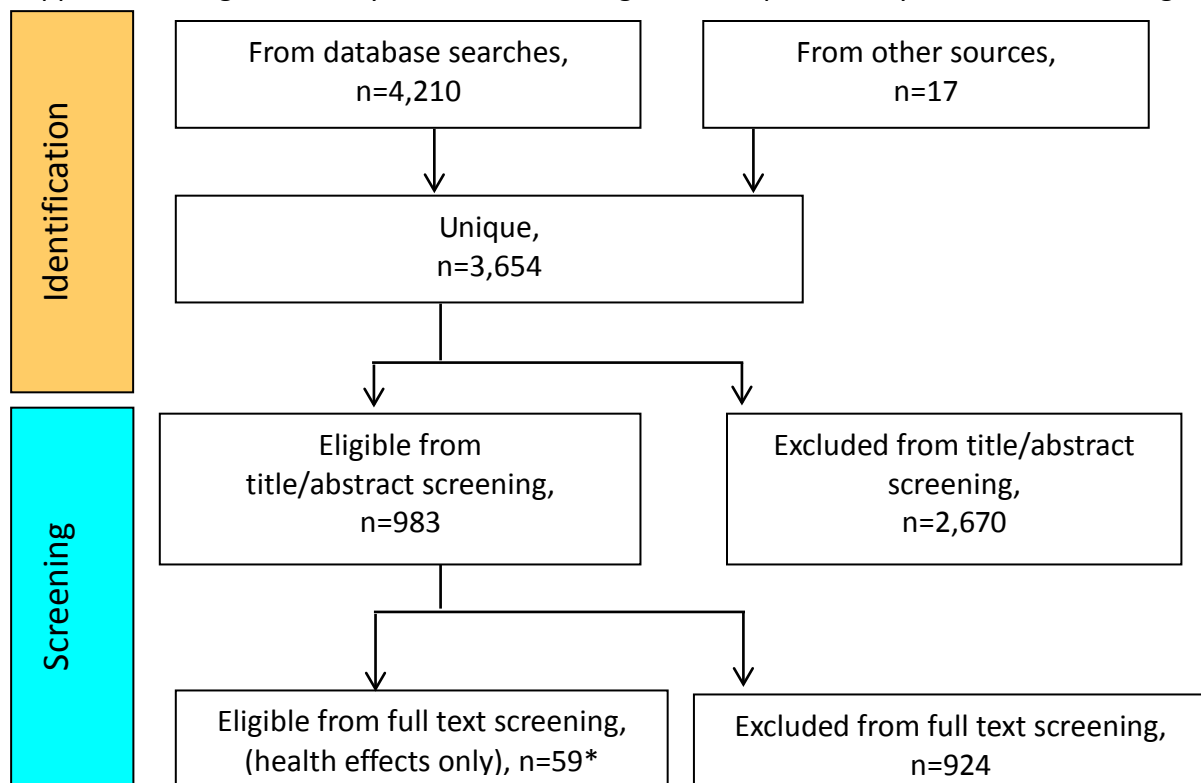
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OSHA (1999). Occupational Safety & Health Administration (OSHA) Technical Manual (OTM), Section VI: Chapter 2 Controlling Occupational Exposure to Hazardous Drugs. Directive number: TED 01-00-015 [TED 1-0.15A]. United States Department of Labor, Washington, DC.

Quansah, R., and Jaakkola, J. J. (2010). Occupational exposures and adverse pregnancy outcomes among nurses: a systematic review and meta-analysis **19**(10), 1851-62.

## Supplemental Data

Supplemental Figure1: Study selection flow diagram from preliminary literature screening



\*Number of references per health effect of 59 references reporting health outcomes:

Acute symptoms, 21

Cancer, 8

Immune, 15

Reproductive, 23

Other, 7