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National Toxicology Program

**Draft NTP Monograph  
on  
Developmental Effects and Pregnancy  
Outcomes Associated with Cancer  
Chemotherapy Use during Pregnancy**

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# Introduction, Methods and Limitations of the Data

Cancer Chemotherapy Use during  
Pregnancy





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# Introduction

Cancer Chemotherapy Use during  
Pregnancy



# Introduction

- ~17 to 100 per 100,000 women are diagnosed with cancer during pregnancy
- Patient and her medical team must determine course of treatment optimal for mom with minimal risk to fetus
  - Most treatments for cancer involve chemotherapy
  - Nearly all cancer chemotherapeutic agents have possible or demonstrable risk to the fetus
- Current medical paradigm suggests:
  - Avoid treatment during the 1<sup>st</sup> trimester, when possible
  - Treatment in 2<sup>nd</sup> and/or 3<sup>rd</sup> trimester does not appear to increase risk of major congenital malformations observed at birth

# Sources of literature

- Majority of data on pregnancy outcomes are reported in case reports and case series, which have small sample sizes
- There are efforts to obtain larger patient samples by systematically collecting data via registries and prospective studies
  - Registries include:
    - Cooper University Hospital in Camden, New Jersey, USA
    - University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma, USA
    - Toronto Hospital of Sick Children in Ontario, Canada
    - University of Frankfurt and German Breast Group, Germany
  - Clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)):
    - MD Anderson Cancer Center, Houston, Texas, USA
    - Katholieke Universiteit, Leuven, Belgium

# Purpose

- Purpose of draft NTP monograph:
  - To summarize the effects of gestational exposure to cancer chemotherapy on pregnancy outcomes in the peer-reviewed literature
    - Of 113 chemotherapy agents currently in use, the draft NTP monograph includes data on all 52 agents for which pregnancy outcomes were documented
  - To serve as a tool for physicians and their patients in making clinical decisions
    - Not intended as a medical advice or clinical guidance

# Health outcomes

- Draft NTP monograph focuses on 5 health outcomes:
  - Primary outcomes:
    - Major congenital malformations associated with treatment during the 1st trimester versus the 2nd and/or 3rd trimester only
    - Early and late spontaneous fetal death
  - Secondary outcomes:
    - Pregnancy complications (e.g., reduction in amniotic fluid and spontaneous preterm labor)
    - Newborn weight and health (e.g., small for gestational weight, fetal/neonatal cardiotoxicity, and transient myelosuppression)
    - Growth and development of gestationally-exposed offspring

## Background information

- To provide context, the draft NTP monograph provides background information on:
  - Prevalence and prognosis of 7 frequently diagnosed cancers in women of reproductive age
  - Individual cancer chemotherapeutic agents, including data on:
    - Mechanism of action
    - Indications
    - Evidence of transfer to fetus or breast milk
    - Developmental toxicity in laboratory animal studies
  - Background information was collected from both primary and secondary sources; it is not the main focus of this evaluation



# Concept development

- Concept for this evaluation was developed following discussion with scientists and clinicians in the United States at the:
  - National Cancer Institute (NCI)
  - National Institute of Child Health and Human Development (NICHD)
  - Food and Drug Administration (FDA) Center for Drug Evaluation and Research
  - National Comprehensive Cancer Network (NCCN)
- Concept was reviewed by the NTP Board of Scientific Counselors on June 21, 2010

## Technical advisors

- Technical advisors provided guidance on sections of the draft monograph, including the content of the appendix tables and agent specific chapters
- Technical advisors for the draft NTP monograph:
  - **Hatem Azim Jr, MD**; Department of Medical Oncology, Jules Bordet Institute, Brussels, Belgium
  - **Elyce Cardonick, MD**; Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Cooper Health System, Camden, NJ
  - **Richard Theriault, DO**; Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX



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# Methods

## Cancer Chemotherapy Use during Pregnancy



# Literature Search Strategy

- Focused on 4 key concepts:
  - Chemotherapy, pregnancy, pregnancy outcomes, and human studies
- Screening criteria for literature search results
  - Inclusion:
    - Pregnancy outcomes of female cancer patients treated with cancer chemotherapy during pregnancy
  - Exclusion:
    - Male cancer patients
    - Non-English language
    - Absence of data on pregnancy outcome
    - Chemotherapy administered for non-cancer health conditions
    - Drugs used to treat side-effects of cancer or its treatments

# Literature Search Results

- Database searched:
  - PubMed
  - Web of Science
  - Scopus
  - Embase
  - Toxnet
- Initial search – through June 7, 2010
- Weekly PubMed searches – from June 7, 2010 through May 15, 2012
- *Total references, n=1425*

+

- Other databases searched:
  - Cochrane Reviews
  - NIH Consensus Documents
  - REPROTOX database
  - MOTHERRISK website
- Review of bibliographies of ~75 review articles

Screening and Data Extraction

*References with pregnancy outcomes included in the Appendix Tables, n=452*

References excluded from final analysis:

- Abstracts, n=6
- Multiple reporting of same case, n=9
- Studies without individual patient data, n=6

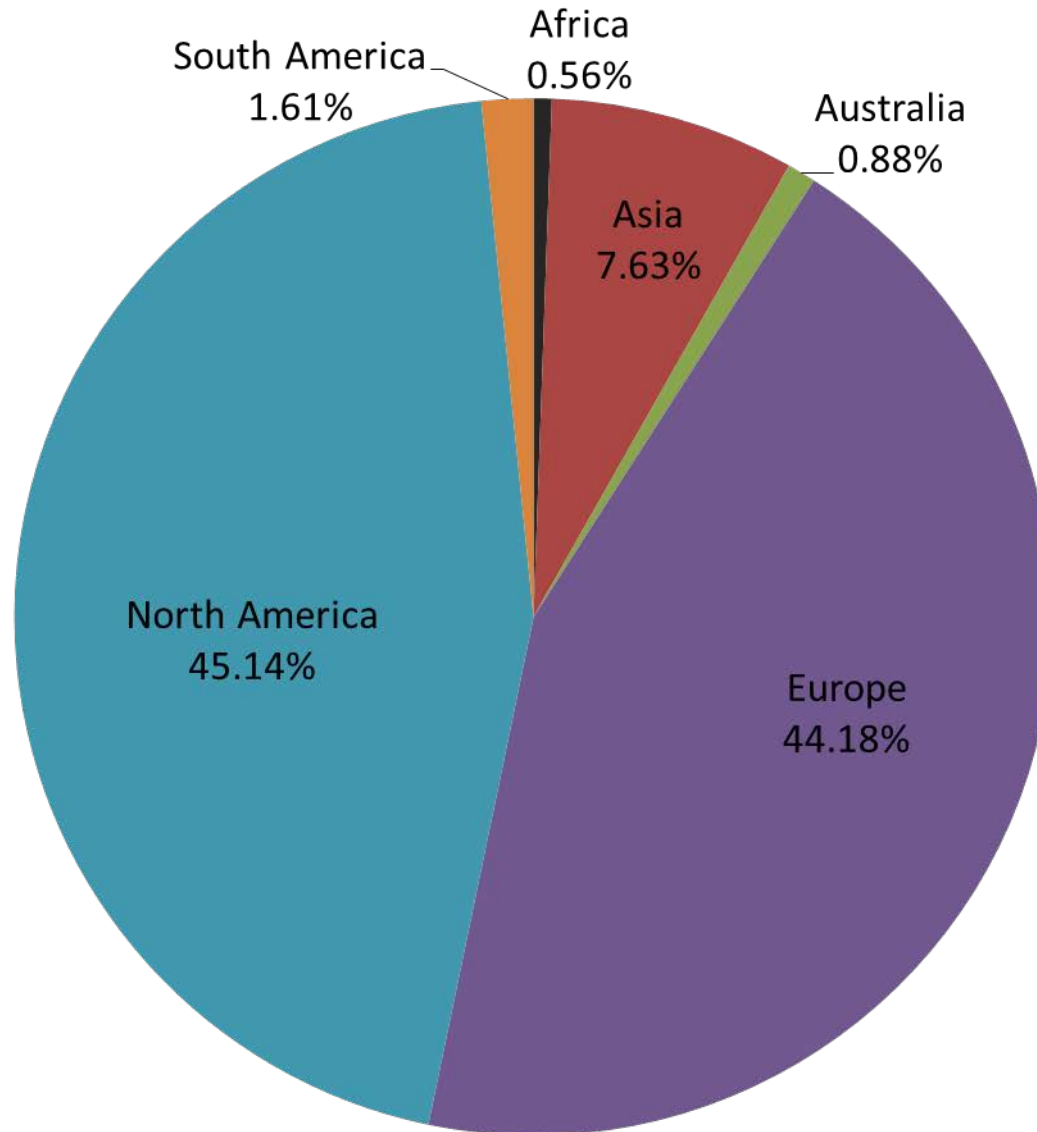
*Main findings based on 431 references (1271 conceptuses)*

## Number of publications by type

Study types	Number of publications	Number of conceptuses per study type
case reports	321	335
case series	84	385
case series, retrospective	9	93
cohort, retrospective	3	31
survey, retrospective	13	267
survey, registry	1	160
<b>Total</b>	<b>431</b>	<b>1271</b>

- Differences in the number of case reports and conceptuses per study due to twin pregnancies and some patients have more than one pregnancy

# Distribution of Cases by Country Regions



## Data extraction

- Individual agent tables (Appendices C, D): Description of pregnancy outcomes of individual cases

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments	Co-treatment (timing)	Delivery route	Gestational age at delivery, weeks	Pregnancy complications and outcome	Follow Up	Reference
Trastuzumab (loading dose, then 2 mg/kg every 3 weeks)	Case report	1	Breast	PC, 1 <sup>st</sup> First@PC	None	NA	6	Induced abortion due to ectopic pregnancy. No histological examination of embryo was performed.	NA	(Berveiller, 2008)
Trastuzumab (4 mg/kg loading dose, then 2 mg/kg every 3 weeks)	Case report	1	Breast	2 <sup>nd</sup> , 3 <sup>rd</sup> First@wk 27 Last@wk 34	Vinorelbine	Vaginal, induced	34	Oligohydramnios; amniotic fluid remained low despite intravenous fluids to mother.  Male infant: 5 lb, 11oz [2580 g], Apgar scores 9, 9 and 10. Newborn was healthy at birth.	At 6 months, healthy with normal development.	(Fanale, 2005)

- Master file: Tally of pregnancy outcomes by publication to calculate total conceptuses evaluated in the draft NTP monograph



# Definitions of the 5 health outcomes

- Congenital malformations (Correa et al 2007; Rasmussen et al 2003)
  - Major: defects that adversely affect health or development
  - Minor: defects that do not adversely affect health or development
- Spontaneous fetal death
  - Early ( $\leq 22$  weeks of gestation; spontaneous abortion)
  - Late ( $> 22$  weeks of gestation; stillbirth)
- Pregnancy complications
  - Reduction in amniotic fluid - any report of anhydramnios, oligohydramnios, or reduced amniotic fluid volume during pregnancy
  - Intrauterine growth restriction (IUGR) - developing fetus' estimated weight is  $< 10^{\text{th}}$  percentile of other fetuses at the same gestational age
  - Spontaneous preterm labor: spontaneous labor occurring at  $< 37$  weeks gestation

# Definitions of the 5 health outcomes (cont'd)

- Newborn weight and health:
  - Small for gestational size (Olsen et al. 2010)
    - Infants with birth weights at <10<sup>th</sup> percentile of other infants at the same gestational age
  - Transient myelosuppression
    - Blood measurement of pancytopenia (anemia), leukopenia, neutropenia, and/or thrombocytopenia at birth
  - Fetal/neonatal cardiotoxicity
    - Diagnosis of arrhythmia, cardiomyopathy, tachycardia, and/or heart failure *in utero* or at birth
  - Growth and development of gestationally-exposed children
    - Focus on physical growth, development of the central nervous system, reproductive system, vision, hematopoietic system, cardiotoxicity, and occurrence of cancer

# Data analysis

- Descriptive statistics
- Data calculated as apparent rates of occurrence
  - Major malformations, spontaneous fetal death per total conceptuses\*
  - Reductions in amniotic fluid, spontaneous preterm labor per stillborn and live born pregnancies
  - Intrauterine growth restriction per stillborn and liveborn conceptuses
  - Small for gestational age per live born conceptuses (newborns)
- Data analyzed in two ways:
  - Overall pooled analysis of any chemotherapy exposure
  - Individual agent exposure (singly and in combination therapy)
- For major malformation data, exposure during the 1<sup>st</sup> trimester was compared to exposure only in the 2<sup>nd</sup> and/or 3<sup>rd</sup> trimester
- Data were compared to general population values to provide context for results

\*Included all fetal deaths. Studies lacking fetal autopsy data were considered normal.



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# Limitations of the Data

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## Limitations of the data

- There were a number of limitations to the NTP's interpretation of the literature on pregnancy outcomes
  - Lack of a referent group
  - Small number of cases for most chemotherapeutic agents
  - Lack of long-term follow up evaluations
  - Publication bias

# Charge Questions

## A. Introduction, Methods and Limitations of the Data

- a. Please comment on whether the scientific information in the text is technically correct, clearly stated, and objectively presented. Please comment on whether the tabular information and its format are easily understandable. Please identify any needed improvements.
- b. Please comment on whether the methods for compiling and presenting the data are appropriate. Please identify any needed improvements.