National Toxicology Program
U.S. Department of Health and Human Services

DRAFT NTP MONOGRAPH ON DEVELOPMENTAL EFFECTS AND PREGNANCY OUTCOMES ASSOCIATED WITH CANCER CHEMOTHERAPY USE DURING PREGNANCY

July 30, 2012

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Peer Review Date: October 1-2, 2012

Table of Contents

List of Tables

List of Figures

Contributors

Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program (DNTP)

Conducted technical evaluation

Kembra L. Howdeshell, PhD (Project Lead)

Michael D. Shelby, PhD

Vickie R. Walker

Kristina A. Thayer, PhD (Director, OHAT)

Office of Liaison, Policy and Review (OLPR), DNTP

Managed peer review and release of the Monograph

Mary Wolfe, PhD (Director, OLPR and Deputy Division Director for Policy)

Danica Andrews

Denise Lasko

Lori White, PhD

GLP Support Services

Provided technical support for development of appendix tables

Judy Stevens

Technical Advisors

Provided scientific input on format and elements of content by reviewing early draft sections of the Monograph

Hatem Azim Jr, MD	Medical Fellow, Department of Medical Oncology, Jules Bordet Institute, Brussels, Belgium
Elyce Cardonick, MD	Associate Professor, Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Cooper Health System, Camden, NJ
Richard L. Theriault, DO	Professor, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Abbreviations

ABVD	doxorubicin (also called adriamycin), bleomycin, vinblastine, and dacarbazine
AGL	acute granulocytic leukemia; same as acute myelogenous leukemia
ALL	acute lymphoblastic leukemia
ALL	acute lymphocytic
AML	acute myeloblastic leukemia
AMML	acute myelomonocytic leukemia
AMSA	amascrine
APL	acute promyelocytic leukemia
ATRA	all-trans retinoic acid
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
Behenoyl-araC	behenoyl cytosine arabinoside
bw	body weight
CDC	Center for Disease Control and Prevention
CGL	chronic granulocytic leukemia; same as chronic myelogenous leukemia
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CML	chronic myeloid leukemia
C-section	Caesarean-section
FDA	Food and Drug Administration (United States)
IT	intrathecal
IU	international units
IUGR	Intrauterine growth retardation
kg	kilogram
µg	microgram
mg	milligram
m^2	meter cubed
NA	not applicable
NCCN	The National Comprehensive Cancer Network
NIEHS	National Institute of Environmental Health Sciences
NS	not specified
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
PC	period of conception
Pt	patient
SLL	small lymphocytic lymphoma
Stanford V	doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone

1.0 EXECUTIVE SUMMARY

Background and Objectives

Estimates of the number of women diagnosed with cancer during pregnancy range from approximately 17 to 100 per 100,000 (Haas 1984, Smith *et al.* 2003). The incidence of most cancers increases with age, thus the frequency of a cancer diagnosis during pregnancy is expected to increase as more women postpone having children to later ages (Martin 2011). Both the disease itself and the modalities available to treat it can pose risks to the health and survival of the woman as well as the fetus. The cancer patient and her clinicians are faced with the challenge of choosing a course of treatment that is optimal for the mother's health and minimizes the risk of potential harm to the unborn baby. Treatment most often involves some form of chemotherapy, and nearly all-chemotherapeutic agents are United States Food and Drug Agency (FDA) Pregnancy Category D,[1] i.e, *investigational or post-marketing data show risk to the fetus*. The evidence of risk to the fetus of chemotherapeutic agents usually comes from studies in laboratory animals.

The patient diagnosed with cancer during pregnancy and her medical team must make difficult choices regarding the use of chemotherapeutic treatment for cancer in the face of considerable uncertainty. The majority of human studies available to help guide decision-making are case reports and case series, which are generally accepted as among the weakest type of epidemiological evidence upon which to reach conclusions with confidence. Nevertheless, these data are what is currently available.

The overall goal of this NTP monograph is to summarize the reports of effects of gestational exposure to cancer chemotherapy on pregnancy outcomes to serve as a resource for the clinical and patient communities. Of the 113 cancer chemotherapeutic agents currently in use, the NTP monograph included data on 52 agents for which pregnancy outcomes following gestational exposure were documented (Perry 2008).

The NTP monograph focuses on the following health outcomes:

1. Major congenital malformations[2] associated with treatment during the first trimester versus the second and/or third trimester only

2. Early and late spontaneous fetal loss

3. Pregnancy complications (e.g., reduction in fetal amniotic fluid and spontaneous preterm labor)

---

[1] See full descriptions of pregnancy categories A, B, C, D, X at this site (accessed April 1, 2010).
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57

[2] Major congenital malformations were identified using guidance from publications from the United States Center for Disease Control and Prevention Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. 2003. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth defects research* 67(3): 193-201, Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. 2007. Reporting birth defects surveillance data 1968-2003. *Birth defects research* 79(2): 65-186.

4. Newborn weight and health (e.g., small for gestational size, fetal/neonatal cardiotoxicity, and transient myelosuppression)

5. Growth and development of gestationally exposed children

In an effort to put these effects in context, this NTP monograph also provides background information on the individual cancer chemotherapeutic agents and a brief review of the prevalence and prognosis of seven frequently diagnosed cancers in women during pregnancy. In particular, the monograph reviews the mechanism of action, indications (i.e., the cancers or other medical conditions which indicate use of the agent), evidence of transfer to fetus or breast milk, and developmental toxicity in laboratory animal studies for each cancer chemotherapy agent. The seven cancers frequently diagnosed in patients during pregnancy reviewed in the monograph are: breast cancer, cervical cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, ovarian cancer, and melanoma.

Methods

A literature search on the topic of cancer and chemotherapy during pregnancy was designed to focus on four key concepts: chemotherapy, pregnancy, pregnancy outcomes, and human studies. Following the screening of the literature search results, a total of 430 studies were identified that reported data on one or more female cancer patients treated with cancer chemotherapeutic agents during the pregnancy and the pregnancy outcome. The evaluation includes studies published through May 15, 2012. In total, the NTP monograph compiles data on 1255 pregnancies and 1271 conceptuses treated with chemotherapy during pregnancy[3].

Collectively, 52 cancer chemotherapeutic agents were administered, individually or in combination therapy, to the pregnant patients. Of these cancer chemotherapeutic agents, 46 agents are considered to be human embryotoxicants and/or teratogens (FDA Pregnancy Category D, n=45 agents or X, n=1 agent (methotrexate)), and three agents (dacarbazine, interferon alpha, and rituximab) are known or possible animal embryotoxicants or teratogens (FDA Pregnancy Category C). Three cancer chemotherapy agents do not have a FDA pregnancy category listing (i.e., amsacrine, behenoyl cytosine arabinoside (Behenoyl-ara-C), and Methyl-glyoxal bis guanyl hydrazone (Methyl-GAG)).

Information on each pregnancy complication and outcome is summarized in tabular format in a master file of all references and by individual cancer chemotherapeutic agents (NTP Monograph Appendix C Tables 1 to 33 and Appendix D Tables 1 to 19). Because treatment typically involves a combination of cancer chemotherapeutic agents, a patient may be represented in multiple agent-specific tables; each table notes any combination therapy co-treatments (when applicable). In addition, information on mechanism of action, route of administration, indications, placental or breast milk transport, and developmental toxicity studies in animals is presented for agents when more than 10 cases were available (NTP Monograph Sections 5.1-5.33). For agents with 10 or fewer cases, the data are organized into tables [d only] (NTP Monograph Appendix D Table 1 to 19); no text summary of the pregnancy outcomes or background information on these agents are included.

---

[3] A total of 1242 female cancer patients were identified from the 431 studies. Thirteen of these patients received treatment during two pregnancies each (1255 pregnancies) and 16 of the pregnancies resulted in twins for a total of 1271 conceptuses.

The human data are summarized by calculating "apparent rates of occurrence" of major congenital malformations, fetal loss, pregnancy complications and outcomes, and growth and development of offspring exposed in utero to cancer chemotherapy. Apparent rates of occurrence are calculated across all studies for any exposure to chemotherapy and for cancer chemotherapeutic agents for which 10 or more cases of exposure were identified. The purpose of examining the studies by individual chemotherapeutic agents (administered either singly or in combination therapy) is to identify whether certain agents or combinations may be more often associated with an adverse health outcome; however, in many cases, the number of exposed cases per agent is small. Statistical comparisons were not undertaken because of the limitations in using this literature base for quantitative analysis; i.e., the majority of these publications were case reports (74.5%; n=321/431 publications) and case series (19.5%; n=84/431 publications). The apparent rates of occurrence are also compared to national data when available; while these comparisons are not statistical analyses, they do provide a point of reference in interpreting the apparent rates of occurrence.

The NTP monograph also reviews primary and secondary literature on seven of the cancer types frequently diagnosed during pregnancy. This section on the seven tumor types reviews the definition and occurrence of each cancer type, the impact of pregnancy on the prognosis of each cancer type, the current cancer chemotherapy regimens used to treat each cancer type, and provides a summary table of the number of reported cases treated with each chemotherapeutic agent. The background information on the chemotherapy agents and seven of the frequently diagnosed cancers during pregnancy is drawn from the most current literature available in order to provide context for the topic of pregnancy outcomes associated with use of cancer chemotherapy during pregnancy, but is not intended to be an exhaustive review of these topics.

Findings

1. <u>Are major congenital malformations more frequently associated with exposure to cancer chemotherapy use in the first trimester versus the second and/or third trimester only?</u>

   Major congenital malformations were more frequently observed in conceptuses exposed to cancer chemotherapy during the first trimester than in conceptuses exposed to cancer chemotherapy in the second and/or third trimester only. Of the 1271 conceptuses evaluated in this monograph, the apparent rate of major malformations was 9.8% (40/410 conceptuses) following exposure to any cancer chemotherapy during the first trimester compared to the apparent rate of 2.7% (22/823 conceptuses) of major malformations following exposure during the second and/or third trimester only; timing of exposure was not specified for 38 conceptuses (none were malformed). As a point of comparison, the prevalence of major congenital malformations in the general population of the United States is about 3% (Correa *et al.* 2007). These data are consistent with the current medical paradigm for treatment of the pregnant cancer patient which is to avoid, whenever possible, administration of cancer chemotherapy during the first trimester due to the vulnerability of organogenesis (gestational weeks 3 through 8) to chemical perturbation (Loibl *et al.* 2006, Rizack *et al.* 2009, Azim *et al.* 2010). Exposure during the second and/or third trimester poses less risk of gross major malformations at birth, but may result in more functional deficits (Moore 2003). When the data were examined by individual chemotherapy agent (administered either singly or in combination therapy), there were no patterns of increased rates of major malformations when examining the data by either an individual agent or classes of agents working via similar mechanisms of action.

2. <u>Is cancer chemotherapy use during pregnancy associated with an increased risk of spontaneous abortions or stillbirth?</u>

The apparent rate of early spontaneous pregnancy loss (≤22 weeks of gestation) following in utero exposure to any cancer chemotherapy (3.6%; 46/1271 conceptuses) appeared to be lower than a pooled estimate of spontaneous abortion in healthy women of 13% (95% CI = 10% to 16%) (Wilcox 2010). In contrast, the apparent rate of late spontaneous fetal death (>22 weeks of gestation) following in utero exposure to any cancer chemotherapy (1.8%; 23/1271 conceptuses) was higher than rates of late spontaneous fetal loss for the general population in the United States from 1990 to 2004 (0.3 to 0.4%) (MacDorman 2005, Martin 2011). When the data were evaluated by individual chemotherapy agent (administered either singly or in combination therapy), late spontaneous fetal loss occurred most frequently following exposure to cytarabine in combination with an anthracycline antibiotic (e.g. daunorubicin, doxorubicin, idarubicin or mitoxantrone); the apparent rate of late fetal loss for cytarabine was 8.6% (13/151 conceptuses).

3. <u>Is cancer chemotherapy use during pregnancy associated with pregnancy complications?</u>

Reduction in amniotic fluid: Of the 1128 pregnancies evaluated in this monograph resulting in stillbirths and live births, the apparent rate of moderate to severe reductions in amniotic fluid (e.g., oligohydramnios and anhydramnios, respectively) was 2.9% (33/1128 pregnancies) for pregnancies gestationally exposed to any cancer chemotherapy. This apparent rate of occurrence of reduction in amniotic fluid is similar to the prevalence of oligohydramnios in the general population, which is reported to occur at a rate of 2.3 to 4% of all pregnancies (Casey *et al.* 2000, March of Dimes 2010). Of interest, 42% of the total pregnancies reporting moderate to severe reductions in amniotic fluid were exposed to trastuzumab (13 of 33 total pregnancies reporting oligohydramnios). Among the pregnancies exposed to trastuzumab that resulted in stillbirths and live births, the apparent rate of oligohydramnios was 68.4% (13/19 pregnancies). The severity of oligohydramnios appeared to increase with continued exposure to trastuzumab; however, this condition also appeared to be reversible if administration of the agent was discontinued until birth (Azim *et al.* 2009).

Spontaneous preterm labor: Preterm birth (<37 weeks gestation) occurred for a majority of the patients administered chemotherapy during pregnancy evaluated in this monograph; these births include spontaneous and induced vaginal deliveries as well as Caesarean-section deliveries. Of these preterm births, spontaneous preterm labor did not appear to be the primary cause of preterm births (apparent rate of spontaneous preterm labor was 5.6%; 63/1128 pregnancies resulting in live births and stillbirths). As a point of comparison, the spontaneous preterm labor rate in the general population of the United States is approximately 8.4% (based on a preterm birth rate of 12% and an estimation that 70% of preterm births are caused by spontaneous preterm labor (Iams and Donovan 2011). Thus, spontaneous preterm labor does not appear to be associated with cancer chemotherapy use.

4. <u>Is cancer chemotherapy use during pregnancy associated with effects on newborn weight and health?</u>

Small for gestational age infants: Small for gestational age (<10th percentile body weight for gestational age) was reported by the authors for 24 newborns out of 1112 liveborn infants evaluated in this monograph. It was not possible to compare the birth weights reported in the literature to a common growth scale due to the international nature of the patient population (e.g.,

differences in geographical location and ethnicity) as well as temporal differences (e.g., the data reviewed in the NTP monograph were collected from 1950-2012). Intrauterine fetal growth restriction was not always a predictor of a small for gestational age newborn. Intrauterine fetal growth restriction was observed in 36 of 1136 total conceptuses of stillbirths and live births evaluated in this monograph. However, only 2 fetuses with intrauterine growth restriction yielded a small for gestational age newborn. It is possible that when the chemotherapy regime is discontinued 2 to 3 weeks prior to birth, the intrauterine growth rate has a chance to catch up.

Transient myelosuppression. Transient myelosuppression was reported in 50 of 1112 newborns gestationally exposed to cancer chemotherapy evaluated in this monograph. This myelosuppression generally resolved within the first 2 to 3 weeks of life; myelosuppression resolved without treatment in the majority of cases. It has been suggested that transient myelosuppression may be avoided if administration of cancer chemotherapy is halted three weeks prior to birth (Sorosky *et al.* 1997). The occurrence of myelosuppression at birth in the general population is not known, because complete blood counts are not regularly evaluated in healthy newborns (Christensen *et al.* 2009).

Fetal/neonatal cardiotoxicity. Some chemotherapeutic agents are known to induce cardiovascular complications in patients directly administered these drugs, such as anthracycline antibiotics (i.e., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone); reviewed in (Gziri *et al.* 2012)). The apparent rate of fetal/neonatal cardiotoxicity (e.g., arrhythmia, cardiomyopathy, tachycardia and heart failure) following gestational exposure to any cancer chemotherapy was 0.6% (7/1136 total conceptuses, including stillbirths and live born infants). These cases of cardiotoxicity did not appear to limited to one class of chemotherapeutic agents: 3 pregnancies were exposed to anthyracyclines in combination therapies {Baumgartner, 2009 #151;Garcia, 1999 #69;Okun, 1979 #691}, 3 pregnancies were exposed to all-trans retinoic acid {Harrison, 1994 #631;Leong, 2000 #252;Takitani, 2005 #525}, and the remaining pregnancy was exposed to cyclosphosphamide and cisplatin {King, 1991 #137}. This overt cardiotoxicity appears to resolve at birth or following treatment shortly after birth as there was no evidence of congenital heart failure at follow-up evaluation of any of these 6 infants.

5. <u>Is cancer chemotherapy use associated with adverse effects on infant growth and development at follow up evaluation</u>?

Exposure to cancer chemotherapy in the second and/third trimesters may cause functional deficits to several organs systems including the ear, eye, heart, nervous system, and reproductive system that are not apparent at birth. Of the studies reviewed in the NTP monograph, normal growth and development were reported for a majority of children exposed in utero to cancer chemotherapy. In most cases, children were not evaluated beyond the second year of life. The few studies, which have conducted longer-term evaluations of the gestationally exposed offspring at ages ranging from 18 months to 20 years, have observed no effects on general health and growth and no increase in auditory, neurological or cardiac morbidity (Amant *et al.* 2012, Aviles *et al.* 2012); however, the authors observed subtle change in cardiac function and neurological outcome, which merit further follow-up evaluation (Amant *et al.* 2012).

Limitations to the approach

There are a number of limitations to the NTP's interpretation of the published reports on pregnancy outcomes, mostly stemming from the necessity of relying on case reports or case series, which limit the ability to reach conclusions with confidence. Specific limitations include:

- **Lack of referent group**. Many studies did not have the pregnancy outcomes for a reference group of cancer patients who elected not to receive cancer chemotherapy during pregnancy as a more direct point of comparison for the patient population. Thus, the ability to conduct statistical analyses was limited. General population rates, when available, were provided as a point of reference to help interpret the NTP's examination of the compiled data.
- **Small number of cases for most chemotherapeutic agents.** In most instances, the number of cases treated with a single agent or common combination therapies was small. This limits the ability to reach conclusions with confidence or to conduct sub-analyses that clinicians and patients might find useful (e.g., assessments of health outcome stratified by cancer type and cancer chemotherapeutic agents/combination therapies). In addition, an estimated 113 cancer chemotherapeutic agents are currently in use (Perry 2008); however, published data were only identified for 52 agents.
- **Lack of long-term follow-up evaluations**. The types of major malformations that occur following first trimester exposure to chemotherapeutic agents relate to organogenesis and are often more easily detected at birth compared to morphological and/or functional deficits that may result from exposure in the second or third trimesters of pregnancy (Buekers and Lallas 1998). Thus, the lack of long-term assessment of these children is a barrier to more fully understanding the potential consequences of exposure that occur after the first trimester.
- **Publication bias**. It is possible that data based on case reports and case series may be influenced by publication bias as adverse pregnancy outcomes are more likely to be reported, while normal pregnancy outcomes may be less likely to be published.

Closing Comments and Research Needs

The NTP recognizes that the decision on how to manage cancer during pregnancy is made on a case-by-case basis by the patient and her clinical team. The overall goal of this NTP monograph is to summarize the reports of effects of gestational exposure to cancer chemotherapy on pregnancy outcomes to serve as a resource for those discussions. Broader participation in registries of cancer during pregnancy and prospective studies of the pregnancy outcomes of pregnant women receiving cancer chemotherapy are needed to fully characterize the effects of gestational exposure to cancer chemotherapy on offspring health and development (see NTP Monograph Appendix E). In particular, there is a need for more long-term evaluations of gestationally exposed offspring to observe possible late-onset adverse health outcomes (e.g., impaired reproductive function). This area of study may benefit from evaluating the pregnancy outcomes and long-term evaluations of gestationally exposed offspring of other populations exposed to cancer chemotherapy during pregnancy, including medical professionals who administer these agents as well as pregnant patients treated with cancer chemotherapeutic agents for other non-cancer medical conditions.

Finally, this evaluation may provide information useful in the development and continued improvement of consensus guidelines for the diagnosis, staging, and treatment of cancer of pregnant women with consideration of the developing fetus. International consensus guidelines have been developed for the treatment of pregnant patients diagnosed with breast cancer (Loibl *et al.* 2006) and gynecological cancers (cervical, vulvar, endometrial, and ovarian) (Amant *et al.* 2009). However, similar guidelines for other frequently diagnosed cancers are currently not available.

2.0 INTRODUCTION

A diagnosis of cancer during pregnancy, while not rare, is infrequent. The rate of occurrence of diagnosis of cancer during pregnancy is often reported as ranging from 17 to 100 per 100,000 women. These estimates are based on the observations of two population-based studies and an institution-based study {Haas, 1984 #3}{Smith, 2003 #639}. Approximately 4 million births occurred in 2009 in the United States (Martin 2011); therefore, this range of rates of occurrence means that between 670 and 4000 pregnant women will be diagnosed with cancer each year in the United States alone. Over the past 20 to 30 years, there has been a trend for women in the United States to begin bearing children later in life. However, this trend may be ending, except among women aged 40 to 44 (Martin 2011). Because the probability of being diagnosed with many types of cancer increases with age, it is to be expected that a diagnosis of cancer while pregnant will be more common with increasing age at pregnancy.

Cancer during pregnancy is a difficult challenge for the patient, her family, and her medical team. Both the cancer itself and the modalities available to treat the cancer can pose risks to the health and survival of the woman and the unborn child. Treatment for cancer most often involves some form of chemotherapy and nearly all chemotherapy agents are FDA Pregnancy Category[4] D, i.e, *investigational or post-marketing data show risk to the fetus*. The current medical paradigm for treatment of the pregnant cancer patient is to avoid, whenever possible, administration of cancer chemotherapy during the first trimester due to the vulnerability of organogenesis to chemical perturbation. Exposure during the second and/or third trimester is thought to pose less risk of adverse developmental effects, but may lead to pregnancy complications (Azim *et al.* 2010, Buekers and Lallas 1998, Loibl 2007, Loibl *et al.* 2006, Rizack *et al.* 2009). Some patients may choose to avoid these risks entirely by terminating the pregnancy or, when possible, delaying chemotherapy treatment until after delivery.

The evidence of risk of the chemotherapeutic agents usually comes from studies in laboratory animals. Developmental toxicity studies in animals are useful for identifying the teratogenic potential of chemotherapy agents and they contribute information used to classify them in the FDA pregnancy categories. Such studies are, however, of somewhat limited use in interpreting much of the literature on human pregnancy outcomes. This is because the developmental toxicity studies in animals typically use high dose exposures throughout the period of organogenesis while exposure during this period is largely avoided in treating pregnant cancer patients.

The relative infrequency of cancer during pregnancy means that prospective studies of these patients and the outcomes of the pregnancies are difficult to conduct. The majority of what is known about the effects of cancer and chemotherapy on pregnancy outcomes is largely based on case reports, case series, and multi-institution retrospective surveys of patients. While such data are not ideal for drawing medical or scientific conclusions, these are the data currently available to aid physicians and patients in making treatment decisions for a cancer diagnosed during pregnancy.

There are ongoing efforts to collect relevant information using registries of cancer during pregnancy as well as prospective studies of pregnancy outcomes following administration of cancer chemotherapy

---

[4] See full descriptions of pregnancy categories A, B, C, D, X at this site (accessed April 1, 2010). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57

during pregnancy (NTP Monograph Appendix E). There are at least two registries of patients with cancer during pregnancy in the United States: Cooper University Hospital in Camden, New Jersey coordinated by Dr. Elyce Cardonick (www.cancerandpregnancy.com) and University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma coordinated by Dr. John Mulvihill. In addition, there are at least two registries for such patients outside of the United States: the Toronto Hospital of Sick Children in Ontario, Canada (www.MotherRisk.com) and the University of Frankfurt and German Breast Group(http://www.germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft/english-summary-.html). In addition, several ongoing clinical trials include prospective studies of pregnancy outcomes at institutions in the United States and internationally (see Appendix D for some examples). Consensus guidelines have been developed for the diagnosis, staging, and treatment of cancer of pregnant women for some of these cancers: breast cancer (Loibl *et al.* 2006), (Amant *et al.* 2010), cervical cancer (Morice *et al.* 2009), and gynecological cancers (Amant *et al.* 2009).

The overall goal of the NTP monograph is to summarize the effects of gestational exposure to cancer chemotherapy on pregnancy outcomes from these studies in order to provide physicians and their patients with a tool to help make clinical decisions. Of the 113 cancer chemotherapeutic agents currently in use, the NTP monograph included data on 52 agents for which pregnancy outcomes following gestational exposure were documented (Perry 2008). The concept for this evaluation was developed following discussions with scientists and clinicians at the National Cancer Institute, National Institute of Child Health and Human Development, Food and Drug Administration Center for Drug Evaluation and Research, and the National Comprehensive Cancer Network. This document is not intended as medical advice or clinical guidance on treatment with cancer chemotherapy during pregnancy.

The NTP monograph focuses on the following health outcomes:

1. Major congenital malformations[5] associated with treatment during the first trimester versus the second and/or third trimester only

2. Early and late spontaneous fetal loss

3. Pregnancy complications (e.g., reduction in fetal amniotic fluid and spontaneous preterm labor)

4. Newborn weight and health (e.g., small for gestational size, fetal/neonatal cardiotoxicity, and transient myelosuppression)

5. Growth and development of gestationally exposed children

In an effort to put these effects in context, this NTP monograph also provides background information on the individual cancer chemotherapeutic agents and briefly reviews the prevalence and prognosis of

---

[5] Major congenital malformations were identified using guidance from publications from the United States Center for Disease Control and Prevention Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. 2003. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth defects research* 67(3): 193-201, Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. 2007. Reporting birth defects surveillance data 1968-2003. *Birth defects research* 79(2): 65-186.

seven frequently diagnosed cancers in women during pregnancy. In particular, the evaluation reviews the mechanism of action, indications, evidence of transfer to fetus or breast milk, and developmental toxicity in laboratory animal studies for each cancer chemotherapy agent. The seven cancers frequently diagnosed in patients during pregnancy reviewed in the monograph are: breast cancer, cervical cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, ovarian cancer, and melanoma. These summaries include a definition of the tumor type, its rate of occurrence during pregnancy, the impact of pregnancy on its prognosis, and the chemotherapy agents used to treat the tumor based on published literature. The monograph also includes the cancer chemotherapy currently recommended for treatment of these cancers.

3.0   METHODS

3.1   Search methods for identification of studies

3.1.1   Electronic searches

For this NTP monograph, a series of literature searches were conducted on April 9, 2010 and June 7, 2010 using the following databases:
- PubMed
- Web of Science
- Scopus
- Embase
- Toxnet

The initial search of all databases was conducted with a focus on four key concepts: chemotherapy, pregnancy, pregnancy outcomes, and human studies. For PubMed, the search was conducted in a series of steps (Appendix B). First, only MeSH terms were combined across the four key concepts to capture the more relevant studies. Then, text words were searched within the 'in process' and 'supplied by publisher' content to retrieve items not yet indexed with MeSH. A final search was done combining the text words to capture all possible records on the subject. The first two search sets were extracted from the final result set to remove items retrieved earlier. For searching the other databases, the text words for each of the four key concepts were combined.

To identify recently published literature on this topic, a weekly keyword search alert of the individual chemotherapeutic agents using the PubMed database (Appendix B) was established. The current draft NTP monograph includes references collected through December 5, 2011. Only studies published in English were considered for this review.

3.1.2   Searching other resources

Websites searched

The following websites were searched to identify systematic reviews or other literature that might have been missed in the database searches

- *The Cochrane Library*
- National Institute of Health Consensus Documents (http://consensus.nih.gov/)
- REPROTOX database (http://www.reprotox.org/Default.aspx)
- MOTHERISK website, Hospital for Sick Children, Toronto, Canada (http://www.motherisk.org/women/cancer.jsp)

Reference lists checked

In addition to the literature searches detailed above, relevant references were also identified by visually searching the bibliographies of original reports and review articles on cancer chemotherapy and pregnancy.

3.2   Criteria for considering studies for this evaluation

3.2.1   Types of studies

Studies reporting pregnancy outcomes

Studies were considered relevant that contained original data regarding the pregnancy outcomes of women treated with cancer chemotherapeutics during pregnancy as well as follow up evaluations of the gestationally-exposed offspring. Of the 1425 studies identified from the literature search, 450 studies were identified as relevant. Finally, of the 436 studies, a total of 431 studies (n=1271 conceptuses) were ultimately included in the NTP monograph after excluding studies without individual data and avoiding duplicate counting of the same cases (Table 1).

The majority of the studies with original data were case reports (i.e., the report of a single patient; 74.4%; n=321/431 publications) and case series (19.5%; n=84/431 publications (Table 4). The NTP monograph categorized the publications reporting on more on more than one patient into the following study types: case series, retrospective case series, retrospective cohort studies, registry surveys and retrospective surveys. Case series are publications of a series of cases from a single hospital, clinic or institution. Retrospective case series are case series with additional data collected at a later time. Retrospective surveys are collections of cases from multiple hospitals obtained from institutional records. Retrospective cohort studies are collections of cases compared to a control group; both are obtained from institutional records. Registry surveys are collections of cases from registries of patients with cancer during pregnancy.

Table 1. Types of studies included in the NTP monograph on developmental effects associated with cancer chemotherapy use during pregnancy.

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

Supplementary literature

Although not the main focus of the evaluation, the NTP monograph also reviewed primary and secondary literature on seven of the cancer types frequently diagnosed during pregnancy. This section on the seven tumor types reviewed: the definition and occurrence of each cancer type, the impact of

pregnancy on the prognosis of each cancer, the current cancer chemotherapy regimen used to treat each cancer, and provided a summary table of the number of reported cases treated with each chemotherapeutic agent. In addition, the summary text for each of the 32 cancer chemotherapy agents with greater than 10 cases also reviewed information on mechanism of action, route, indications, evidence of placental or breast milk transport, and animal developmental toxicity studies of the agent. The background information on seven of the frequently diagnosed cancers during pregnancy and the chemotherapy agents was drawn from the most current literature available in order to provide context for topic of pregnancy outcomes following cancer chemotherapy during pregnancy, but was not intended to be an exhaustive review of these topics. Many of the studies evaluating the progression of cancer during pregnancy were identified in the literature search identified in Appendix B. Additional studies on cancer type and background information on the chemotherapy agents were identified by reviewing bibliographies of primary and secondary literature as well as separate targeted PubMed searches for these topics.

3.2.2   *Types of studies excluded*

All relevant publications were included in the tables for the individual cancer chemotherapeutic agents. However, eleven publications were excluded from the text analyses of the 32 agents with greater than 10 cases reported. Six publications were excluded because they were published abstracts only, including publications of 5 case reports and one retrospective survey (Cortes *et al.* 2008, Fogliatto and Brum 2005, Ibrahim *et al.* 2006, Morton *et al.* 1995, Sotiropoulos and Adamidou 2004, Thomas and Andes 1982). Four studies were excluded from the text analyses because they lacked individual patient data on type of cancer chemotherapy treatment, timing of exposure during pregnancy, and/or pregnancy outcome; these studies included 3 retrospective surveys and 1 retrospective cohort study (Ibrahim *et al.* 2006, Janov *et al.* 1992, Kawamura *et al.* 1994){Germann, 2005 #75}. In addition, a retrospective cohort study by Lishner et al. (Lishner *et al.* 1992) was not included because they provided individual patient data for only one of 48 pregnant women with Hodgkin disease (only 1 of 22 who received chemotherapy), and that same case was reported in another retrospective cohort study from the same laboratory group (Zemlickis *et al.* 1992).

3.2.3   *Dual reporting of the same cases*

There were some instances when the same case or cases were reported in more than one publication. For these cases, the most recent publication was considered; thus, the number of cases and pregnancy outcomes in the text analysis was adjusted to count each case only once. Notes were added to each reference, as well as in the footnotes of the each pertinent cancer chemotherapeutic agent table to identify which reference was used to count the dual reported case(s). A total of six case reports (Decker *et al.* 2006, Herold *et al.* 2001, Kimby *et al.* 2004, Merimsky *et al.* 1999, Reynoso and Huerta 1994, Terada *et al.* 1997) were subsequently reported in case series or retrospective surveys, three case series (Aviles *et al.* 1990, Peccatori *et al.* 2009, Pizzuto *et al.* 1980) were subsequently reported in other case series or retrospective case series, and one retrospective survey (Hensley and Ford 2003) reported in a subsequent retrospective survey (Pye *et al.* 2008). One exception was a twin pregnancy that was first reported in a case series (Reynoso *et al.* 1987) and later published as case report with subsequent follow up on the children exposed in utero (Zemlickis *et al.* 1993); this review counted the twin pregnancy using the case series, but did include the additional details of the follow up evaluation from the case report.

3.2.4   Types of patients

The NTP monograph focuses on the pregnancy outcomes of women who were pregnant while receiving chemotherapy treatment for cancer. Pregnant women diagnosed with cancer were not included if they did not receive cancer chemotherapy during the pregnancy (e.g., due to spontaneous or induced abortion, or deferral of treatment with chemotherapy until after pregnancy). Male cancer patients were not included in this review.

3.2.5   Types of interventions

Interventions included

All cancer chemotherapeutic agents that were reported to be administered to female cancer patients during pregnancy were included in the current review (Table 2). A table was created for each agent, which reported the cases (pregnant patients with cancer) exposed to the single agent as well as combination chemotherapy, including the agent. In addition, summary text was written for each agent with greater than 10 reported cases (see **Data Collection and Analysis** below). The draft NTP monograph identified each cancer chemotherapeutic agent by its common name, not by its brand name, as there may be more than one manufacturer for an agent.

Table 2. Cancer Chemotherapy Agents reviewed in the NTP Monograph, including the numbers of reported conceptuses exposed to each agent singly or in combination chemotherapy, and the location of each agent table or summary and table in the review.

Chemotherapeutic agent	Number of reported conceptuses	Location in this review
5-Fluorouracil	175	Text section 5.2, Appendix C Table 1
6-Mercaptopurine	84	Text section 5.3, Appendix C Table 2
6-Thioguanine	49	Text section 5.4, Appendix C Table 3
Actinomycin D	13	Text section 5.5, Appendix C Table 4
All-*trans* retinoic acid	29	Text section 5.6, Appendix C Table 5
Amasacrine	2	Appendix D Table 1
Behenoyl cytosine arabinoside	3	Appendix D Table 2
Bleomycin	95	Text section 5.7, Appendix C Table 6
Busulfan	31	Text section 5.8, Appendix C Table 7
Capecitabine	1	Appendix D Table 3
Carboplatin	17	Text section 5.9, Appendix C Table 8
Carmustine	3	Appendix D Table 4
Chlorambucil	10	Appendix D Table 5
Cisplatin	101	Text section 5.10, Appendix C Table 9
Cyclophosphamide	408	Text section 5.11, Appendix C Table 10
Cytarabine	151	Text section 5.12, Appendix C Table 11
Dacarbazine	57	Text section 5.13, Appendix C Table 12
Dasatinib	3	Appendix D Table 6

Chemotherapeutic agent	Number of reported conceptuses	Location in this review
Daunorubicin	106	Text section 5.14, Appendix C Table 13
Docetaxel	20	Text section 5.15, Appendix C Table 14
Doxorubicin	420	Text section 5.16, Appendix C Table 15
Epirubicin	69	Text section 5.17, Appendix C Table 16
Etoposide	42	Text section 5.18, Appendix C Table 17
Fludarabine	2	Appendix D Table 7
Gemcitabine	3	Appendix D Table 8
Hydroxyurea	68	Text section 5.19, Appendix C Table 18
Idarubicin	22	Text section 5.20, Appendix C Table 19
Ifosfamide	11	Text section 5.21, Appendix C Table 20
Imatinib	157	Text section 5.21, Appendix C Table 21
Interferon alpha	43	Text section 0, Appendix C Table 22
Irinotecan	2	Appendix D Table 9
Lapatinib	1	Appendix D Table 10
Lomustine	1	Appendix D Table 11
Methyl-GAG	3	Appendix D Table 12
Methotrexate	83	Text section 5.24, Appendix C Table 23
Mitoxantrone	17	Text section 5.25, Appendix C Table 24
Nilotinib	1	Appendix D Table 13
Nimustine	1	Appendix D Table 14
Nitrogen mustard	30	Text section 5.26, Appendix C Table 25
Oxalplatin	5	Appendix D Table 15
Paclitaxel	31	Text section 5.27, Appendix C Table 26
Procarbazine	31	Text section 5.28, Appendix C Table 27
Rituximab	24	Text section 5.29, Appendix C Table 28
Streptozotocin	1	Appendix D Table 16
Tamoxifen	14	Text section 5.30, Appendix C Table 29
Teniposide	2	Appendix D Table 17
Trastuzumab	20	Text section 5.31, Appendix C Table 30
Triethylenemelamine	6	Appendix D Table 18
Vinblastine	73	Text section 5.32, Appendix C Table 31
Vincristine	223	Text section 5.33, Appendix C Table 32
Vindesine	1	Appendix D Table 19
Vinorelbine	15	Text section 5.34, Appendix C Table 33

Interventions excluded

Some cancer chemotherapeutic agents administered during pregnancy were excluded from the NTP monograph. Aminopterin and demecolcine were not included in this review because they are no longer used as cancer drugs. Asparaginase was not included because it is a naturally occurring enzyme in humans. In addition, drugs used to treat inflammation (e.g., prednisone) or other side effects of the cancer chemotherapeutic agents (e.g., leucovorin and mesna) were not included in this evaluation. The effect of radiation therapy during pregnancy was not the focus of this evaluation; however, its use as a co-treatment with cancer chemotherapy was reported in the NTP monograph when administered to pregnant patients.

3.2.6   Types of outcome measures

To be included in the evaluation, studies had to present pregnancy outcomes following administration of cancer chemotherapy during pregnancy. The primary outcomes were always reported in the study. In the absence of In the case of the secondary outcomes, studies lacking detail on these outcomes were interpreted as normal pregnancy outcomes with exception of myelosuppression. Long-term adverse effects on growth and development were age-specific and were only reported in some of the studies included the NTP monograph.

Primary Adverse Outcomes

- Major or minor congenital malformations in fetuses or newborns
- Spontaneous fetal death, early (≤ 22 weeks gestation) and late (>22 weeks gestation)

Secondary Adverse Outcomes

- Pregnancy complications, including but not limited to:
  o Intrauterine growth restriction
  o Reduced/absent amniotic fluid
  o Spontaneous preterm labor
- Preterm birth
- Small for gestational age infants
- Adverse health issues in newborns; e.g., myelosuppression, cardiotoxicity
- Adverse effects on growth and development of the children

Spontaneous fetal death

Spontaneous fetal death was categorized as early spontaneous fetal death (also called spontaneous abortion) occurring at ≤ 22 weeks of gestation and late spontaneous fetal death occurring at >22 weeks of gestation. Late spontaneous fetal death was also called intrauterine fetal death and fetal demise. The following fetal losses were not included in the tally of spontaneous fetal death: induced abortion, hysterotomy, and maternal death. However, the NTP monograph did compile data on all pregnancies ending by hysterotomy, induced abortion, and maternal death in an effort to gather information on all possibly data on pregnancy complications and fetal autopsy results.

Identification of major and minor congenital malformations

Congenital malformations were categorized as major or minor following the guidelines published by the Centers for Disease Control and Prevention (CDC) in the United States (Correa *et al.* 2007, Rasmussen *et al.* 2003). Major congenital malformations are defects that adversely affect health or development, such as heart defects or cleft lip and palate; whereas minor congenital defents do not adversely affect health or development, such as pectus excavatum or hip subluxation. The nomenclature used to

describe congenital malformations in the studies reporting pregnancy outcomes was not always consistent with the nomenclature currently used by the CDC; the discrepancy may, in part, be due the fact that the literature covers a period of approximately 60 years and the fact that many of the studies originated outside of the United States. For malformations not included in either publication, birth defect experts at the CDC were contacted for clarification. The following malformations were identified as minor: double cartilage rings in one or both ears, bilateral ureteral reflux, adherence of the iris to the cornea, pilonidal sinus (also called a pilonidal or sacral dimple), and unilateral renal dilation, "assuming that 'dilation' is being used synonymously with mild hydronephrosis" (personal communication, Drs. Adolfo Correa and Richard Olney, CDC, September 17, 2011).

Intrauterine growth restriction

Intrauterine growth restriction refers to poor growth of a fetus in the womb during pregnancy. Specifically, it means the developing fetus' estimated weight is less than 90% (<10th percentile) of other fetuses at the same gestational age (http://www.nlm.nih.gov/medlineplus/ency/article/001500.htm).

Reduced amniotic fluid

Anhydramnios is the absence of amniotic fluid. Oligohydramnios is the reduction of amniotic fluid levels, which can be identified using several criteria including: amniotic fluid index less than the 95% (<5th percentile) for gestational age, an amniotic fluid index of less than 5 cm or amniotic fluid levels less than 300 mL. In the current review, some researchers also reported reductions in amniotic fluid. Thus, reductions in amniotic fluid included all pregnancies reporting a more general description of reductions in amniotic fluid as well as those cases reporting anhydramnios and oligohydramnios.

Spontaneous preterm labor

Spontaneous preterm labor was spontaneous labor occurring at <37 weeks of gestation. For the purposes of this review, pregnancies with transient spontaneous labor were included in the calculation of total of pregnancies with spontaneous preterm labor.

Preterm birth

Preterm birth was defined as birth at <37 weeks of gestation. Preterm delivery can be further divided into two categories: early preterm deliveries, which are births at ≤33 weeks 6 days of gestation and late preterm deliveries, which are births at 34 weeks 0 days to 36 weeks 6 days of gestation; referred to as <34 weeks of gestation and 34-36 weeks of gestation, respectively in this review.   Early preterm births are associated with higher rates of short and long term morbidity and mortality compared to the late preterm births, while late preterm births have outcomes similar to infants born at term (Moster *et al.* 2008). Births reported during the "7th month" of gestation or earlier are considered early preterm births, while births reported in the "9th month" of gestation or "at term" are considered term. Births reported in the "8th month" of gestation or "near term" were not included in the tally of births by delivery age because it was not possible to discern whether they were late preterm or term deliveries.

Small for gestational age infants

Small for gestational age is a term used to identify infants with birth weights at less than 90% (<10th percentile) of other infants at the same gestational age. The NTP monograph relied upon the authors' reports to identify newborns who were small for gestational age. Infants were included if it was stated that they were "small for gestational age", "intrauterine growth restricted newborns" or other descriptors defined by the authors as <10th percentile for birth weight for gestional age. It was not possible to reliably compare the birth weights by gestational age to a common intrauterine growth

curve (i.e., Olsen et al. {Olsen, 2010 #1081}), due to differences in geographical location (e.g., different countries), ethnicity as well as temporal differences in the literature (e.g., literature was published from 1950 to 2012).

Adverse health effects in newborns

Information is included on two of the primary adverse health effects suspected to occur in newborns following exposure to chemotherapy agents in utero, including myelosuppression and cardiotoxicity. Health effects likely caused by preterm birth were also summarized in the text summary for each cancer chemotherapeutic agent.

Long-term adverse effects on growth and development of children

The results of all reported follow up health examinations of individuals exposed to chemotherapy in utero are included in this monograph, regardless of their age at examination. Any reported adverse health effect is included in this monograph with a focus on physical growth, development of the central nervous system, reproductive system, vision, hematopoietic system, cardiotoxicity, and occurrence of cancer. The information is found in the text and in the "Follow up" column of the chemotherapy agent tables.

3.3   Data Collection and Analysis

3.3.1   Data collection

Data are organized into tables for individual cancer chemotherapeutic agents, which include cases exposed to the agent alone or, more commonly, in combination with other cancer chemotherapeutic agents (Table 2). The following data are entered into the pertinent individual cancer chemotherapy table for each case: dose and schedule of cancer chemotherapeutic agent, cancer type, time of exposure during pregnancy, co-exposure to other cancer chemotherapeutic agents, route of delivery, gestational age of fetus at delivery, pregnancy outcomes, and follow up evaluations of the infant. Time of exposure during pregnancy was primarily identified as: during the period of conception (PC), first trimester (through 13 weeks 6 days of gestation), second trimester (14 to 27 weeks 6 days of gestation) and 3rd trimester (28 to 42 weeks of gestation). When available, the gestational age at first and last exposure to the chemotherapeutic agent was also included. Route of delivery categories included: vaginal or Caesarian-section (C-section). Vaginal births were further categorized into: induced births (vaginal, induced) or spontaneous vaginal birth (vaginal) as reported in the publication. Studies lacking information on the route of delivery were considered to be spontaneous vaginal births. Pregnancy outcomes included pregnancy complications, birth weight, sex and Apgar score at birth, presence or absence of congenital malformations, and newborn health. Follow up evaluations included reports of growth and development of infants following dismissal from the hospital. Bold bracketed statements were used to note items of information not provided in a publication, limitations noted in the study, conclusions that differ from those of the authors, and data conversions conducted by OHAT for purposes of analysis.

3.3.2   Data analysis

Data were described by descriptive statistics. Quantitative statistical comparisons were not undertaken because of the limitations in using a largely case report-derived literature for quantitative analysis. Data were presented as an overall pooled analysis of exposure to any chemotherapy, and as well as by

individual agent (both singly and in combination therapy) to identify those agents that may be more often associated with an adverse health outcome.

Data were analyzed as apparent rates of occurrence based on the total number of reported pregnancies exposed to cancer chemotherapy for the following outcomes: oligohydramnios, intrauterine growth restriction, spontaneous fetal loss, and major congenital malformations. These apparent rates of occurrence may or may not reflect the actual, exact rates of occurrence for the population. For major congenital malformations, data were analyzed by comparing the apparent rates of occurrence following exposure during the first trimester to apparent rates following second and/or third trimester only to evaluate the vulnerability of the first trimester (period of organogenesis) to embryotoxicity or teratogenicity. For reductions in amniotic fluid, data compared the apparent rates of occurrence following exposure in the first trimester only to exposure during the second and/or third trimester to observe whether second and/or third trimester exposure was more likely to influence this effect. The apparent rates of occurrence for other outcomes were reported simply for exposure to any cancer chemotherapy or individual agent exposure, but an analysis of trimester exposed was not conducted.

The apparent rates of occurrence were also compared to published population studies; while these comparisons were not statistical analyses, the population studies did provide points of reference in interpreting the apparent rates of occurrence. Greater confidence was placed on data for individual agents with greater number of exposed cases (e.g., cyclophosphamide, n=405 cases and cytarabine, n=148 cases).

The apparent occurrence of major congenital malformations include major congenital malformations in both newborns and fetuses from any type of fetal death (spontaneous or induced). For cases reporting fetal death (of any type), lack of fetal autopsy data or gross observations of the fetus at birth was considered a normal fetus (i.e., not malformed). Similarly, infants were considered to be free of major congenital malformations if the publication lacked data on whether the infant had a congenital malformation or if it reported that the infant was "normal".

3.3.3   Publication bias

It is possible that data from largely case reports and registries of cancer during pregnancy may be influenced by publication bias as adverse pregnancy outcomes may be more likely to be reported, while normal pregnancy outcomes may be less likely to be published. It is also possible that the apparent rates of occurrence from the published studies may underreport the population incidence of adverse developmental effect; for example, a lack of examination of the aborted fetus following early spontaneous pregnancy loss may under detect the total number of malformed conceptuses associated with cancer chemotherapy use during pregnancy.

4.0   CANCER DIAGNOSED DURING PREGNANCY: BACKGROUND INFORMATION ON SEVEN FREQUENTLY DIAGNOSED CANCERS

In an effort to report the provide context for the developmental effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy, this section of the monograph presents background material on seven of the types of cancer most frequently diagnosed during pregnancy; i.e., cancer of the breast, cervix, and ovary, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and melanoma (Sections 4.1 to 4.7). While there is disagreement in the literature on which specific cancer

types are most frequently diagnosed during pregnancy, these seven were selected from two large population-based studies of California (Smith et al. 2001) and Germany (Haas 1984). Breast cancer was identified as most frequently-occurring cancer during pregnancy in a population study in California for the period 1992 to 1997 (Smith et al. 2001), while breast cancer was the second most frequent cancer following cervical cancer in a population study in Germany for the period 1970 to 1979 (Haas 1984). These seven cancers are also among the cancers most frequently diagnosed in women of reproductive age. In the current evaluation of the literature, the NTP discovered that leukemia was the most commonly reported cancer treated with chemotherapy during pregnancy followed by breast cancer; for example, 40.7% of the cases reviewed in the NTP monograph were leukemia patients (n=486 cases, including acute and chronic leukemia), while 27.3% of the cases were breast cancer patients (n=326 cases).

4.1 Breast Cancer & Pregnancy

4.1.1 Definition of breast cancer:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/breast*; accessed February 2, 2011).

"**[Breast cancer is]** cancer that forms in tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that make milk). It occurs in both men and women, although male breast cancer is rare."

Table 3 Estimated new cases and deaths from breast cancer in the United States in 2010

	Female	Male
New Cases	207,090	1,970
Deaths	39,840	390
Source: *http://www.cancer.gov/cancertopics/types/breast* (accessed February 2, 2011)		

4.1.2 Occurrence rate during pregnancy:

Three population-based studies and several smaller studies addressed the rate of occurrence of pregnancy-associated breast cancer.

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of breast cancer diagnosed during pregnancy to be 0.051/1000 (approximately 1/19,000) obstetric deliveries. This figure is based on 246 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Breast cancer was the most common cancer diagnosed during pregnancy in this study.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to make similar calculations. Based on 2,103,112 live births among women aged 15-44, 28 cases of breast cancer were diagnosed during pregnancy. The calculated occurrence of breast cancer in this study is approximately 0.013/1000 live births or about 1/77,000, second in descending rank order following cancer of the cervix for this population.

Ives et al. (Ives *et al.* 2005) conducted a study of women in Western Australia diagnosed with gestational breast cancer (diagnosis during pregnancy or up to one year following pregnancy) from January 1982 through December 2000. Based on a total of 148 cases, they estimated that breast cancer affects 23.6 per 100,000 pregnancies. Two-thirds of these cases were diagnosed postpartum, so approximately 7.9/100,000 (0.079/1000 or 1/13,000) were diagnosed during pregnancy.

The estimated frequencies of occurrence for these three large studies differ by only about 6-fold. Considering the different periods in which they were conducted and the very different geographic locations of the studies (United States, Germany, and Australia), such differences might be expected.

Some smaller studies report figures that are higher than the population-based studies cited above. For example, Parente et al. (Parente *et al.* 1988) reported 8 breast cancer cases in 12,500 pregnancies at the Bronx-Lebanon Hospital Center in New York City from 1980 to 1985, giving figures of 0.64/1000 or about 1/1500 pregnancies. Ranges of frequencies of occurrence are often cited in the literature, such as 1/1000 to 1/5000 (Pereg *et al.* 2008) and 1/3000 to 1/10,000 (Petrek 1994). Some of these differences might be attributed to the definition of pregnancy-associated breast cancer, which sometimes includes diagnosis of the tumor up to 12 months postpartum. The current NTP monograph focuses on breast cancer treated during pregnancy because these are the cases where the conceptus might be exposed to chemotherapy agents.

4.1.3   Impact of pregnancy on prognosis:

First, it must be recognized that increases in the size and density of the breasts during pregnancy and lactation make it more difficult for the patient or the clinician to detect masses in the breasts. This is thought to lead to a delay in diagnosis of some tumors and, hence, the presence of more advanced stage tumors in many pregnant breast cancer patients when compared to their non-pregnant counterparts.

 Zemlickis et al. (Zemlickis *et al.* 1992), using records at the Princess Margaret Hospital in Toronto Canada for the period 1958 to 1987, identified 118 cases of breast cancer and pregnancy (one case had two pregnancies). Fourteen cases were diagnosed before conception, 42 while pregnant, 55 after delivery or termination, and for 8 cases, time of conception relative to diagnosis was not available. Cases and controls were matched for stage of the tumor at diagnosis, age at diagnosis, and age at first treatment. Survival probability was determined in 102 cases and 269 controls. They concluded that there was no statistical difference in the survival of the pregnant and non-pregnant cases or between the cases diagnosed before or during pregnancy and their matched controls.

Ishida et al. (Ishida *et al.* 1992) conducted a case-control study, collecting information on breast cancer cases diagnosed between 1970 and 1988 in 18 medical institutions in Japan. Cases diagnosed during pregnancy (n=72) or lactation (n=120, within two years of delivery) were compared to non-pregnant, non-lactating cases (n=191) matched for age, period of treatment, and institution. They reported that the 5-year and 10-year survival rates of subjects were significantly lower than those of the controls, in accordance with stage and lymph node metastases.

Petrek (Petrek 1994) provided a review of the evidence for pregnancy impacting the prognosis of breast cancer. She noted that women with pregnancy-associated breast cancer are more likely to have positive lymph nodes and less likely to have tumors smaller than 2 cm than non-pregnant patients. Furthermore, patients with negative lymph nodes, whether pregnancy-associated or not, had the same 5-year survival rate. For patients with pregnancy-associated breast cancers that were operable, the 10-

year survival rate was 25% when lymph nodes were positive and 77% when lymph nodes were negative. In comparison, non-pregnant patients had 10-year survival rate of 41% when lymph nodes were positive and 75% when lymph nodes were negative. The differences were not statistically significant. It was concluded that pregnancy-associated breast cancer had a worse prognosis only because it was associated with more advanced disease at presentation. In a subsequent review, Petrek and Seltzer (Petrek and Seltzer 2003) reached similar conclusions, noting that pregnant women had a 2.5-fold higher risk of diagnosis with metastatic breast cancer and a significantly decreased chance of a Stage I diagnosis.

Bonnier et al. (Bonnier *et al.* 1997) reported the results of a case-control study based on cases from 23 institutions in France. For the years 1986 through 1993, they identified 154 cases of pregnancy-associated breast cancer (diagnosed during pregnancy or up to 6 months postpartum) and 308 cases of non-pregnancy-associated breast cancer. Sixty-two cases were diagnosed while pregnant. Cases and controls were matched center by center for age and date of beginning treatment. When compared to the non-pregnancy-associated cases, the pregnancy-associated cases were found to have: (1) a significantly higher proportion of inflammatory breast cancer and, therefore, more patients with metastases at diagnosis, (2) a significantly longer median delay between the first signs of cancer and a definite diagnosis, (3) significantly higher proportions of large clinical tumors and lymph node involvement, and (4) a higher proportion of histologically large tumors. They concluded that overall 5-year recurrence-free survival, metastasis-free survival, and overall survival were significantly lower in the pregnancy-associated cases, and that pregnancy was an independent and significant prognostic factor for metastasis-free survival and overall survival.

Ibrahim et al. (Ibrahim *et al.* 2000) reported the results of a study comparing survival among 72 pregnancy-associated breast cancer patients (only patients diagnosed while pregnant) and 216 non-pregnant breast cancer patients seen at the King Faisal Specialist Hospital in Riyadh, Kingdom of Saudi Arabia, between January 1992 and December 1996. Each pregnant patient was matched with three non-pregnant patients for age, tumor stage, and year of diagnosis. They concluded that there was no significant difference in survival between the two groups, and that advanced tumor stage was the only independent prognostic variable influencing overall survival.

Reed et al. (Reed *et al.* 2003), using the Norwegian Cancer Registry and the Medical Birth Registry, compared survivals of women diagnosed with breast cancer while pregnant (n=20), during lactation (n=102), and those who gave birth more than 9 months after diagnosis (n=51). They report that survival was significantly lower in the pregnancy and lactation cases than in those diagnosed at a later time. They note that tumors in the pregnant and lactating groups were of higher histological grade with a higher occurrence of lymph-node metastases, consistent with earlier studies.

Bladström et al. (Bladstrom *et al.* 2003) reported the results of a population-based study investigating the relationship between time of diagnosis since giving birth to a child and breast cancer survival. They used Swedish population registries to identify 14,693 parous women less than 45 years old and diagnosed with breast cancer between 1958 and 1999. Their analysis showed that women diagnosed while pregnant had a significantly worse prognosis for 5-year and 10-year overall survival rates compared to women diagnosed <10 years since childbirth. Survival of women diagnosed up to 10 years after giving birth showed improving survival rates up to approximately 8 years, at which time the survival rate curves appeared to plateau. They concluded that time since childbirth is a strong prognostic factor for survival. These analyses did not take into account such factors as tumor size, stage of the disease, or metastases at diagnosis.

Rodriguez et al. (Rodriguez *et al.* 2008), using the California Cancer Registry to identify breast cancer cases diagnosed between 1991 and 1999, identified pregnancy-associated, invasive breast cancer diagnosed: during pregnancy (n=179), at delivery (n=8), or within 1 year postpartum (n=610). They identified 4,177 non-pregnant women diagnosed with breast cancer during the same period. This cohort was used as the age-matched control group. They concluded that pregnancy has a modest independent affect on survival, with worse survival in pregnant cases, even when controlled for stage of disease, size of tumor, hormone receptor status, age, race, and type of surgery.

Beadle et al. (Beadle *et al.* 2009) reported the results of a retrospective cohort study involving 104 pregnancy-associated breast cancer cases in women age 35 or younger and treated at the University of Texas MD Anderson Cancer Center. Fifty-one women developed breast cancer during pregnancy and 53 women developed it within 1 year postpartum. When compared to a cohort of breast cancer patients whose disease was not pregnancy-associated, they found that pregnancy-associated breast cancer patients presented with more advanced disease than non- pregnancy-associated breast cancer cases but there were no statistical differences in the 10-year actuarial rates of locoregional recurrence, distant metastases, or overall survival.

Halaska et al. (Halaska 2009 #103) reported the results of a retrospective matched controlled study comparing time to relapse and overall survival in pregnancy-associated breast cancer patients and non-pregnant beast cancer patients. Thirty-two pregnancy-associated breast cancer patients diagnosed while pregnant (n=16) or within one year following delivery (n=16) were identified from medical records (1995-2007) of two hospitals, Ioannina University Hospital, Ioannina, Greece and University Hospital Motol, Prague, Czech Republic. These 32 cases were matched with 32 non-pregnant cases based on age at diagnosis, tumor size, axillary lymph node status, and presence or absence of metastatic deposits. The authors reported no statistically significant difference in time to relapse between the 32 pregnancy-associated breast cancer patients and the non-pregnant controls. However, a statistically significant worse prognosis for time to relapse was noted for the cases diagnosed within one year following delivery, but not for those diagnosed while pregnant. There was no statistically significant difference in overall survival between the 32 pregnancy-associated cases and the controls, or for those diagnosed while pregnant or those diagnosed following delivery.

Stensheim et al. (Stensheim *et al.* 2009), using data from the Cancer Registry and the Medical Birth Registry of Norway, compared the cause-specific survival of several cancer types, including breast cancer diagnosed in pregnant (59 cases) and non-pregnant (13,106 cases) patients. For breast cancer, they reported no elevation for risk of cause-specific death (hazard ratio, 1.23; 95%CI, 0.83 to 1.81) in patients diagnosed while pregnant.

Moreira et al. (Moreira *et al.* 2010) recently reported a retrospective, paired case-control study that compared overall survival of women diagnosed with breast cancer while pregnant or up to 12 months postpartum (n=87) and non-pregnant (n=252) breast cancer patients. They found that overall survival of the pregnant breast cancer patients was significantly shorter than survival of non-pregnant patients. Prognostic factor analysis showed that pregnancy, size of primary tumor, distant metastasis, and grade of malignancy were independent factors associated with overall survival.

Johansson et al. (Johansson *et al.* 2011) reported the results of a population-based cohort study investigating the relationship between pregnancy-associated breast cancer and survival. They used Swedish population registries to identify 15,721 women diagnosed with breast cancer between the ages of 15 and 44 years from 1963 to 2002; 1,110 were diagnosed while pregnant or up to 2 years after the

pregnancy. For the entire cohort, their analyses found higher overall mortality rates among younger (<40 years old) versus older patients (40 to 44 years old), among patients diagnosed from 1963 to 1989 compared to those diagnosed from 1990 to 2002, and among patients with lower educational levels. Comparing pregnancy-associated cases with all non-pregnant cases, they found a higher mortality rate in the pregnancy-associated cases (61.9 per 1000 person years) than in the non-pregnant cases (37.6 per 1000 person years). When pregnancy-associated cases were divided based on time between delivery and diagnosis, the poorest prognosis (highest mortality) was observed in cases diagnosed 4 to 6 months following delivery (adjusted hazard ratio 2.45, 95%CI 1.83-3.29). For cases diagnosed during pregnancy, the adjusted hazard ratio for mortality rates was 1.85, 95%CI 1.34-2.56. Among other subgroups extending out to diagnosis 2 years after delivery, hazard ratios ranged from 1.28 to 1.64. (Hazard ratios are based on the slopes of survival curves for two different groups.) These analyses did not take into account such factors as tumor size, stage of the disease, or metastases at diagnosis.

Azim et al. (Azim Jr *et al.* 2011) reported results of a case-control study addressing the prognosis of breast cancer patients diagnosed during pregnancy. Pregnancy-associated breast cancer patients (n=65) and controls (n=130) were identified from the records of the European Institute of Oncology in Milan, Italy and were matched for age, year of surgery, tumor size, and nodal status. Based on follow-up at four years, the authors report that pregnancy-associated breast cancer cases had a worse disease-free survival than controls (HR 2.3; 95% CI 1.0 to 6.5). There was no significant in overall survival.

Ali et al. (Ali *et al.* 2012) reported results of a case-control study addressing the prognosis of 40 breast cancer patients diagnosed while pregnant or within one year of delivery; 40 nonpregnant breast cancer patients matched for age and stage of tumor at diagnosis served as controls. All cases were identified from medical records of patients treated at Magee-Women's Hospital at the University of Pittsburgh Medical Center between 1990 and 2005. Median duration of follow-up was 100 months (range 10-190 months) in the pregnancy group and 103 months (range 6-201 months) in the nonpregnant group. The authors report that the rate of relapse and death was significantly higher in the pregnancy-associated breast cancer group. Further, for both overall survival and disease free survival, pregnancy was an independent adverse prognostic factor when controlled for age and tumor stage.

The majority of studies cited above show that survival is worse in pregnancy-associated breast cancer patients than in their non-pregnant counterparts. While more advanced stages at diagnosis in pregnant patients could explain a shorter overall survival, at least three studies (Bonnier *et al.* 1997, Moreira *et al.* 2010, Rodriguez *et al.* 2008) report that pregnancy is an independent prognostic factor in the survival of pregnancy-associated breast cancer patients. It should be noted that these studies vary in the populations studied with regard to the time of diagnosis relative to the pregnancy, from cases limited to those diagnosed only during pregnancy to those including cases diagnosed up to 6 months, 1 year, 2 years, or 10 years following delivery.

4.1.4   *Chemotherapy agents used to treat breast cancer:*

The National Comprehensive Cancer Network (NCCN) guidelines include various combinations of chemotherapy agents for treatment of breast cancer (NCCN Guidelines 2011). The NCCN guidelines note that in pregnant patients, considerations and selection of optimal local and systemic therapy are similar to that recommended for non-pregnant patients, and that chemotherapy should not be administered during the first trimester. They further note that safety data are insufficient to recommend general use of taxanes during pregnancy and that the use of trastuzumab is contraindicated during pregnancy. However, as noted by Mir et al. (Mir *et al.* 2010), and as can be seen in the sections of

this report on docetaxel and paclitaxel, accumulating results suggest a generally favorable toxicity profile for use of these agents during the second and third trimesters.

Chemotherapy agents listed for invasive breast cancer include various combinations of docetaxel, doxorubicin, cyclophosphamide, paclitaxel, 5-fluorouracil, epirubicin, methotrexate, trastuzumab, and (NCCN Guidelines 2011). It is worth noting that these guidelines are not specific for pregnant patients, for whom treatment with methotrexate is generally avoided.

Kardinal and Cole provide a thorough presentation and discussion of the use of chemotherapy in breast cancer in the The Chemotherapy Source Book (Kardinal and Cole 2008).

The numbers of breast cancer studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below.

Table 4 Chemotherapy agents used to treat breast cancer reviewed in the NTP monograph

Chemotherapy agent	Number of studies*	Number of cases*
5-Fluorouracil, Appendix C Table 1	27	149
Capecitabine, Appendix D Table 3	1	1
Carboplatin, Appendix C Table 8	1	1
Cyclophosphamide, Appendix C Table 10	36	258
Docetaxel, Appendix C Table 14	9	18
Doxorubicin, Appendix C Table 15	39	246
Epirubicin, Appendix C Table 16	17	59
Lapatinib, Appendix D Table 11	1	1
Methotrexate, Appendix C Table 22	11	24
Mitoxantrone, Appendix C Table 23	1	2
Paclitaxel, Appendix C Table 25	7	14
Tamoxifen, Appendix C Table 28	10	10
Trastuzumab, Appendix C Table 29	16	17
Vincristine, Appendix C Table 31	4	5
Vinorelbine, Appendix C Table 32	5	10
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

4.2 Cervical Cancer & Pregnancy

4.2.1 Definition of cervical cancer:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/cervical*: accessed March 0, 2011).

"**[Cervical cancer is]** cancer that forms in tissues of the cervix (the organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). Cervical cancer is almost always caused by human papillomavirus (HPV) infection.

Table 5 Estimated new cases and deaths from cervical (uterine cervix) cancer in the United States in 2010:

New cases	12,200
Deaths	4,210
http://www.cancer.gov/cancertopics/types/cervical(accessed March 10, 2011)	

4.2.2 Occurrence rate during pregnancy:

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of "invasive and malignant" cervical cancer diagnosed during pregnancy to be 0.036/1000 (approximately 1/28,000) obstetric deliveries. This figure is based on 175 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Cervical cancer was the second most common cancer diagnosed during pregnancy or at delivery in this study, following cancer of the breast.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to provide similar information. Based on 2,103,112 live births among women aged 15-44, 229 cases of cervical cancer were diagnosed during pregnancy. Based on these numbers, the occurrence rate of cervical cancer in this study is approximately 0.11/1000 live births or about 1/9,000, the most frequently observed cancer type in this study.

Occurrence rates have been reported in other smaller studies. For example, Hacker et al. (Hacker *et al.* 1982) reviewed the literature from 1960 to 1979 and reported that for carcinoma in situ, the incidence was 1.3/1000 or approximately 1/770 pregnancies and for invasive carcinomas the numbers were 0.45/1000 or approximately 1/2205 pregnancies. Combining both in situ and invasive cancer types, the numbers were 0.807/1000 or approximately 1/1240 pregnancies based on 800 cases in 991,536 pregnancies. Duggan et al. (Duggan *et al.* 1993) report an incidence of invasive cervical cancer diagnosed and/or treated during pregnancy of 0.12/1000 or approximately 1/8000 pregnancies based on 27 cases among 195,168 deliveries between 1980 and 1991 at the Southern California Department of Obstetrics and Gynecology. Allen et al. (Allen *et al.* 1995) report the experience of a hospital in Australia between 1981 and 1995. Based on 19 cases of cervical cancer in 83,971 pregnancies, the figures are 0.23/1000 or 1/4419 pregnancies.

Based on these selected studies, there is about a 12-fold range in the estimated occurrence rates of invasive cervical cancer diagnosed during pregnancy, from 0.036/1000 (Smith *et al.* 2003) to 0.45/1000 (Hacker *et al.* 1982).

4.2.3   Impact of pregnancy on prognosis:

There is general agreement in seven papers published between 1990 and 2005 that pregnancy does not change the prognosis of cervical cancer.

Baltzer et al. (Baltzer *et al.* 1990) reported on the survival of 40 pregnant cases with carcinoma of the cervix compared to 426 non-pregnant patients with cervical cancer. The cases were collected from the gynecologic departments at four universities in Germany. At 1 year follow-up, they found no significant difference in the survival rates of the two groups.

Zemlickis et al. (Zemlickis *et al.* 1991), using cases from the Princess Margaret Hospital in Toronto Canada (1958 to 1984), report no statistically significant difference in 30-year survivals between 34 cases compared to 89 matched controls.

Hopkins and Morley (Hopkins and Morley 1992) reviewed the records of the University of Michigan Medical Center (1960 to 1989) and identified 53 patients diagnosed with cervical cancer during pregnancy or in the first 6 months postpartum. They compared the survival of 35 of these cases with stage IB disease (the only stage group large enough for statistical analysis) to 170 non-pregnant cases and found no significant difference in >10 year survival of the two groups.

Sood et al. (Sood *et al.* 1997), using records from the University of Iowa Hospitals and Clinics (from 1960 to 1994), conducted a retrospective case-control study of 26 women diagnosed with cervical cancer during pregnancy and treated with radiation. They concluded that there were no statistically significant differences in recurrence rates or survival between the pregnant group and the controls.

Stensheim et al. (Stensheim *et al.* 2009), using data from the Cancer Registry and the Medical Birth Registry of Norway, compared the cause-specific survival of several cancer types, including cervical cancer diagnosed in pregnant (80 cases) and non-pregnant (5865 cases) patients. For cervical cancer, they reported no elevation in the risk of cause-specific death (hazard ratio, 0.89; 95%CI, 0.52 to 1.53) in patients diagnosed while pregnant.

Pettersson et al. (Pettersson *et al.* 2010) used the records at the Radiumhemmet in Stockholm, Sweden, to study characteristics of cervical cancer over a 90-year period from 1914 to 2004. They compared survival of 41 patients diagnosed with carcinoma of the cervix while pregnant or within 6 months postpartum with 82 similar non-pregnant patients matched for age, stage, and histopathology. They report no significant difference in actuarial 10-year survival rates between these two groups.

Three literature reviews address the issue of prognosis of patients with cervical cancer during pregnancy. Antonelli et al. (Antonelli *et al.* 1996) conclude that literature supports the view that tumor characteristics and maternal survival are not adversely affected by pregnancy. Germann et al. (Germann *et al.* 2005) state that the majority of the studies in the literature do not report on a difference in the prognosis of invasive cervical cancer during pregnancy and Van Calsteren et al. (Van Calsteren *et al.* 2005) conclude that overall prognosis appears to be similar to the non-pregnant state.

4.2.4 *Chemotherapy agents used to treat cervical cancer:*

Surgery and radiation therapy are commonly used in treating cervical cancer. In advanced and metastatic disease, chemotherapy is also used. The National Comprehensive Cancer Network lists first-line combination therapies as cisplatin/paclitaxel, carboplatin/paclitaxel, cisplatin/topotecan, and cisplatin/gemcitabine. Possible first-line single agent therapies are cisplatin (preferred), carboplatin, or paclitaxel. Second-line therapies include bevacizumab, docetaxel, 5-fluorouracil, gemcitabine, ifosfamide, irinotecan, mitomycin, topotecan, pemetrexed, and vinorelbine (NCCN Guidelines 2011).

Holstein and Hohl provide a thorough presentation and discussion of the use of chemotherapy in cervical cancer in the The Chemotherapy Source Book (Holstein and Hohl 2008).

The numbers of cervical cancer studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below.

Table 6 Chemotherapy agents used to treat cervical cancer reviewed in the NTP monograph

Chemotherapy agent	Number of studies*	Number of cases*
5-Fluorouracil, Appendix C Table 1	1	1
Bleomycin, Appendix C Table 6	1	1
Carboplatin, Appendix C Table 8	1	1
Cisplatin, Appendix C Table 9	20	33
Cytarabine, Appendix C Table 11	1	1
Paclitaxel, Appendix C Table 25	3	6
Vincristine, Appendix C Table 31	5	6
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

4.3   Hodgkin Lymphoma & Pregnancy

4.3.1   Definition of Hodgkin lymphoma:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/hodgkin;* accessed March 21, 2011).

"**[Hodgkin lymphoma is]** a cancer of the immune system that is marked by the presence of a type of cell called the Reed-Sternberg cell; it is also called Hodgkin disease. The two major types of Hodgkin lymphoma are classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. Symptoms include the painless enlargement of lymph nodes, spleen, or other immune tissue. Other symptoms include fever, weight loss, fatigue, or night sweats.

Table 7 Estimated new cases and deaths from Hodgkin lymphoma in the United States in 2010

New cases	8,490
Deaths	1,320
http://www.cancer.gov/cancertopics/types/hodgkin (accessed March 21, 2011)	

4.3.2   Occurrence rate during pregnancy:

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of Hodgkin disease diagnosed during pregnancy to be 0.022/1000 (approximately 1/45,000) obstetric deliveries. This figure was based on 107 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Hodgkin lymphoma was the sixth most common cancer diagnosed during pregnancy in this study, following breast, cervix, thyroid, melanoma, and ovary.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to provide similar data. Based on 2,103,112 live births among women aged 15-44, 15 cases of Hodgkin lymphoma were diagnosed during pregnancy. The calculated rate of occurrence of Hodgkin lymphoma in this study was approximately 0.007/1000 live births or about 1/143,000. Lymphomas **[type not specified; likely Hodgkin and non-Hodgkin combined]** were fourth in descending rank order following cancer of the cervix, breast, and ovary.

4.3.3   Impact of pregnancy on prognosis:

Smith et al. (Smith *et al.* 1958) studied women aged 15 to 50 who were registered at Walter Reed Army Hospital (Washington, District of Columbia) with Hodgkin disease between 1942 and 1957. Of 56 such women, eighteen gave birth during the course of their disease. They concluded that "In no case was it possible to say that the course of the disease had been altered one way or another by the coincidence of pregnancy." They pointed out, however, that there was not full agreement on this point in the literature.

Barry et al. (Barry *et al.* 1962) reviewed the charts of 347 patients with Hodgkin disease treated between 1910 and 1959 at the Memorial Hospital for Cancer and Allied Diseases and the James Ewing Hospital in New York. Eighty-four of these patients, between the ages of 18 and 40, had one or more pregnancies associated with Hodgkin disease. Compared to an age-matched, non-pregnant control group, there was no difference in survival curves or median survival times.

Lishner et al. (Lishner *et al.* 1992) reviewed the records of all women with Hodgkin disease registered at the Princess Margaret Hospital, Toronto, Canada, between 1958 and 1984. Thirty-three cases of patients with Hodgkin disease and pregnancy were compared with 67 non-pregnant matched controls. They found no statistical difference in the 20-year survival of the two groups. Further, there was no statistical difference in the distribution of stages at diagnosis between pregnant and non-pregnant cases.

Gelb et al. (Gelb *et al.* 1996) reviewed the records of 17 women diagnosed with Hodgkin disease while pregnant and 12 diagnosed with non-Hodgkin lymphoma while pregnant at the Stanford University Medical Center since 1987. They noted that Hodgkin disease cases survived significantly longer than those with non-Hodgkin lymphoma. Although they did not compare their cases with matched controls, they concluded that the clinical behavior of Hodgkin disease during pregnancy did not appear to differ from that outside of the pregnancy setting.

4.3.4   *Chemotherapy agents used to treat Hodgkin lymphoma:*

The National Comprehensive Cancer Network guidelines list three combination therapies for the treatment of classical Hodgkin lymphoma (NCCN Guidelines 2010) they are:

- ABVD (Doxorubicin (also called adriamycin), bleomycin, vinblastine, and dacarbazine)

- Stanford V (Doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone)

- BEACOPP (Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

Peterson provides a thorough presentation and discussion of the use of chemotherapy in Hodgkin lymphoma in the The Chemotherapy Source Book (Peterson 2008).

The numbers of Hodgkin lymphoma studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below.

Table 8 Chemotherapy agents used to treat Hodgkin lymphoma reviewed in the NTP monograph

Chemotherapy Agent	Number of Studies*	Number of Cases*
6-Mercaptopurine, Appendix C Table 2	1	1
Bleomycin, Appendix C Table 6	12	48
Chlorambucil, Appendix D Table 5	3	4
Cisplatin, Appendix C Table 9	1	1
Cyclophosphamide, Appendix C Table 10	7	9
Cytarabine, Appendix C Table , 11	1	1
Dacarbazine, Appendix C Table 12	11	44
Doxorubicin, Appendix C Table 13	13	51
Epirubicin, Appendix C Table 16	1	4
Etoposide, Appendix C Table 17	2	2
Interferon alpha, Appendix C Table 21	1	1
Lomustine, Appendix D Table 12	1	1
Nitrogen Mustard, Appendix C Table 24	17	27
Procarbazine, Appendix C Table 26	15	27
Rituximab, Appendix C Table 27	1	1
Triethylenemelamine, Appendix D Table 19	3	3
Vinblastine, Appendix C Table 30	24	66
Vincristine, Appendix C Table 31	15	26
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

4.4   Non-Hodgkin Lymphoma & Pregnancy

4.4.1   *Definition of non-Hodgkin lymphoma (NHL):*

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/non-hodgkin;* accessed March 18, 2011).

"**[Non-Hodgkin lymphoma is]** any of a large group of cancers of lymphocytes (white blood cells). Non-Hodgkin lymphoma can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and they can be formed from either B-cells or T-cells. B-cell non-Hodgkin lymphomas include: Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell non-Hodgkin lymphomas include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Lymphomas that occur after bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas. Prognosis and treatment depend on the stage and type of disease.

Table 9 Estimated new cases and deaths from non-Hodgkin lymphoma in the United States in 2010

New cases	65,540
Deaths	20,210
http://www.cancer.gov/cancertopics/types/non-hodgkin (accessed March 18, 2011)	

The National Comprehensive Cancer Network lists 14 different tumor types under Non-Hodgkin Lymphoma (NCCN Guidelines 2011):

- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- Follicular Lymphoma

- Marginal Zone Lymphoma

- Mantle Cell Lymphoma

- Diffuse Large B-Cell Lymphoma

- Burkitt Lymphoma

- Lymphoblastic Lymphoma

- AIDS-Related B-Cell Lymphoma

- Primary Cutaneous B-Cell Lymphoma

- Peripheral T-Cell Lymphoma

- Mycosis Fungoides/Sézary Syndrome

- Adult T-Cell Leukemia/Lymphoma

- Extranodal NK/T- Cell Lymphoma, nasal type

- Post-Transplant Lymphoproliferative Disorders

Bierman and Armitage (Bierman and Armitage 2008) present a version of the World Health Organization classification of Non-Hodgkin lymphomas. This classification scheme contains 28 categories, many of which are included in the lists presented above.

4.4.2   Occurrence rate during pregnancy:

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of lymphoma, not otherwise specified, diagnosed during pregnancy to be 0.007/1000 (approximately 1/143,000) obstetric deliveries. This figure is based on 33 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Lymphoma, not otherwise specified was the ninth most common cancer diagnosed during pregnancy in this study.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to provide similar data. Based on 2,103,112 live births among women aged 15-44. Table 1 of the Haas publication notes 19 cases of lymphoma and Table II notes 15 cases of Hodgkin lymphoma diagnosed during pregnancy. If it is assumed that the four remaining lymphomas (19-15=4) are non-Hodgkin lymphoma, the calculated rate of occurrence of non-Hodgkin lymphoma in this study is approximately 0.002/1000 live births or about 1/525,000. Lymphoma, not otherwise specified, was fourth in descending rank order following cancer of the cervix, breast, and ovary.

4.4.3   Impact of pregnancy on prognosis:

Few primary data on the impact of pregnancy on the prognosis of Non-Hodgkin lymphoma were found. With regard to pregnancy and Non-Hodgkin lymphoma, Lishner et al. (Lishner *et al.* 1994) stated "…whether each of them affects the course of the other is still debated." They continued, "…there is evidence to suggest that pregnancy does not affect the course of lymphoma when properly treated."

Steiner-Salz et al. (Steiner-Salz *et al.* 1985), based on 5 pregnancy-associated cases, noted that clinical progression of the lymphoma took place quite quickly in the early and later immediate postpartum periods.

4.4.4   Chemotherapy agents used to treat Non-Hodgkin lymphoma:

The following are the first-line chemotherapy agents (for young patients without co-morbidities) from the NCCN guidelines for the various forms of non-Hodgkin lymphoma (NCCN Guidelines 2011).

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL):

  CLL without del (11q) or del (17p): fludarabine+cyclophosphamide+rituximab; fludarabine+rituximab; pentostatin+cyclophosphamide+rituximab; bendamustine+rituximab

CLL with del (17p): fludarabine+cyclophosphamide+rituximab; fludarabine+rituximab; methylprednisolone+rituximab; alemtuzumab+rituximab; bendamustine+rituximab

CLL with del (11q): fludarabine+cyclophosphamide+rituximab; bendamustine+rituximab; pentostatin+cyclophosphamide+rituximab

- Follicular lymphoma: bendamustine+rituximab; rituximab+cyclophosphamide+ Doxorubicin+vincristine+prednisone; rituximab+cyclophosphamide+vincristine+ prednisone; fludarabine+rituximab; fludarabine+mitoxantrone+dexamethasone; rituximab (single agent)

- Marginal zone lymphomas: It appears that the chemotherapy agents recommended for the treatment of the marginal zone lymphomas are the same as those for follicular cell lymphomas.

- Mantle cell lymphoma (aggressive therapy): Cyclophosphamide+vincristine+ doxorubicin+dexamethasone alternating with high-dose methotrexate+cytarabine + rituximab; rituximab+cyclophosphamide+vincristine+doxorubicin+prednisone alternating with rituximab+high-dose cytarabine; rituximab+methotrexate augmented with cyclophosphamide+doxorubicin+vincristine+prednisone; rituximab+cyclophosphamide+doxorubicin+vincristine+prenisone followed by rituximab+ifosfamide+carboplatin+cytarabine; rituximab+cyclophosphamide+doxorubicin+vincristine+prednisone alternating with rituximab+dexamethasone+cisplatin+cytarabine

- Diffuse large B-cell lymphoma: Rituximab+cyclophosphamide+doxorubicin+ vincristine+prednisone; etoposide+prednisone+vincristine+cyclophosphamide+ doxorubicin+rituximab

  Burkitt lymphoma: Cyclophosphamide+prednisone+ifosfamide+methotrexate+ leucovorin+vincristine+dexamethasone+doxorubicin+etoposide+cytarabine; cyclophosphamide+doxorubicin+vincristine+methotrexate+rituximab; etoposide+prednisone+vincristine+cyclophosphamide+doxorubicin+rituximab; cyclophosphamide+vincristine+doxorubicin+dexamethasone+methotrexate+cytarabine+rituximab

- Lymphoblastic lymphoma: Vincristine+daunomycin+prednisone+L-asparaginase+ cytarabine (intrathecal, IT)+methotrexate (IT); prednisone+vincristine+daunorubicin+ asparaginase+methotrexate (IT); cyclophosphamide+cytarabine+ 6-mercaptopurine+methotrexate (IT); cyclophosphamide+daunorubicin+vincristine+ prednisone+asparaginase; cyclophosphamide+vincristine+doxorubicin+dexamethasone alternating with methotrexate+cytarabine/methotrexate (IT)

- AIDS-related B-cell lymphoma: Cyclophosphamide+vincristine+doxorubicin+ methotrexate alternating with ifosfamide+etoposide+cytarabine; etoposide+prednisone+ vincristine+cyclophosphamide+doxorubicin; cyclophosphamide+doxorubicin+etoposide+rituximab

- Primary cutaneous B-cell lymphoma: Cyclophosphamide+doxorubicin+vincristine+ prednisone+rituximab; etoposide+prednisone+vincristine+cyclophosphamide+ doxorubicin+rituximab

- Peripheral T-cell lymphoma: Cyclophosphamide+doxorubicin+vincristine+prednisone; cyclophosphamide+doxorubicin+vincristine+etoposide+prednisone; cyclophosphamide+ doxorubicin+vincristine+prednisone followed by ifosfamide+carboplatinetoposide; cyclophosphamide+doxorubicin+vincristine+prednisone followed by ifosfamide+etoposide+epirubicin; cyclophosphamide+vincristine+doxorubicin+dexamethasone alternating with methotrexate+cytarabine

- Mycosis fungoides/Sezary syndrome (systemic therapies):

  Category A (SYST-CAT A): exatrone, all-trans retinoic acid, isotretinoin, interferons alpha and gamma, vorinostat, romidepsin, denileukin diftitox or methotrexate

  Category B (SYST-CAT B): Doxorubicin (liposomal) or gemcitabine

  Category C (SYST-CAT C): Doxorubicin (liposomal), gemcitabine, denileukiin diftitox, romidepsin or pralatrexate

- Adult T-cell leukemia/lymphoma: Cyclophosphamide+doxorubicin+vincristine+prednisone; etoposide+prednisone+vincristine+cyclophosphamide+doxorubicin; cyclophosphamide+vincristine+ doxorubicin+dexamethasone alternating with high dose methotrexate+cytarabine

- Extranodal NK/T-cell lymphoma, nasal type: Dexamethasone+methotrexate+ifosfamide+asparaginase+etoposide; dexamethasone+ etoposide+ifosfamide+carboplatin; etoposide+ifosfamide+cisplatin+dexamethasone

- Post-transplant lymphoproliferative disorder: Rituximab+cyclophosphamide+doxorubicin+vincristine+prednisone; rituximab+cyclophosphamide+doxorubicin+vincristine+prednisone+etoposide

Bierman and Armitage provide a thorough presentation and discussion of the use of chemotherapy the treatment of Non-Hodgkin lymphoma in The Chemotherapy Source Book (Bierman and Armitage 2008).

The numbers of Non-Hodgkin and Burkitt lymphoma cancer studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below. Only studies where the authors designated the disease as non-Hodgkin lymphoma or Burkitt lymphoma are included.

Table 10 Chemotherapy agents used to treat non-Hodgkin lymphoma reviewed in the NTP monograph

Chemotherapy Agent	Number of Studies*	Number of Cases*
6-Mercaptopurine, Appendix C Table 2	2	2
Bleomycin, Appendix C Table 6	9	21
Chlorambucil, Appendix D Table 5	3	3
Cisplatin, Appendix C Table 9	2	2
Cyclophosphamide, Appendix C Table 10	37	70
Cytarabine, Appendix C Table , 11	6	14
Doxorubicin, Appendix C Table 15	26	52
Epirubicin, Appendix C Table 16	3	6
Etoposide, Appendix C Table 17	7	12
Hydroxyurea, Appendix C Table 18	1	1
Ifosfamide, Appendix D Table 9	2	2
Methotrexate, Appendix C Table 22	6	11
Mitoxantrone, Appendix C Table 23	1	1
Procarbazine, Appendix C Table 26	1	1
Rituximab, Appendix C Table 27	11	23
Teniposide, Appendix D Table 18	2	2
Triethylenemelamine, Appendix D Table 19	1	1
Vincristine, Appendix C Table 31	34	68
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

4.5   Leukemia & Pregnancy

4.5.1   Definition of leukemia:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/leukemia;* accessed March 18, 2011).

"**[Leukemia is]** cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream.

Table 11 Estimated new cases and deaths from Leukemia in the United States in 2010

New Cases	207,090
Deaths	39,840
http://www.cancer.gov/cancertopics/types/leukemia (accessed March 18, 2011)	

4.5.2   Occurrence rate during pregnancy:

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of leukemia (not otherwise specified) diagnosed during pregnancy to be 0.014/1000 (approximately 1/71,000) obstetric deliveries. This figure is based on 67 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Leukemia was the seventh most common cancer diagnosed during pregnancy, following breast, cervix, thyroid, melanoma, ovary, and Hodgkin lymphoma.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to provide similar data. Based on 2,103,112 live births among women aged 15 to 44 years, 8 cases of leukemia (not otherwise specified) were diagnosed during pregnancy. The calculated occurrence of leukemia in this study is approximately **0.004/1000** live births or about 1/263,000, and was seventh in descending rank order following cancers of the cervix, breast, ovary, lymphoma, melanoma, and brain.

4.5.3   Impact of pregnancy on prognosis:

The types of leukemia are numerous and the nomenclature used to identify the various types has evolved over time. At present, the United States National Cancer Institute web site (*http://seer.cancer.gov/statfacts/html/leuks.html;* accessed April 18, 2011) lists four basic types: acute lymphocytic (ALL), chronic lymphocytic (CLL), acute myeloid (AML), and chronic myeloid (CML). It is important to keep in mind that the acute leukemias require prompt and aggressive therapy while the chronic forms, particularly CLL, may permit delay of therapy or less aggressive therapies in the pregnant patient.

While there are more published studies of pregnancy outcomes in leukemia patients than for other cancers, primary data on the impact of pregnancy on the prognosis of leukemia is difficult to find.

Nicholson (Nicholson 1968) concluded that there is no good evidence that pregnancy has a deleterious effect on leukemia. Using reports from the literature (1959 to 1965), he calculated median survival

times from clinical onset to death. For 98 cases of acute leukemia, median survival was 5 months and in 44 cases of CML, it was 38 months; both survival rates were similar to survival rates of non-pregnant adult females.

Catanzarite and Ferguson (Catanzarite and Ferguson 1984) conducted a literature review (1972 to 1982) of pregnant patients with acute lymphocytic leukemia or acute nonlymphocytic leukemia. Based on survival of 18 of 34 of these patients for 6 months or longer postpartum, they concluded that survival was consistent with the 6- to 12-month median survival reported for adults treated for acute leukemia.

Caligiuri and Mayer (Caligiuri and Mayer 1989) reviewed the literature (1975 to 1988) and concluded that there was no evidence suggesting that pregnancy alters the incidence, natural history, or prognosis of acute leukemia. They further concluded that, based on a median survival of 38 months in 202 pregnant women with chronic lymphocytic leukemia, survival was not significantly different from the expected survival time for non-pregnant patients.

The publications that address this issue are in general agreement that pregnancy does not influence the course of leukemia, but few data are presented or cited to support this position.

4.5.4   Chemotherapy agents used to treat leukemia:

The National Comprehensive Cancer Network guidelines for treating acute myeloid leukemia (NCCN Guidelines 2011) include various combinations of the following agents: 5-azacytidine, 6-mercaptopurine, all-*trans* retinoic acid, arsenic trioxide, cladribine, clofarabine, cytarabine, daunorubicin, decitabine, etoposide, hydroxyurea, idarubicin, methotrexate, and mitoxantrone. NCCN guidelines for treating chronic myelogenous leukemia (NCCN Guidelines 2011) recommend one the following agents: imatinib, nilotinib, or dasatinib**.** The numbers of leukemia studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below.

Table 12 Chemotherapy agents used to treat leukemia reviewed in the NTP monograph

Chemotherapy Agent	Number of Studies*	Number of Cases*
6-Mercaptopurine, Appendix C Table 2	44	78
6-Thioguanine, Appendix C Table 3	33	46
All-trans retinoic acid, Appendix C Table 5	25	28
Amsacrine, Appendix D Table 1	1	1
Behenoyl cytosine arabinoside, Appendix D Table 2	3	3
Busulfan, Appendix C Table 7	23	30
Chlorambucil, Appendix D Table 5	2	2
Cyclophosphamide, Appendix C Table 10	17	27
Cytarabine, Appendix C Table 11	72	134
Dasatinib, Appendix D Table 6	3	6
Daunorubicin, Appendix C Table 13	55	108
Doxorubicin, Appendix C Table 15	18	40

Epirubicin, Appendix C Table 16	1	1
Etoposide, Appendix C Table 17	5	5
Fludarabine, Appendix D Table 7	2	2
Hydroxyurea, Appendix C Table 18	20	57
Idarubicin, Appendix C Table 19	16	23
Imatinib, Appendix C Table 20	21	151
Interferon alpha, Appendix C Table 21	20	33
Methotrexate, Appendix C Table 22	23	39
Methyl-GAG, , Appendix D Table 13	3	3
Mitoxantrone, Appendix C Table 23	10	14
Nilotinib, Appendix D Table 14	1	1
Nitrogen mustard, Appendix C Table 24	1	1
Triethylenemelamine, Appendix D Table 19	1	1
Vincristine, Appendix C Table 31	46	89
Vindesine, Appendix D Table 20	1	1
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

4.6   Ovarian Cancer & Pregnancy

4.6.1   Definition of ovarian cancer:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/ovarian;* accessed March 10, 2011).

"**[Ovarian cancer is]** cancer that forms in tissues of the ovary (one of a pair of female reproductive glands in which the ova, or eggs, are formed). Most ovarian cancers are either ovarian epithelial carcinomas (cancer that begins in the cells on the surface of the ovary) or malignant germ cell tumors (cancer that begins in egg cells).

Table 13 Estimated new cases and deaths from ovarian cancer in the United States in 2010

New cases	21,880
Deaths	13,850
http://www.cancer.gov/cancertopics/types/ovarian (accessed March 10, 2011)	

4.6.2   Occurrence rate during pregnancy:

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of ovarian cancer diagnosed during pregnancy to be 0.024/1000 (approximately 1/42,000) obstetric deliveries. This figure was based on 115 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Ovarian cancer was the fifth most common cancer diagnosed during pregnancy in this study, following cancer of the breast, cervix, and thyroid, and melanoma. In a follow up study three years later, Leiserowitz et al. (Leiserowitz *et al.* 2006) reported an occurrence rate of 0.0179/1000 deliveries, (approximately 1/56,000) based on 87 cases in 4,846,505 deliveries. If the 115 cases with tumors of low malignant potential are included, the rate is 0.0416/1000 deliveries or about 1/24,000. Of the 202 total cases, 90 were diagnosed prenatally, 48 at the time of delivery, and 64 in the 12 months following delivery.

Dgani et al. (Dgani *et al.* 1989) reported 23 cases of malignant ovarian tumors diagnosed in pregnancy in Israel between 1960 and 1984. The total number of deliveries in this period was 1,083,652, giving an occurrence rate of 0.021/1000 or 1/47,115.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to provide similar data. Based on 2,103,112 live births among women of ages 15 to 44 years, 19 cases of ovarian cancer were diagnosed during pregnancy. The calculated occurrence rate of ovarian cancer in this study was approximately 0.009/1000 live births or about 1/110,000, third in descending rank order following cancer of the cervix and breast.

These four population-based studies report malignant ovarian cancer rates of occurrence ranging from 0.009/1000 to 0.024/1000, about a 2.7-fold range.

Other smaller published studies present varying rates of occurrence of ovarian cancer. Behtash et al. (Behtash *et al.* 2008) reported 0.083/1000 deliveries at the Vali-Asr Hospital in Tehran, Iran between

1991 and 2002 based on 23 cases. Zhao et al. (Zhao *et al.* 2006), using records from the Peking Union Medical College Hospital, 1985 to 2003, reported 0.073/1000 pregnancies based on 22 cases; two cases were diagnosed 4 weeks postpartum, one case was an ectopic pregnancy, and one was diagnosed 2 weeks following an abortion. Machado et al. (Machado *et al.* 2007), using records from a hospital in Murcia, Spain (1987 to 2005) reported the ovarian cancer cases over a 19 year period . There were 131,149 deliveries and 15 cases of ovarian cancer were diagnosed for a rate of occurrence of 0.11/1000. Removing the two cases that were diagnosed postpartum, the number is 0.09/1000 deliveries or about 1/11,000 for those diagnosed while pregnant or during delivery. Whitecar et al. (Whitecar *et al.* 1999) reviewed records from numerous Army medical facilities and the University of Texas Medical Center from 1989 to 1994. Based on 170,577 live births and 8 cases of malignant ovarian tumors or tumors of low malignant potential, the rate of occurrence was 0.047/1000 live births or approximately 1/21,000. Sayedur Rahman et al. (Sayedur Rahman *et al.* 2002), used records from the University of Garyounis in Benghazi, Libya and the King Faisal University College of Medicine in Dammam, Saudi Arabia (1976 to 2000), reported on the experience with ovarian cancer. Based on 9 cases of ovarian carcinoma in 112,050 deliveries, the rate of occurrence was 0.08/1000 deliveries or 1/12,450. Ueda and Ueki (Ueda 1996 #884) reported 5 cases of malignant ovarian tumors associated with pregnancy among 8,420 deliveries at the Department of Obstetrics and Gynecology, Osaka Medical College between 1979 and 1995. This gives an occurrence rate of 0.59/1000 deliveries or about 1/1684. Finally, Munnell (Munnell 1963) reported three ovarian cancers associated with pregnancy among 54,292 deliveries at the Columbia Presbyterian Medical Center in New York between 1947 and 1961. This gives an occurrence rate of 0.056/1000 deliveries or about 1/18,000.

4.6.3   *Impact of pregnancy on prognosis:*

While several papers contain statements suggesting a lack of impact of pregnancy on the prognosis of ovarian cancer, only one paper containing primary data on the possible impact of pregnancy on the clinical course of ovarian cancer was found.

Stensheim et al. (Stensheim *et al.* 2009), using data from the Cancer Registry and the Medical Birth Registry of Norway, compared the cause-specific survival of several cancer types, including ovarian cancer diagnosed in pregnant (38 cases) and non-pregnant (2688 cases) patients. For ovarian cancer, they reported no elevation in risk of cause-specific death (hazard ratio, 0.46; 95%CI, 0.17 to 1.23) in patients diagnosed while pregnant.

4.6.4   *Chemotherapy agents used to treat ovarian cancer:*

Surgery is a primary therapy in treating ovarian cancer. Neo-adjuvant and adjuvant chemotherapies are also used. Ovarian tumors are known to be sensitive to platinum-based agents such as cisplatin and carboplatin, which are used as single agents or in combination with a number of other agents.

The NCCN Guidelines provide an extensive list of chemotherapy agents for treating epithelial ovarian cancer. Preferred agent combinations for platinum sensitive cancers include carboplatin/paclitaxel, carboplatin/docetaxel, carboplatin/gemcitabine, carboplatin/liposomal doxorubicin, and cisplatin/gemcitabine; single agents are carboplatin and cisplatin. Single agent treatments for platinum resistant tumors include docetaxel, etoposide, gemcitabine, liposomal doxorubicin, paclitaxel, and topotecan. Other potentially active single agents include altretamine, capecitabine, cyclophosphamide, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, pemetrexed, and vinorelbine, as well as the the hormonal therapies anastrozole, letrozole, leuprolide acetate, megestrol acetate, and tamoxifen (NCCN Guidelines 2011).

For malignant germ cell tumors of the ovary, NCCN recommends postoperative chemotherapy with the combination bleomycin/etoposide/platinum. For recurrent germ cell tumors, NCCN lists the following combination and single agent therapies: cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/ifosfamide, paclitaxel/carboplatin, paclitaxel/gemcitabine, etoposide/ifosfamide/cisplatin, vinblastine/ifosfamide/cisplatin, vincristine, dactinomycin/cyclophosphamide, paclitaxel/ifosfamide/cisplatin and docetaxel or paclitaxel (NCCN Guidelines 2011).

Holstein and Hohl (Holstein and Hohl 2008) provide a thorough presentation and discussion of the use of chemotherapy in ovarian cancer in the The Chemotherapy Source Book.

The numbers of ovarian cancer studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below.

Table 14 Chemotherapy agents used to treat ovarian cancer reviewed in the NTP monograph

Chemotherapy Agent	Number of Studies*	Number of Cases*
Actinomycin D, Appendix C Table 4	4	4
Bleomycin, Appendix C Table 6	13	18
Carboplatin, Appendix C Table 8	9	11
Cisplatin, Appendix C Table 9	33	42
Cyclophosphamide, Appendix C Table 10	14	14
Docetaxel, Appendix C Table 14	1	1
Doxorubicin, Appendix C Table 15	4	4
Etoposide, Appendix C Table 17	14	19
Irinotecan, Appendix D Table 10	1	1
Paclitaxel, Appendix C Table 25	8	8
Vinblastine, Appendix C Table 30	3	3
Vincristine, Appendix C Table 31	6	6
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

4.7   Melanoma & Pregnancy

4.7.1   Definition of melanoma:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/melanoma*; accessed March 10, 2011).

"**[Melanoma is]** a form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.

Table 15 Estimated new cases and deaths from melanoma in the United States in 2010

New cases	68,130
Deaths	8,700
http://www.cancer.gov/cancertopics/types/melanoma (accessed March 10, 2011)	

4.7.2   Occurrence rate during pregnancy:

Smith et al. (Smith *et al.* 2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of melanoma diagnosed during pregnancy to be 0.031/1000 obstetric deliveries, approximately 1/32,000. This figure is based on 149 cases in 4,846,505 deliveries, counting twins or multiple births as one obstetric delivery. Melanoma was the fourth most common cancer diagnosed during pregnancy in this study, following cancer of the breast, cervix, and thyroid.

Haas (Haas 1984) used records from the National Cancer Registry of the German Democratic Republic from 1970 through 1979 to present similar data. Based on 2,103,112 live births among women aged 15-44, 12 cases of melanoma were diagnosed during pregnancy. The calculated occurrence rate of melanoma in this study is approximately 0.006/1000 live births or about 1/167,000, 5th in descending rank order following cancer of the cervix, breast, ovary, and lymphoma.

Uncertainties regarding the occurrence rate of melanoma during pregnancy are reflected in other publications. For example, Chalas and Valea (Chalas and Valea 1996), based on a retrospective analysis, stated that the incidence was 0.14/1000 pregnancies. Pavlidis (Pavlidis 2002), based on a review of the literature (1970 to 1996), cited a figure of 2.6/1000 deliveries. Smith and Randall (Smith and Randall 1969) presented figures from two hospitals, one in New York and one in Tennessee. At the hospital in New York, four cases were observed among 1400 deliveries over a 3-year period (1964-1967) for an occurrence of 2.8/1000. At the hospital in Tennessee, three cases were observed in 9400 deliveries over a 7-year period (1960 to 1967) for an occurrence of 0.3/1000 deliveries.

These estimated occurrence rates range from 0.006/1000 to 2.8/1000. The substantial differences in the estimated frequencies with which melanoma occurs during pregnancy are not unexpected considering the differences with which melanoma occurs in different age groups, populations, and geographic regions, as well as the differences in the sizes and natures of the studies cited. It is noteworthy that, according to Leachman et al. (Leachman *et al.* 2007), the incidence of melanoma per 100,000 person-years increases from 1.7 among 15-19 year-old Caucasian females to 17.1 in women 40 to 44 years of age.

4.7.3   Impact of pregnancy on prognosis:

Early reports (Kjems and Krag 1993, Pack and Scharnagel 1951) suggested that pregnant patients with melanoma had more advanced lesions and shorter survival times than non-pregnant melanoma patients. However, numerous studies, including some larger case-controlled studies with longer follow-up periods, did not observe a difference in survival between pregnant and non-pregnant melanoma patients (Colbourn *et al.* 1989, Houghton *et al.* 1981, Lens *et al.* 2004, MacKie *et al.* 1991, McManamny *et al.* 1989, O'Meara *et al.* 2005, Travers *et al.* 1995).

Slingluff et al. (Slingluff *et al.* 1990) studied 100 women, age 19-40, diagnosed with melanoma during pregnancy and compared them to a group of 86 age-matched women who were not pregnant when diagnosed. **[It appears these cases were patients at the Duke University Medical Center. The time period over which patients were diagnosed is not provided.]** With a mean follow-up of 6.8 years from diagnosis, they report no significant difference in the survival of the pregnant and non-pregnant cases. However, they report the pregnant patients had a higher incidence of lymph node metastases and, among cases diagnosed with stage 1 disease, a significantly shorter time to development of lymph node metastases and a significantly shorter disease-free interval than the non-pregnant group. Reintgen et al. (Reintgen *et al.* 1985) had earlier reported similar results as Slingluff et al. (Slingluff *et al.* 1990); i.e., no difference in actuarial survivals of women diagnosed with melanoma while pregnant compared to a control population, but a significantly shorter disease-free interval in the pregnant patients compared to controls.

Leachman et al. (Leachman *et al.* 2007) reviewed the available literature on the survival of pregnant versus non-pregnant melanoma patients and noted that stage I-II melanoma does not behave more aggressively in pregnant patients. They further noted that there were fewer reported cases of pregnant patients with stage III-IV melanoma, thus it is unknown whether pregnancy may or may not influence the more advanced stages of this cancer type.

Stensheim et al. (Stensheim *et al.* 2009), using data from the Cancer Registry and the Medical Birth Registry of Norway, compared the cause-specific survival of several cancer types, including malignant melanoma, diagnosed in pregnant (160 cases) and non-pregnant (4460 cases) patients. For melanoma, they reported a slightly elevated risk of cause-specific death (hazard ratio, 1.52; 95%CI, 1.01 to 2.31) in patients diagnosed while pregnant.

Using a mouse melanoma model, Khosrotehrani et al. (Khosrotehrani *et al.* 2011) reported that tumor growth, metastasis, and mortality were higher in pregnant mice than in non-pregnant mice. Further, intratumoral lymphangiogenesis was higher in the pregnant animals, as was the expression of vascular endothelial growth factor A. They then compared the number of intratumoral lymphatic vessels in melanoma tissue from pregnant and non-pregnant women and found the number of these vessels to be significantly higher in tumors from pregnant women (Khosrotehrani *et al.* 2011). Several papers report that there is no difference in survival of pregnant and non-pregnant patients. These results, along with findings of shorter time to lymph node metastasis, a shorter disease free interval in pregnant patients, and one study reporting a small elevation of risk of cause-specific death leave questions regarding the possible impact of pregnancy on the prognosis of melanoma.

4.7.4   Chemotherapy agents used to treat melanoma:

Surgery is the first-line treatment of primary melanoma, but radiation therapy and chemotherapy are also considered in some cases.

Few chemotherapy options are available for melanoma patients and the drugs that are used have not been shown to increase survival (Leachman *et al.* 2007). Dacarbazine alone or in combination with temozolamide, cisplatin, vinblastine, and/or interferon alpha appears to be the chemotherapy regimen of choice for melanoma (Leachman *et al.* 2007, NCCN Guidelines 2011).

Anderson (Anderson 2008) provides a thorough presentation and discussion of the use of chemotherapy in advanced melanoma in the The Chemotherapy Source Book.The numbers of melanoma studies and cases found in the chemotherapy agent tables and the agents used to treat them are shown below.

Table 16 Chemotherapy agents used to treat melanoma reviewed in the NTP monograph

Chemotherapy Agent	Number of Studies*	Number of Cases*
Carmustine, Appendix D Table 4	2	2
Cisplatin, Appendix C Table 9	3	3
Dacarbazine, Appendix C Table 12	6	8
Interferon alpha, Appendix C Table 21	4	4
Nimustine, Appendix D Table 15	1	1
Tamoxifen, Appendix C Table 28	2	2
Vincristine, Appendix C Table 31	1	1
*Many studies report on multiple chemotherapy agents and many patients are treated with multiple chemotherapy agents so the same study or case may appear in multiple agent tables.		

5.0 CANCER CHEMOTHERAPEUTIC AGENTS ADMINISTERED DURING PREGNANCY: OVERALL ANALYSIS AND AGENT SPECIFIC SUMMARIES

In the studies reviewed in the NTP monograph, 52 cancer chemotherapeutic agents were administered, individually or in combination therapy, to pregnant patients (Table 5). Of these cancer chemotherapeutic agents, 46 agents are considered to be human embryotoxicants and/or teratogens (FDA Pregnancy Category D, n=45 agents or X, n=1 agent (methotrexate)), and three agents (dacarbazine, interferon alpha, and rituximab) are known or possible animal embryotoxicants or teratogens (FDA Pregnancy Category C). Three cancer chemotherapy agents do not have a FDA pregnancy category listing (i.e., amsacrine, behenoyl cytosine arabinoside (Behenoyl-ara-C), and Methyl-glyoxal bis guanyl hydrazone (Methyl-GAG)). Of the 52 cancer chemotherapy agents used during pregnancy, the NTP monograph reviews the background information and developmental effects of 32 individual agents (administered singly or in combination therapy) (Sections 5.2-5.33) These agents were selected for review because there were published reports of pregnancy outcomes of 10 or greater number of cases. These agents can be classified into seven groups of mechanism of action: anti-metabolites, DNA alkylating agents, DNA intercalating/corss-linking agents, microtubule inhibitors, topoisomerase II inhibitor, oxygen free radical generator and agents that target specific receptors or cell-signalling pathway components (also called targeted agents). The agents are listed by mechanism of action in Table 17.

Table 17 Mechanism of action of the 33 cancer chemotherapeutic agents reviewed in the NTP monograph for which pregnancy outcomes were reported for greater than 10 cases.

Anti-metabolites	DNA intercalating/cross-linking agents	Topoisomerase II inhibitor
• *5-Fluorouracil* • *6-Mercaptopurine* • *6-Thioguanine* • *Cytarabine* • *Hydroxyurea* • *Methotrexate* **DNA alkylating agents** • *Busulfan[a]* • *Cyclophosphamide[a]* • *Dacarbazine* • *Ifosfamide[a]* • *Nitrogen mustard[a]* • *Procarbazine*	• *Actinomycin D* • *Carboplatin* • *Cisplatin* • *Daunorubicin* • *Doxorubicin* • *Epirubicin* • *Idarubicin* • *Mitoxantrone[b]* **Microtubule function inhibitors** • *Docetaxel* • *Paclitaxel* • *Vinblastine* • *Vincristine* • *Vinorelbine*	• *Etoposide* **Oxygen free radical generator** • *Bleomycin* **Targeted therapies** • *All-trans retinoic acid* • *Imatinib* • *Interferon alpha* • *Rituximab* • *Tamoxifen* • *Trastuzumab*

5.1 OVERALL ANALYSIS BASED ON ANY CHEMOTHERAPY EXPOSURE

The NTP monograph compiled data on a total of 1242 female cancer patients treated with any cancer chemotherapy during pregnancy. These patients were administered cancer chemotherapy during 1255 pregnancies and 1271 conceptuses based on 13 patients having 2 pregnancies each and 16 twins (Table 18). Of these 1255 pregnancies, 402 pregnancies were exposed to cancer chemotherapy in the first trimester, including 7 sets of twins (417 conceptuses). A total of 823 pregnancies were exposed to cancer chemotherapy in the second and/or third trimester only, including 9 sets of twins (841 conceptuses). The timing of exposure was not specified for 38 pregnancies (38 conceptuses).

Major and minor congenital malformations. Major congenital malformations were more frequently observed in conceptuses exposed to cancer chemotherapy during the first trimester than in conceptuses exposed to cancer chemotherapy in the second and/or third trimester only. Of the 1271 conceptuses evaluated in this monograph, the apparent rate of major malformations was 9.8% (40/410 conceptuses) following exposure to any cancer chemotherapy during the first trimester compared to the apparent rate of 2.7% (22/823 conceptuses) of major malformations following exposure during the second and/or third trimester only. Timing of exposure was not specified for 38 conceptuses, and none of these conceptuses were malformed. Minor malformations were reported in 26 infants (Figure 1; Appendix A Table 1); the majority of these infants were exposed during the second and/or third trimester only.

Fetal death. Fetal death occurred in 155 singleton pregnancies (155 conceptuses) among the studies reviewed in the NTP monograph (Table 20). Spontaneous abortion was reported for 46 pregnancies and 22 pregnancies ended in intrauterine fetal death (also called stillbirth in this evaluation). In addition, 9 pregnancies ended due to maternal or maternal/fetal death {Feliu, 1988 #233}{Greenlund, 2001 #93;Nicholson, 1968 #783;Roboz, 1979 #542;Rothberg, 1959 #789;Zuazu, 1991 #467} and 1 pregnancy was terminated by hysterotomy {Mennuti, 1975 #288}. The remaining fetal deaths were due to induced abortions.

Table 18 Pooled pregnancy outcome data associated with cancer chemotherapy use during pregnancy.

		Trimester Exposed		
Number of conceptuses	**Overall total**	**1st**	**2nd and/or 3rd only**	**Not specified**
Total	1271	410	823	38
Malformed	62	40	22	0
Live newborns	1112	292	788	32
Induced abortion	79	67	12	0
Spontaneous abortion	47	40	3	4
Intrauterine fetal demise	24	7	15	2
Other fetal loss	9	4	5	0
Children at follow up[a]	703	133	539	31
[a] This number does not include 24 infants who died in the first 4 months of life				

Pregnancy complications. The NTP also compiled information on pregnancy complications potentially associated with cancer chemotherapy use during pregnancy. Two of the more frequently reported pregnancy complications were reduced amniotic fluid and spontaneous preterm labor. Of the 1136 pregnancies evaluated in this monograph resulting in stillbirths and live births, the apparent rate ofmoderate to severe reductions in amniotic fluid (e.g., oligohydramnios and anhydramnios, respectively) was 2.9% (33/1138 pregnancies) for pregnancies gestationally exposed to any cancer chemotherapy. Preterm birth (<37 weeks gestation) occurred for a majority of the patients administered chemotherapy during pregnancy evaluated in this monograph; these births include spontaneous and induced vaginal deliveries as well as Caesarean-section deliveries.

Of these preterm births, spontaneous preterm labor did not appear to be the primary cause of preterm births (apparent rate of spontaneous preterm labor was 5.5%; 63/1136 pregnancies resulting in live births and stillbirths); this number included 7 cases with transient preterm labor that resolved on its own or with treatment. Other frequently occurring pregnancy complications included: preeclampsia (n=17 cases, including one case complicated by gestational diabetes and spontaneous preterm labor), eclamptic seizures (n=1 case), maternal hypertension (n=3 cases), premature rupture of membranes (n=18, including 6 cases with spontaneous preterm labor and one case with fetal distress), premature detachment of placenta (n=2 cases), signs of placental insufficiency (n=1 case), placental ischemia (n=2 cases), maternal tonic-clonic seizures (n=1 case), maternal septicemia (n=1 case), mother severely ill (n=1 case), maternal respiratory issues (n=1 case) and maternal death (n=1 case). Also, fetal distress occurred in three additional cases, including one case with spontaneous preterm labor.

Intrauterine growth restriction and small for gestational age infants. Intrauterine fetal growth restriction (10th percentile for estimated fetal weight in the womb) was observed in 36 of 1136 total pregnancies (including stillbirths and live births) evaluated in the NTP monograph. At birth, small for gestational age (<10th percentile body weight for gestational age) was reported by the authors for 24 newborns out of 1112 liveborn infants evaluated in this monograph. Interestingly, only 2 of the 36 pregnancies with intrauterine growth restriction observed during pregnancy yielded a small for gestational age newborn {Hsu, 1995 #111;Nakajima, 2004 #316}.

Newborn health. Regarding newborn health issues, transient myelosuppression was reported in 50 of 1112 newborns gestationally exposed to cancer chemotherapy evaluated in this monograph; however, complete blood counts were not reported for every infant. This myelosuppression was transient, usually resolving within the first 2 to 3 weeks of life. Fetal and/or neonatal cardiotoxicity was observed in 7 of 1138 total conceptuses (including stillbirths and live births). Cardiotoxicity in the fetus/neonate was identified as arrhythmia , cardiomyopathy, tachycardia, and heart failure {Baumgartner, 2009 #151;Harrison, 1994 #631;Leong, 2000 #252;Takitani, 2005 #525}{Garcia, 1999 #69}{King, 1991 #137;Okun, 1979 #691}. This overt cardiotoxicity appeared to resolve at birth or following treatment shortly after birth with no lasting cardiac effects reported at follow up evaluation at ages ranging from 3 months to 4 years (n=6 children; n=1 infant without follow up data).

Twenty-four of 1112 live born infants died within the first 4 months of life. Fifteen of the infants who died were born preterm, 2 were born at term and gestational age at delivery was not stated for 4 infants. Of the 15 infants who died in the first week of life, 2 infants died of malformations observed prior to chemotherapy {Rouzi, 2009 #376;Thomas, 1976 #910}. For the remainder, it is not possible to determine whether the mortality was associated with a direct effect of the chemotherapy agent, or whether the mortality was a consequence of prematurity. Of the remaining infant mortalities, four infants died of infections {Aviles, 1988 #772}{Dilek, 2006 #212;Ruiz Reyes, 1961 #750}, one died of a severe autoimmune disease at age 13 weeks {Cardonick, 2010 #7}, three infants died following

decreasing kidney function {Beale, 2009 #155}{Weber-Schoendorfer, 2008 #526} , one infant died of multiple organ failure {Witzel, 2008 #24}. The remaining infant death involved respiratory infection, and autopsy revealed multiple malformations {Diamond, 1960 #544}.

Growth and development of children. Follow up evaluations were reported for 703 of 1112 live born infants of the studies reviewed in the NTP monograph; this number does not include the 24 infants who died in the first 4 months of life. Normal growth and development were reported for a majority of children exposed in utero to cancer chemotherapy (calculating final number). In most cases, children were not evaluated beyond the second year of life.   There was only one report of a child (a male twin) developing cancer following exposure to cancer chemotherapy; the mother was administered cyclophosphamide during the period of conception and throughout pregnancy, and his female twin had normal growth and development (Zemlickis *et al.* 1993).

Figure 1. Apparent rates of major congenital malformations (± 95% confidence interval) reported following cancer chemotherapy used during the pregnancy. Data are presented as any chemotherapy exposure or by individual agent, singly or in combination therapy.
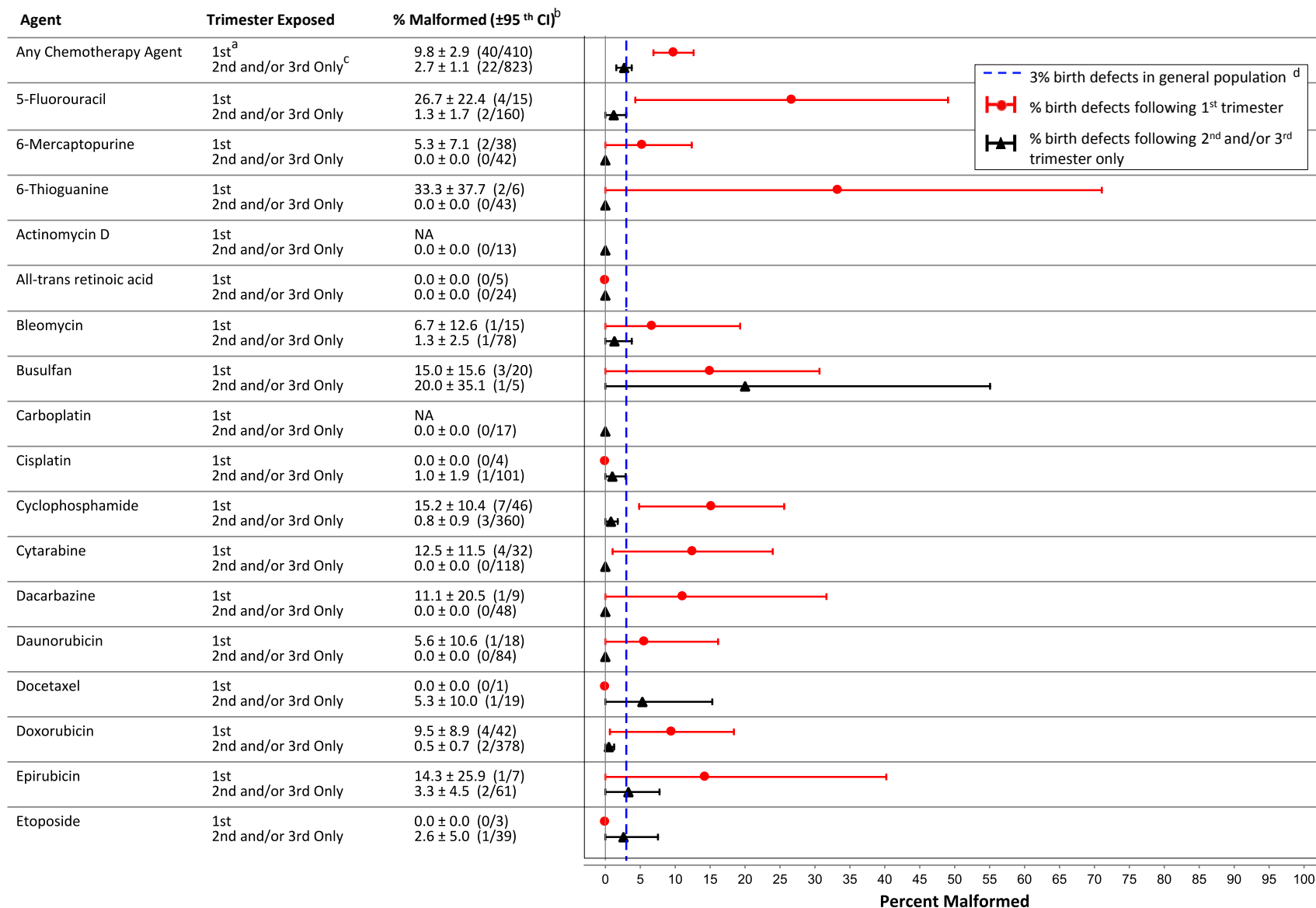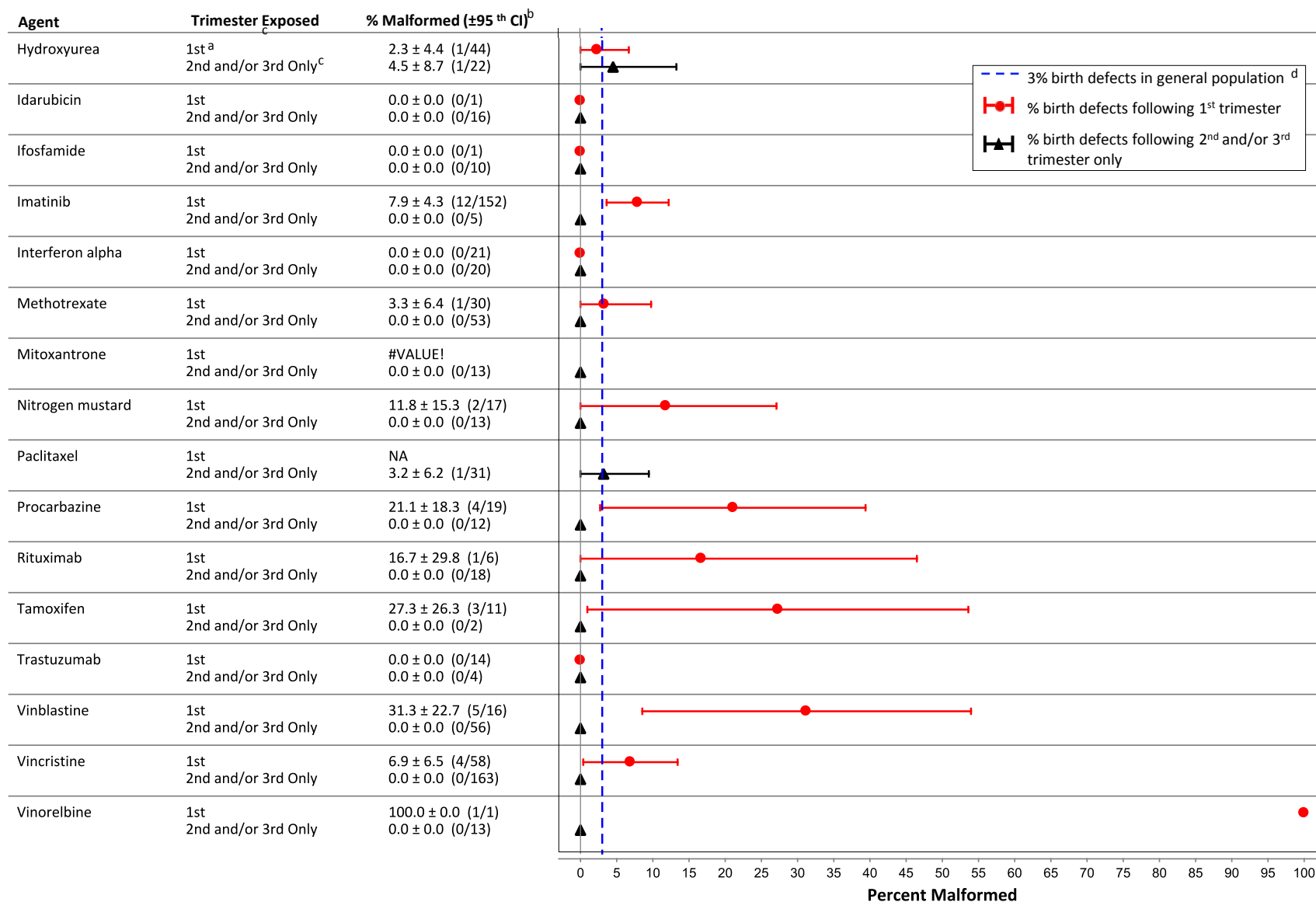

Agent	Trimester Exposed	% Malformed (±95th CI)[b]
Any Chemotherapy Agent	1st[a]	9.8 ± 2.9 (40/410)
	2nd and/or 3rd Only[c]	2.7 ± 1.1 (22/823)
5-Fluorouracil	1st	26.7 ± 22.4 (4/15)
	2nd and/or 3rd Only	1.3 ± 1.7 (2/160)
6-Mercaptopurine	1st	5.3 ± 7.1 (2/38)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/42)
6-Thioguanine	1st	33.3 ± 37.7 (2/6)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/43)
Actinomycin D	1st	NA
	2nd and/or 3rd Only	0.0 ± 0.0 (0/13)
All-trans retinoic acid	1st	0.0 ± 0.0 (0/5)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/24)
Bleomycin	1st	6.7 ± 12.6 (1/15)
	2nd and/or 3rd Only	1.3 ± 2.5 (1/78)
Busulfan	1st	15.0 ± 15.6 (3/20)
	2nd and/or 3rd Only	20.0 ± 35.1 (1/5)
Carboplatin	1st	NA
	2nd and/or 3rd Only	0.0 ± 0.0 (0/17)
Cisplatin	1st	0.0 ± 0.0 (0/4)
	2nd and/or 3rd Only	1.0 ± 1.9 (1/101)
Cyclophosphamide	1st	15.2 ± 10.4 (7/46)
	2nd and/or 3rd Only	0.8 ± 0.9 (3/360)
Cytarabine	1st	12.5 ± 11.5 (4/32)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/118)
Dacarbazine	1st	11.1 ± 20.5 (1/9)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/48)
Daunorubicin	1st	5.6 ± 10.6 (1/18)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/84)
Docetaxel	1st	0.0 ± 0.0 (0/1)
	2nd and/or 3rd Only	5.3 ± 10.0 (1/19)
Doxorubicin	1st	9.5 ± 8.9 (4/42)
	2nd and/or 3rd Only	0.5 ± 0.7 (2/378)
Epirubicin	1st	14.3 ± 25.9 (1/7)
	2nd and/or 3rd Only	3.3 ± 4.5 (2/61)
Etoposide	1st	0.0 ± 0.0 (0/3)
	2nd and/or 3rd Only	2.6 ± 5.0 (1/39)

Legend:
- - - - 3% birth defects in general population [d]
⊢●⊣ % birth defects following 1st trimester
⊢▲⊣ % birth defects following 2nd and/or 3rd trimester only

Percent Malformed

Figure 1. (cont'd) Apparent rates of major congenital malformations.

Agent	Trimester Exposed[c]	% Malformed (±95 th CI)[b]
Hydroxyurea	1st [a]	2.3 ± 4.4 (1/44)
	2nd and/or 3rd Only[c]	4.5 ± 8.7 (1/22)
Idarubicin	1st	0.0 ± 0.0 (0/1)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/16)
Ifosfamide	1st	0.0 ± 0.0 (0/1)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/10)
Imatinib	1st	7.9 ± 4.3 (12/152)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/5)
Interferon alpha	1st	0.0 ± 0.0 (0/21)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/20)
Methotrexate	1st	3.3 ± 6.4 (1/30)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/53)
Mitoxantrone	1st	#VALUE!
	2nd and/or 3rd Only	0.0 ± 0.0 (0/13)
Nitrogen mustard	1st	11.8 ± 15.3 (2/17)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/13)
Paclitaxel	1st	NA
	2nd and/or 3rd Only	3.2 ± 6.2 (1/31)
Procarbazine	1st	21.1 ± 18.3 (4/19)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/12)
Rituximab	1st	16.7 ± 29.8 (1/6)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/18)
Tamoxifen	1st	27.3 ± 26.3 (3/11)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/2)
Trastuzumab	1st	0.0 ± 0.0 (0/14)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/4)
Vinblastine	1st	31.3 ± 22.7 (5/16)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/56)
Vincristine	1st	6.9 ± 6.5 (4/58)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/163)
Vinorelbine	1st	100.0 ± 0.0 (1/1)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/13)

Legend:
- – – – 3% birth defects in general population [d]
- % birth defects following 1st trimester
- % birth defects following 2nd and/or 3rd trimester only

Percent Malformed (x-axis: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100)

[a]Some of the conceptuses exposed during the 1st trimester were also exposed during the 2nd and 3rd trimester. [b]The 95% confidence interval is calculated from the pooled data.; left whisker of the 95% confidence interval is truncated at 0%. [c]Data on exposure to individual agents in the 2nd and/or 3rd trimester only are adjusted to remove the major malformations that were not likely caused by exposure during this period (see Methods, Appendix A Table 1). [d]Prevalence in the United States of birth defects in the general population (3%) {Correa, 2007 #1108}; this is not a null hypothesis comparison.

Table 19 Incidence of spontaneous abortion[a] and stillbirth[b] following cancer chemotherapy use during pregnancy to any cancer chemotherapy or individual agents (singly or in combination therapy).

Exposure	Spontaneous abortion (affected/total conceptuses)	Stillbirth (affected/total conceptuses)
Any Chemotherapy	3.6% (46/1271)	1.7 % (22/1271)
Specific Agent:		
5-Fluorouracil	1.7% (3/175)	0.6% (1/175)
6-Mercaptopurine	7.1% (6/84)	3.6% (3/84)
6-Thioguanine	2.0% (1/49)	8.2% (4/49)
Actinomycin D	0% (0/13)	0% (0/13)
ATRA	3.4% (1/29)	3.4% (1/29)
Bleomycin	0.0% (0/95)	1.1% (1/95)
Busulfan	3.2% (1/31)	0.0% (0/31)
Carboplatin	5.9% (1/17)	0.0% (0/17)
Cisplatin	1.0% (1/101)	1.0% (1/101)
Cyclophosphamide	1.2% (5/408)	1.2% (5/408)
Cytarabine	4.0% (6/151)	8.6% (13/151)
Dacarbazine	1.8% (1/57)	1.8% (1/57)
Daunorubicin	4.7% (5/106)	9.4% (10/106)
Docetaxel	0.0% (0/20)	0.0% (0/20)
Doxorubicin	0.7% (3/420)	1.2% (5/420)
Epirubicin	2.9% (2/69)	2.9% (2/69)
Etoposide	0.0% (0/42)	4.8% (2/42)
Hydroxyurea	1.5% (1/68)	7.4% (5/68)
Idarubicin	0.0% (0/22)	13.6% (3/22)
Ifosfamide	0% (0/1)	9.1% (1/11)
Imatinib	12.1% (19/157)	1.3% (2/157)
Interferon alpha	0.0% (0/43)	0.0% (0/43)
Methotrexate	4.8% (4/83)	2.4% (2/83)
Mitoxantrone	5.9% (1/17)	5.9% (1/17)
Nitrogen mustard	6.7% (2/30)	0.0% (0/30)
Paclitaxel	0.0% (0.31)	0.0% (0/31)
Procarbazine	3.2% (1/31)	0.0% (0/31)
Rituximab	4.2% (1/24)	8.3% (2/24)
Tamoxifen	0.0% (0/14)	0% (0/14)
Trastuzumab	0.0% (0/20)	0.0% (0/20)
Vinblastine	1.4% (1/73)	1.4% (1/73)
Vincristine (223)	3.1% (7/223)	3.6% (8/223)
Vinorelbine (15)	0% (0/15)	0% (0/15)

[a]Defined as early spontaneous fetal loss, age 22 weeks gestation or younger.
[b]Defined as late spontaneous fetal death, age 23 weeks gestation to term.

Table 20 Reductions in amniotic fluid following cancer chemotherapy use during the pregnancy. Data are presented as any chemotherapy exposure or by individual agent, singly or in combination therapy.

Exposure	Absent or reduced amniotic fluid[a] (affected/total pregnancies with live births and stillbirths)
Any Chemotherapy Agent	2.9% (33/1128)
Specific Agents:	
5-Fluorouracil	0.6% (1/169)
6-Mercaptopurine	1.4% (1/74)
6-Thioguanine	2.3% (1/43)
Actinomycin D	7.7% (1/13)
ATRA	7.7% (2/26)
Bleomycin	2.2% (2/91)
Busulfan	0.0% (0/28)
Carboplatin	6.3% (1/16)
Cisplatin	5.2% (5/97)
Cyclophosphamide	1.3% (5/388)
Cytarabine	4.7% (6/128)
Dacarbazine	0.0% (0/51)
Daunorubicin	3.6% (3/84)
Docetaxel	15.0% (3/20)
Doxorubicin	1.5% (6/410)
Epirubicin	0.0% (0/66)
Etoposide	9.8% (4/41)
Hydroxyurea	0.0% (0/57)
Idarubicin	15.8% (3/19)
Ifosfamide	36.4% (4/11)
Imatinib	0.0% (0/99)
Interferon alpha	2.4% (1/41)
Methotrexate	1.4% (1/73)
Mitoxantrone	6.7% (1/15)
Nitrogen mustard	0.0% (0/24)
Paclitaxel	6.5% (2/31)
Procarbazine	0.0% (0/24)
Rituximab	4.3% (1/23)
Tamoxifen	14.3% (2/14)
Trastuzumab	68.4% (13/19)
Vinblastine	1.5% (1/68)
Vincristine	1.5% (3/199)
Vinorelbine	13.3% (2/15)

[a]Includes pregnancies with anhydramnios, oligohydramnios and reports of reduced amniotic fluid.

Table 21 Pregnancy complications reported following cancer chemotherapy use during the pregnancy. Data are presented as any chemotherapy exposure or by individual agent, singly or in combination therapy.

	Intrauterine growth restriction (affected/total conceptuses from live births and stillbirths)	Small for gestational age[d] (affected/total live born infants)
Any Chemotherapy	3.2% (36/1136)	2.2% (24/1112)
Specific Agents		
5-Fluorouracil	0.6% (1/170)	3.0% (5/169)
6-Mercaptopurine	1.3% (1/75)	0.0% (0/73)
6-Thioguanine	4.7% (2/43)	0.0% (0/39)
Actinomycin D	7.7% (1/13)	0.0% (0/13)
ATRA	7.4% (2/27)	0.0% (0/26)
Bleomycin	6.5% (6/93)	2.2% (2/92)
Busulfan	0.0% (0/28)	0.0% (0/28)
Carboplatin	6.3% (1/16)	6.3% (1/16)
Cisplatin	7.1% (7/99)	2.0% (2/98)
Cyclophosphamide	1.0% (4/391)	3.1% (12/386)
Cytarabine	7.8% (10/128)	0.0% (0/116)
Dacarbazine	3.8% (2/52)	2.0% (1/51)
Daunorubicin	7.1% (6/85)	0.0% (0/75)
Docetaxel	10.0% (2/20)	0.0% (0/20)
Doxorubicin	1.9% (8/413)	2.9% (12/408)
Epirubicin	1.5% (1/66)	0.0% (0/64)
Etoposide	22.0% (9/41)	2.6% (1/39)
Hydroxyurea	3.3% (2/60)	0.0% (0/55)
Idarubicin	21.1% (4/19)	6.3% (1/16)
Ifosfamide	27.3% (3/11)	0.0% (0/10)
Imatinib	0.0% (0/99)	0.0% (0/99)
Interferon alpha	4.7% (2/43)	0.0% (0/43)
Methotrexate	2.6% (2/76)	4.1% (3/74)
Mitoxantrone	20.0% (3/15)	7.1% (1/14)
Nitrogen mustard	0.0% (0/24)	0.0% (0/24)
Paclitaxel	3.2% (1/31)	3.2% (1/31)
Procarbazine	0.0% (0/24)	0.0% (0/24)
Rituximab	4.3% (1/23)	4.8% (1/21)
Tamoxifen	0.0% (0/14)	0.0% (0/14)
Trastuzumab	10.0% (2/20)	5.3% (1/19)
Vinblastine	2.9% (2/69)	1.5% (1/68)
Vincristine	2.0% (4/201)	1.6% (0/193)
Vinorelbine	0.0% (0/15)	0.0% (0/14)

Table 22 Spontaneous preterm labor and preterm birth in pregnancies exposed to cancer chemotherapy. Data are presented as any chemotherapy exposure or by individual agent, singly or in combination therapy.

Exposure	Spontaneous preterm labor[a] (affected/total pregnancies with live births and stillbirths)	Preterm birth[b] (affected/total pregnancies with live births reporting gestational age at birth[c])
Any Chemotherapy	5.6% (63/1128)	Not available
Specific Agents:		
5-Fluorouracil	3.6% (6/169)	74.5% (38/51)
6-Mercaptopurine	17.6% (13/74)	53.4% (31/58)
6-Thioguanine	11.6% (5/43)	52.8% (19/36)
Actinomycin D	23.1% (3/13)	72.7% (8/11)
ATRA	15.4% (4/26)	88.0% (22/25)
Bleomycin	4.4% (4/91)	40.0% (24/60)
Busulfan	7.1% (2/28)	23.8% (5/21)
Carboplatin	6.3% (1/16)	92.3% (12/13)
Cisplatin	5.2% (5/97)	78.9% (60/76)
Cyclophosphamide	6.2% (24/388)	57.0% (86/151)
Cytarabine	7.0% (9/128)	54.5% (54/99)
Dacarbazine	0.0% (0/51)	51.9% (14/27)
Daunorubicin	8.3% (7/84)	65.6% (40/61)
Docetaxel	0.0% (0/20)	71.4% (10/14)
Doxorubicin	3.9% (16/410)	56.4% (88/156)
Epirubicin	3% (2/66)	72.4% (21/29)
Etoposide	7.3% (3/41)	56.3% (18/32)
Hydroxyurea	3.5% (2/57)	39.1% (9/23)
Idarubicin	0.0% (0/19)	91.7% (11/12)
Ifosfamide	0.0% (0/11)	90.0% (9/10)
Imatinib	1.0% (1/99)	12.0% (3/25)
Interferon alpha	0.0% (0/41)	27.5% (11/40)
Methotrexate	12.3% (9/73)	44.4% (20/45)
Mitoxantrone	6.7% (1/15)	100.0% (11/11)
Nitrogen mustard	4.2% (1/24)	29.4% (5/17)
Paclitaxel	9.7% (3/31)	70.8% (17/24)
Procarbazine	4.2% (1/24)	25.0% (4/16)
Rituximab	8.7% (2/23)	58.8% (10/17)
Tamoxifen	21.4% (3/14)	72.7% (8/11)
Trastuzumab	0.0% (0/19)	55.6% (10/18)
Vinblastine	1.5% (1/68)	47.1% (16/34)
Vincristine	8.5% (17/199)	49.7% (76/153)
Vinorelbine	0.0% (0/15)	64.3% (9/14)

[a]Includes 7 pregnancies with transient preterm spontaneous labor (Section 5.1)
[b]Preterm birth includes spontaneous and induced vaginal births, and Caesarian-section births.
[c]Data included in this table are based on reported individual infant's gestational age at birth. Term was considered ≥37 weeks of gestation (see Section 3.2.6 Methods).

5.2   5-FLUOROURACIL

5.2.1   *Mechanism of action, route of administration, and indications*

5-Fluorouracil is a pyrimidine analogue that belongs to a class of chemotherapy drugs known as anti-metabolites. It enters the cell using the same transport mechanisms as the nucleotide uracil and is converted into several active metabolites. These active metabolites of 5-fluorouracil disrupt thymidine synthase, an enzyme that is responsible for the production of thymidylate which, in turn, is important for DNA replication and repair (Longley *et al.* 2003). A second mechanism of action is the incorporation of an active metabolite of 5-fluorouracil into RNA, thus disrupting its normal processing and function. 5-Fluorouracil is administered intravenously in the treatment of cancer. It is indicated for cancers of the colon, rectum, breast, stomach and pancreas (Sandoz 2011). It is also used in the treatment of head and neck cancers (Specenier and Vermorken 2009).

5.2.2   *Evidence of placental and breast milk transport*

Placenta and breast milk transport of 5-fluorouracil in humans has not been documented; however, there are published reports of placental transfer of the drug in mouse and rat studies. When injected into pregnant C57BL/K mice on gestation day 10, 5-fluorouracil rapidly crossed the placenta and distributed throughout the embryo as measured at 24 to 67 hours (Dagg *et al.* 1966). Boike et al. (Boike *et al.* 1989) reported that 5-fluorouracil also readily crossed the placenta of pregnant rats administered the drug intravenously on gestation day 21, leading to dose-dependent increases of the drug in fetal plasma. In the rat fetus, 5-fluorouracil was poorly eliminated, which may explain the observed fetal toxicity at dosage levels lower than maternal toxicity (50 mg/kg versus 230 mg/kg, fetal versus maternal LD_{50}) (reviewed in Boike et al. (Boike *et al.* 1989)). Van Calsteren et al. (Van Calsteren *et al.* 2010) administered 5-fluorouracil in combination with cyclophosphamide and epirubicin or doxorubicin (adriamycin) to pregnant baboons in a study of placental transport of cancer chemotherapeutics; however, no data on placental transport of 5-fluorouracil were provided in their publication. There are no published reports of breast milk transfer of 5-fluorouracil in humans or in animal models; however, the low molecular weight of the drug (approximately 130 g/mol) suggests it is likely transfered into breast milk (Boike *et al.* 1989).

5.2.3   *Laboratory animal developmental toxicity*

Teratogenic effects have been observed following parenteral administration of 5-fluorouracil to mice, rats, and hamsters at doses equivalent to the usual human intravenous dose **[12 mg/kg]** (Sandoz 2011). For example, intraperitoneal injections of 10 to 40 mg/kg on gestation days 10 through 13 produced skeletal defects in two strains of mice, such as hind paw anomalies, cleft palate, and micrognathia (Dagg 1960, Dagg *et al.* 1966). Similar malformations have been observed in rats following intraperitoneal doses of 12 to 37 mg/kg on gestation days 9 and 12, and in hamsters following intramuscular doses of 3 to 9 mg/kg on gestation days 8 and 11 of gestation. Embryotoxicity (increased resorptions or embryolethality) were observed in hamsters at the same doses that caused malformations. In contrast, administration of 5-fluorouracil at doses of 40 mg/kg to monkeys on gestation days 20 and 24, during organogenesis, did not induce malformations. Pregnancy loss was induced at doses higher than 40 mg/kg bw in monkeys (Sandoz 2011).

5.2.4   *Human gestational exposure and effects*

5-Fluorouracil is assigned the FDA Pregnancy Category D. There were 174 published cases of patients administered 5-fluorouracil during pregnancy from 18 case reports, 10 case series, 1 retrospective case

series, 2 retrospective cohort studies, 5 retrospective survey studies, and 1 registry surveys (Appendix C Table 1). Among the 174 patients, 5-fluorouracil was used to treat breast cancer (n=161 cases), colorectal cancer (n=5 cases), colon cancer (n=2 cases), and one case each of cancers of the bowel, rectum, cervix and pancreas. Type of cancer was not specified for two cases (Van Calsteren *et al.* 2010). 5-Fluorouracil was administered during 174 pregnancies for a total of 175 exposed conceptuses, due to one twin pregnancy (Jeppesen and Osterlind 2011). 5-Fluorouracil was administered during the 1st trimester in 14 pregnancies (15 conceptuses due to one twin pregnancy) and during the 2nd and/or 3rd trimester only in 114 pregnancies. The timing of exposure was not identified for 46 singleton pregnancies from two case series (Hahn *et al.* 2006, Jameel and Jamil 2007). These 46 pregnancies were likely treated in the 2nd and 3rd trimester as the studies reported that the gestational age of initiation of chemotherapy ranged from 11-34 weeks (median 23 weeks (Hahn *et al.* 2006)) or 12-33 weeks (mean = 22 weeks (Jameel and Jamil 2007)). Therefore, we calculated that 160 singleton pregnancies (160 conceptuses) were exposed to 5-fluorouracil only in the 2nd and/or 3rd trimester.

Fetal loss was reported in six pregnancies exposed in utero to 5-fluorouracil. Spontaneous abortion occurred in three cases exposed during the 1st trimester and co-exposed to: methotrexate (Ring *et al.* 2005, Zemlickis *et al.* 1992), or epirubicin and cyclophosphamide (Giacalone *et al.* 1999); no fetal autopsy data were reported. Major malformations were observed in fetuses from two induced abortions. Skeletal malformations and micrognathia were observed in a fetus from an induced abortion following exposure in the 1st trimester and co-exposure to cyclophosphamide, epirubicin and radiation therapy, followed by cyclophosphamide and methotrexate in the 2nd trimester (Leyder *et al.* 2010). Skeletal malformations included: shortened 2nd and 3rd fingers, clinodactyly of the 5th finger, skin syndactyly of the 1st and 2nd fingers, a short 1st toe and osseous syndactyly of the 4th and 5th metatarsal bones (Leyder *et al.* 2010). Autopsy of a second induced abortus revealed several malformations including: bilateral radial aplasia and absent thumbs, absence of 1 or 2 fingers on each hand, a single umbilical artery and a hypoplastic aorta, an imperforate anus, a common bladder and rectum, renal dysplasia as well as underdevelopment or absence of multiple organs (Stephens *et al.* 1980). This fetus was exposed in the 1st and 2nd trimesters beginning in the 11th week of gestation and was co-exposed to diagnostic X-rays in the 1st trimester (Stephens *et al.* 1980). Furthermore, the authors stated the case "most likely involved a basic genetic or chromosomal abnormality, but that 5-fluorouracil may have affected ongoing development of some structures" (Stephens *et al.* 1980). One intrauterine fetal death occurred at 25 weeks gestation following 1st trimester exposure and co-exposure to methotrexate (Peres *et al.* 2001); no fetal autopsy data were reported.

Of the 169 live-born infants exposed in utero to 5-fluorouracil, malformations were reported in nine infants. Major malformations occurred in two infants with 1st trimester exposure to 5-fluorouracil. One infant had hypertelorism, microcephaly, low set ears, and a right palmar simian crease following exposure to 5-fluorouracil and methotrexate from 1st trimester (gestation week 7.5) through 3rd trimester (gestation week 28.5) and radiotherapy in the 2nd trimester (Bawle *et al.* 1998). Another newborn had multiple skeletal deformities of the hand, flat nasal bridge, high arched palate, ventriculomegaly, colpocephaly, and a bicuspid aortic valve following exposure in the period of conception, 1st and 2nd trimesters and co-treatment with doxorubicin and cyclophosphamide (Paskulin *et al.* 2005). Inguinal hernia, a minor malformation, was reported in an infant following exposure in the 1st and 2nd trimester and co-treatment with cyclophosphamide (Giannakopoulou *et al.* 2000). Major malformations were observed in three infants exposed in the 2nd and/or 3rd trimester only. Hemi-hypertrophy of the lower extremity was observed in one infant following 2nd and 3rd trimester exposure (Cardonick *et al.* 2010). Hahn et al. (Hahn *et al.* 2006) reported that one infant with clubfoot and another infant with Down syndrome following in utero exposure in the 2nd and 3rd trimesters only with

co-exposure to doxorubicin and cyclophosphamide. Minor malformations were reported in four additional infants exposed to 5-fluorouracil in the 2nd and/or 3rd trimester only. Congenital bilateral ureteral reflux (n=1 infant) (Hahn *et al.* 2006) and doubled cartilage rings (n=1 infant) (Van Calsteren *et al.* 2010) were observed following 2nd and 3rd trimester exposure and co-exposure to doxorubicin and cyclophosphamide. One infant had a bilateral small protuberance on phalanx 5 following exposure in the 2nd and 3rd trimester and co-treatment with epirubicin and cyclophosphamide (Van Calsteren *et al.* 2010). In addition, one infant had a hemangioma on its abdomen, which the authors deemed was not due to chemotherapy (Ring *et al.* 2005); the infant was exposed 2nd and/or 3rd trimester and co-treated with cyclophosphamide and methotrexate**. [It is possible that the infant with the hemangioma was, instead, treated with cyclophosphamide and cotreated with either doxorubicin or epirubicin; the authors did not report the treatments of individual patients.]** One infant born at 31 weeks amenorrhea died 8 days after birth; no cause of death was diagnosed (Giacalone *et al.* 1999).

A variety of pregnancy complications and health effects were reported with the administration of 5-fluorouracil during pregnancy. Fetal growth restriction was reported in two pregnancies (Cordoba *et al.* 2010), including one case with fetal growth inhibition caused by placental insufficiency (Ring *et al.* 2005). Two pregnancies suffered from oligohydramnios (Cordoba *et al.* 2010) or a progressive reduction in amniotic fluid (Stephens *et al.* 1980). Preeclampsia was reported in two pregnancies {Berry, 1999 #484}{Kuerer, 2002 #495}, eclamptic seizures {Muller, 1996 #1332}, maternal hypertension in one pregnancy {Turchi, 1988 #433}, premature rupture of the membranes in one pregnancy {Jeppesen, 2011 #1091}, and spontaneous preterm labor occurred in 5 pregnancies {Berry, 1999 #484;Giannakopoulou, 2000 #84;Sharma, 2009 #391}, including one case report that stated "signs of premature delivery" (Andreadis *et al.* 2004). Of the 51 pregnancies reporting individual gestational ages at delivery, early preterm delivery (<34 weeks) was reported for 11 newborns (21.6%), late preterm delivery (34-36 weeks) was reported for 27 infants (52.9%) and 13 newborns (25.5%) at term. Small for gestational age was reported for 5 infants by the authors {Bawle, 1998 #903}{Berry, 1999 #484}{Cardonick, 2010 #7}{Giacalone, 1999 #78}{Zemlickis, 1992 #576}. Breathing difficulties were observed in 22 infants, ranging from transient tachypnea to respiratory distress (Berry *et al.* 1999, Cardonick *et al.* 2010, Giacalone *et al.* 1999, Giannakopoulou *et al.* 2000, Ginopoulos *et al.* 2004, Hahn *et al.* 2006, Ring *et al.* 2005, Stadler and Knowles 1971). Myelosuppression occurred in 5 infants, including: anemia (n=2 infants) (Cuvier *et al.* 1997, Giacalone *et al.* 1999), leucopenia (n=2 infants) (Berry *et al.* 1999, Giacalone *et al.* 1999), neutropenia and thrombocytopenia (n=1 infant) (Hahn *et al.* 2006). Jaundice was reported in three infants (Cardonick *et al.* 2010, Jeppesen and Osterlind 2011) and a subarachnoid hemorrhage occurred in one infant (Hahn *et al.* 2006). Follow-up evaluations were available for 136 infants ranging in age from 6 weeks to 17 years; age at follow-up evaluation was not specified for one child (Stadler and Knowles 1971). Normal growth and development were reported for all but four children. At 8.5 years, one child had verbal expressive difficulties, including a stuttering problem, and an intelligence quotient of 70 (Bawle *et al.* 1998). Delayed growth and neuromotor development at age 3 years were reported for a child diagnosed with skeletal malformations, a bicuspid aortic value and brain anomalies at birth (Paskulin *et al.* 2005). Two additional children were healthy with special needs: Down syndrome and attention deficit-hyperactivity disorder, respectively (Hahn *et al.* 2006).

5.2.5   *Summary of pregnancy outcomes for 5-fluorouracil*

In utero exposure to 5-fluorouracil was documented for 174 pregnancies, including one twin pregnancy (175 conceptuses). Of the 14 pregnancies (15 conceptuses, including one set of twins) exposed during the 1st trimester, major congenital malformations were observed in two infants and two fetuses terminated by induced abortion. One newborn with 1st trimester exposure had hypertelorism, microcephaly, low set ears, and a right palmar simian crease (Bawle *et al.* 1998). A second infant had

multiple skeletal deformities of the hand and skull, ventriculomegaly, colpocephaly, and a bicuspid aortic valve (Paskulin *et al.* 2005). In addition, fetal loss occurred in 6 cases and two of the fetuses had major malformations. One induced abortus had skeletal malformations of the hands and feet, and skin syndactyly of the 1st and 2nd fingers (Leyder *et al.* 2010). Another induced abortus had bilateral radial aplasia and absent thumbs, absence of 1 or 2 fingers on each hand, a single umbilical artery and hypoplastic aorta, an imperforate anus, and the absence, underdevelopment or misdevelopment of multiple organs (Stephens *et al.* 1980); the authors reported that they could not clearly attribute these effects to 5-fluorouracil. A minor malformation was observed one infant following exposure during the 1st trimester: inguinal hernia (Giannakopoulou *et al.* 2000). Fetal autopsy data were not provided for three spontaneous abortions and one intrauterine fetal death following exposure during the 1st trimester. The total percent occurrence of major malformations following 1st trimester exposure to 5-fluorouracil was 26.7% (4/15 conceptuses).

There were 160 pregnancies (160 conceptuses) exposed in the second and/or third trimester only, including 46 pregnancies in which chemotherapy was initiated in gestational week 11 thorough 34 (Hahn *et al.* 2006, Jameel and Jamil 2007), which were assumed to be exposed primarily in the 2nd and/or 3rd trimester only. Major malformations were observed in three infants with exposure in the 2nd and 3rd trimesters only, including hemihypertrophy of the lower extremity (n=1 infant) (Cardonick *et al.* 2010), clubfoot (n=1 infant) and Down syndrome (n=1 infant) (Hahn *et al.* 2006). Minor malformations were observed in four infants, including: congenital bilateral ureteral reflux (n=1 infant) (Hahn *et al.* 2006), hemangioma (n=1 infant) (Ring *et al.* 2005), doubled cartilage rings in both ears (n=1 infant) and bilateral small protuberance on phalanx 5 (n=1 infant) (Van Calsteren *et al.* 2010). The total percent occurrence of major malformations following exposure in the 2nd and/or 3rd trimester only to 5-fluorouracil was 1.9% (3/160 conceptuses).

Pregnancy complications and health effects in infants with in utero exposure to 5-fluorouracil included oligohydramnios or reduction in amniotic fluid (n=2 pregnancies) (Cordoba *et al.* 2010, Stephens *et al.* 1980), and intrauterine growth restriction (n=2 infants) (Cordoba *et al.* 2010, Ring *et al.* 2005). Other pregnancy complications were preeclampsia (n=2 pregnancies), hypertension (n=1 pregnancy), premature rupture of the membranes (n=1 pregnancy), and spontaneous preterm labor (n=6 pregnancies). Of the 51 pregnancies reporting individual gestational ages at delivery, preterm delivery (<37 weeks) was reported for 38 infants. Five infants were identified as small for gestational age by the authors (Berry *et al.* 1999, Cardonick *et al.* 2010, Giacalone *et al.* 1999, Zemlickis *et al.* 1992){Bawle, 1998 #903}. Common infant health effects included: respiratory distress and transient breathing difficulties (n=22 infants), transient myelosuppression (n=5 infants), and jaundice (n=3 infants). One infant had a cerebral hemorrhage. One infant died 8 days after birth; no cause of death was diagnosed (Giacalone *et al.* 1999). Of the 101 infants with follow-up examinations at ages ranging from 2 months to 17 years, all had normal growth and development except four children. One child had verbal expressive difficulties and an intelligence quotient of 70 at age 8.5 years (Bawle *et al.* 1998) and delayed growth and neuromotor development were reported for another child at age 3 years (Paskulin *et al.* 2005). Two additional children were healthy with special needs: Down syndrome and attention deficit-hyperactivity disorder (Hahn *et al.* 2006).

In conclusion, the total occurrence of major malformations in 5-fluorouracil-exposed pregnancies was 2.3% (7/175 conceptuses). The occurrence of major malformations following exposure to 5-fluorouracil during the first trimester (4/15 conceptuses) was much higher than the prevalence of birth defects in the general population (26.7 ± 22.4% versus 3%). The occurrence of major malformations following exposure to 5-fluorouracil in the 2nd and/or 3rd trimester only (3/160 conceptuses) was similar to the

prevalence of birth defects in the general population (1.9 ± 2.1% versus 3%). Of the three major malformations, Down syndrome was unlikely to have been the result of 2nd and/or 3rd trimester chemotherapy exposure. Therefore, a revised occurrence of major malformations possibly attributed to 5-fluorouracil exposure in the 2nd and/or 3rd trimester only is 1.3 ± 1.7% (2/147 conceptuses).

5.3   6-MERCAPTOPURINE

5.3.1   *Mechanism of action, route of administration, and indications*

6-Mercaptopurine is a purine analog that belongs to a class of chemotherapy drugs known as anti-metabolites. It is active during the S-phase of the cell cycle. The drug is a metabolite of the immunosuppressive drug azathioprine. 6-Mercaptopurine is phosphorylated intracellularly to the biologically active mono- and triphosphate forms. The monophosphate form inhibits purine synthesis and the triphosphate can be incorporated into DNA and RNA, thereby inhibiting DNA synthesis and function and altering RNA processing and translation (Perry 2008). 6-Mercaptopurine is administered orally and is indicated for treatment of acute lymphocytic leukemia (Teva 2011).

5.3.2   *Evidence of placental and breast milk transport*

Placental transfer and breast milk transport have not been studied following direct administration of 6-mercaptopurine in humans. However, studies documented a lack of or low level of exposure of the fetus to the metabolite 6-mercaptopurine (specifically, 6-methylmercaptopurine (6-MMP) following administration of azathioprine to pregnant mothers. No 6-MMP was detected in the umbilical cord artery or vein after delivery, while 6-MMP was detected in maternal blood at time of delivery following daily administration of azathioprine for Crohn disease and autoimmune hepatitis (de Boer *et al.* 2005). Low levels of both azathioprine (9 to 25% of maternal dose) and 6-mercaptopurine (5 to 13% of maternal dose) were detected in fetal blood at 2.5 to 6 hours following administration of radiolabelled-azathioprine to 3 women on the 9th, 14th, and 15th weeks of gestation, respectively (Saarikoski and Seppala 1973). Breast milk transfer of 6-mercaptopurine during treatment for cancer in humans is not known. However, there are several studies showing an absence of or very low level of exposure to 6-mercaptopurine in breast milk following oral maternal exposure to azathioprine. Coulam et al. (Coulam *et al.* 1982) reported low concentrations of 6-mercaptopurine in the breast milk of two patients receiving daily azathioprine. Peak levels of the 6-mercaptopurine were 3.4 and 4.5 ng/mL after 2 and 8 hours, respectively, of a 75 mg oral dose of azathioprine (patient 1) and 18 ng/mL 2 hours after dosing (patient 2). Moretti et al. (2006) did not detect 6-mercaptopurine in multiple samples from two patients collected at several time points within a 24 hour period after administrations (level of detection at 5 ng/mL) (Moretti *et al.* 2006). Sau et al. (Sau *et al.* 2007) detected 6-mercaptopurine in only one of 31 breast milk samples from 10 women treated with azathioprine for lupus, Crohn disease, or renal transplant; there was 1.2 and 7.6 ng/mL at 3 and 6 hours, respectively, after ingestion of azathioprine on day 28 postpartum. In contrast, 6-mercaptopurine was not detected in the blood of their respective neonates (Sau *et al.* 2007). Gardiner et al. (Gardiner *et al.* 2006) reported a similar absence of 6-mercaptopurine in neonatal blood following consumption of breast milk from mothers who were treated with azathioprine.

5.3.3   *Laboratory animal developmental toxicity*

6-Mercaptopurine induced teratogenic effects in mice, rats and rabbits when administered during the period of organogenesis. The drug is generally administered parenterally (by injection) to animals, while the drug is administered orally (a less bioavailable route) in humans. In their review of the animal toxicology literature for 6-mercaptopurine, Polifka and Friedman (Polifka and Friedman 2002) converted the maximal human daily dose of 5 mg/day to a parenteral equivalent based on oral bioavailability resulting in maximal parenteral equivalent dose in humans of 2.35 mg/kg/day. The following animal data were reviewed in Polifka and Friedman (Polifka and Friedman 2002). Exposure to a single injection of 6-mercaptopurine (37.5 to 156 times the human maximal parenteral equivalent dose) during organogenesis induced cleft palate, skeletal malformations, urogenital anomalies and other

malformations as observed in rat fetuses. Multiple doses of 6-mercaptopurine (equivalent to <1 to 6.25 times the human maximal parenteral equivalent dose) caused defects of the brain, skull and distal limbs. No malformations were observed in rat fetuses when 6-mercaptopurine was administered during organogenesis at doses that were <1 to 12 times the human maximal parental equivalent dose, while an increase in embryonic death occurred when the drug was administered during the time of implantation at doses that were 2 to 12 times the human maximal parental equivalent dose. Fetal death and similar malformations were reported in mice, rabbits and hamsters at 6-mercaptopurine doses varying from <1 to 125 times (mice), in the human range (rabbits) or 29 to 162 times (hamsters) the human maximal parenteral equivalent dose.

5.3.4 Human gestational exposure and effects

6-Mercaptopurine is classified as FDA Pregnancy Category D. There were 81 patients treated with 6-mercaptopurine during pregnancy identified from 23 case reports, 14 case series, 5 retrospective case series, 1 registry survey, 5 retrospective surveys, and 1 retrospective cohort study (Appendix C Table 2). Among these 81 patients, 6-mercaptopurine was primarily used to treat acute leukemia, including: acute **[no classification given]** (n=3 cases); acute lymphocytic (n=32 cases); acute myelogenous leukemia (also called acute granulocytic leukemia; n=30 cases), acute myelomonocytic leukemia (n=2 cases), acute promyelocytic leukemia (n=2 cases), and acute stem cell leukemia (n=1 case). It was also used to treat chronic myelogenous leukemia (also called chronic granulocytic leukemia; n=7 cases), and non-Hodgkin lymphoma (n=1 case). The cancers of three additional patients treated with 6-mercaptopurine were listed only as leukemia (n=1 case), lymphocytic leukemia (probably sub-acute; n=1 case), and not specified (n=1 case). A total of 83 pregnancies were exposed in utero to 6-mercaptopurine for a total of 84 conceptuses, due to two patients having two pregnancies each (Aviles and Niz 1988, Diamond *et al.* 1960) and another patient giving birth to twins (Turchi and Villasis 1988). 6-Mercaptopurine was administered in the 1st trimester in 38 pregnancies and in the 2nd and/or 3rd trimester only in 41 pregnancies (42 conceptuses due to one twin pregnancy); timing of exposure was not specified in 4 pregnancies.

Fetal loss occurred in 11 singleton pregnancies exposed in utero to 6-mercaptopurine. Spontaneous abortions ended five pregnancies and all had been exposed in the 1st trimester. Two spontaneous abortions had normal fetuses that were exposed during conception and the 1st trimester and co-exposed to nitrogen mustard (Hoover and Schumacher 1966), or during the 1st and 2nd trimester and co-exposed to aminopterin and demecolcine (Smith *et al.* 1958). No fetal autopsy data were available for the remaining three spontaneous abortions including: one pregnancy exposed in the 1st and 2nd trimesters (Boggs *et al.* 1962), one pregnancy exposed in the 1st trimester (Zemlickis *et al.* 1992), and one fetus exposed during conception and the 1st trimester and co-exposed to methotrexate and vincristine (Bergstrom and Altman 1998). No fetal autopsy data were available for an induced abortion at 16 weeks gestation following exposure during the 1st trimester (Zuazu *et al.* 1991). Polydactyly was reported in one stillborn fetus following exposure during the 1st through 3rd trimesters and co-exposure to cyclophosphamide (Mulvihill *et al.* 1987). One maternal and fetal death occurred following exposure in the 1st and 2nd trimesters (Nicholson 1968). Two fetal losses occurred following 2nd and/or 3rd trimester only: one intrauterine fetal death was reported following exposure during 2nd trimester and no fetal autopsy data were provided (Greenlund *et al.* 2001), and one maternal death resulting in death of a normal fetus following exposure in the 2nd trimester (Neu 1962). One additional stillbirth occurred following in utero exposure to 6-mercaptopurine (Parekh *et al.* 1959); however, timing of exposure was not reported.

Of the 73 live-born infants following 6-mercaptopurine exposure during pregnancy, malformations were observed in three newborns. One infant had a major malformation: cleft palate as well as bilateral microphthalamia and corneal opacities, and poorly developed external genitalia (Diamond *et al.* 1960); this infant had been exposed to 6-mercaptopurine and radiation therapy in the first weeks of pregnancy (i.e., 1st trimester exposure), then to busulfan from 1st and 3rd trimesters with the addition of 6-mercaptopurine again in the 3rd trimester. At 10 weeks, this infant died and the autopsy observed hypoplasia of the thyroid and ovaries, disseminated cytomegaly, and other abnormalities (Diamond *et al.* 1960). Minor malformations were observed in one infant. An asymptomatic cardiac murmur was reported in one infant following exposure during the 1st through 3rd trimesters (Li and Jaffe 1974). Slight cardiomegaly, not considered a malformation, was observed in an infant who was diagnosed and treated for congestive heart failure (Okun *et al.* 1979). This infant was exposed in the 2nd trimester and co-treated with vincristine, cyclophosphamide, asparaginase, daunorubicin, and radiation therapy; and was previously exposed to vincristine and intrathecal methotrexate in the 1st trimester (Okun *et al.* 1979). There were no malformations in infants exposed to 6-mercaptopurine during the 2nd and/or 3rd trimester only. Six additional newborns died in infancy. One infant died at 21 days of septicemia and another infant died at 90 days of gastroenteritis (Aviles and Niz 1988). The remaining four infants who died within hours of birth were born prematurely without malformations (Merskey and Rigal 1956, O'Leary and Bepko 1963, Rothberg *et al.* 1959); three of these infants had respiratory distress.

There were several pregnancy complications and infant health effects following in utero exposure to 6-mercaptopurine. Transient oligohydramnios was observed in one pregnancy (Hansen *et al.* 2001) and one fetus had intrauterine growth restriction (Morishita *et al.* 1994). Other pregnancy complications included: preeclampsia (n=1 pregnancy) {Coopland, 1969 #714}, premature separation of the placenta (n=1 pregnancy) {Morishita, 1994 #306}, premature rupture of membranes (n=4 pregnancies) {Doney, 1979 #215}{Gondo, 1990 #88}{Okun, 1979 #691}{Ravenna, 1963 #671}, and spontaneous preterm labor (n=13 pregnancies, including one case also reporting premature rupture of membranes) {Diamond, 1960 #544}{Frenkel, 1960 #765}{Hansen, 2001 #105}{Lee, 1962 #600}{Loyd, 1961 #748}{McConnell, 1973 #814}{Merskey, 1956 #797}{Neu, 1962 #819}{Nicholson, 1968 #783}{O'Leary, 1963 #798}{Rothberg, 1959 #789}{Gondo, 1990 #88}. Of the 58 pregnancies reporting age at delivery, early preterm delivery (<34 weeks) occurred for 13 infants (22.4%), late preterm delivery (34-36 weeks) occurred for 18 infants (31.0%) and 27 infants were delivered at term (46.6%). No infants were reported as small for gestational age by the authors. Respiratory distress was observed in three early preterm infants who died hours after birth (cited above) and in one infant who recovered (Valappil *et al.* 2007). Myelosuppression was reported in five infants, including anemia (McConnell and Bhoola 1973), bone marrow suppression (Okun *et al.* 1979), slight leukocytopenia {Khurshid, 1978 #818}, leukocytopenia and thrombocytopenia (Gondo *et al.* 1990), and pancytopenia (Aviles and Niz 1988, Pizzuto *et al.* 1980). One infant had polycythemia (Dara *et al.* 1981) and three infants had jaundice (Dara *et al.* 1981, Hansen *et al.* 2001, Valappil *et al.* 2007). Other health effects included Cushingoid appearance at birth (Doney *et al.* 1979), meconium aspiration syndrome (Hansen *et al.* 2001), and a normal infant with chromosome breakage (Schleuning and Clemm 1987). Follow-up examinations were available on 52 infants (including one set of twins) at ages ranging from 6 weeks to 22 years. Normal growth and development were reported for all but one infant. One infant, who had anemia at birth, was discharged from the hospital at 5 months with anemia and, at age 9 months, had normocytic anemia with a slightly palpable spleen (McConnell and Bhoola 1973). An infant treated for congestive heart failure shortly after birth had normal growth and development at age 1 year (Okun *et al.* 1979).

5.3.5 *Summary of pregnancy outcomes for 6-mercaptopurine*

In utero exposure to 6-mercaptopurine was documented for 83 pregnancies with a total of 84 conceptuses, including one set of twins. Of the 38 singleton pregnancies exposed during the 1st trimester, major malformations were reported in one infant and one stillborn fetus. Cleft palate was reported in an infant who died at 10 weeks of age (Diamond *et al.* 1960). This infant also had bilateral microphthalmia and corneal opacities, underdevelopment of the external genitalia, hypoplasia of the ovary and thyroid glands, and disseminated cytomegaly (Diamond *et al.* 1960). One infant had a minor malformation following exposure during the 1st trimester: an asymptomatic cardiac murmur (Li and Jaffe 1974). Polydactyly, a major malformation was observed in one stillborn fetus (Mulvihill *et al.* 1987). In addition, fetal loss occurred in seven additional pregnancies following exposure in the 1st trimester. Normal fetuses were reported following two spontaneous abortions (Hoover and Schumacher 1966, Smith *et al.* 1958). No fetal data were available for the remaining three spontaneous abortions (Bergstrom and Altman 1998, Boggs *et al.* 1962, Zemlickis *et al.* 1992), one induced abortion (Zuazu *et al.* 1991), and one maternal and fetal death (Nicholson 1968). The total occurrence of major malformations following 1st trimester exposure is 5.3% (2/38 conceptuses). Of the 41 pregnancies (42 conceptuses due to one set of twins) exposed in the 2nd and/or 3rd trimester only, one infant had a health anomaly which was not considered a malformation: slight cardiomegaly (Okun *et al.* 1979). This infant was diagnosed and successfully treated for congestive heart failure (Okun *et al.* 1979). Fetal loss occurred in two pregnancies following exposure in the 2nd and/or 3rd trimester only: one intrauterine fetal death without fetal autopsy data (Greenlund *et al.* 2001), and a maternal death causing the death of a normal fetus (Neu 1962). The total percent occurrence of major malformations following 2nd and/or 3rd trimester only was 0% (0/42 conceptuses). Another stillbirth was reported, but timing of exposure was not specified (Parekh *et al.* 1959).

A variety of pregnancy complications occurred with gestational exposure to 6-mercaptopurine. Transient oligohydramnios was observed in one pregnancy (Hansen *et al.* 2001) and one fetus had intrauterine growth restriction (Morishita *et al.* 1994). Preterm delivery occurred for 31 of 58 infants with data on gestational age at delivery. Other health effects were observed in the newborns, including respiratory distress (n=4 infants), myelosuppression (n=5 infants) and jaundice (n=3). There were seven infant deaths. Four early preterm infants died within hours of birth (Merskey and Rigal 1956, O'Leary and Bepko 1963, Rothberg *et al.* 1959), and one malformed and underdeveloped infant died at 10 weeks (mentioned above). One infant each died of septicemia at 21 days and gastroenteritis at 90 days (Aviles and Niz 1988). Of the 52 infants with follow-up evaluations at ages ranging from 6 weeks to 22 years, normal growth and development were reported for all, but one infant. One infant had normocytic anemia at 9 months of age; this infant had been diagnosed with anemia at birth (McConnell and Bhoola 1973).

In conclusion, the total occurrence of major malformations in 6-mercaptopurine-exposed pregnancies was 2.4% (2/84 conceptuses). The occurrence of major malformations following exposure to 6-mercaptopurine during the 1st trimester (2/38 conceptuses) was slightly higher than the prevalence of birth defects in the general population (5.3 ± 7.1% versus 3%). The occurrence of major malformations following exposure to 6-mercaptopurine in the 2nd and/or 3rd trimester only (0/42 conceptuses) was not higher than the prevalence of birth defects in the general population (0% versus 3%).

5.4   6-THIOGUANINE

5.4.1   Mechanism of action, route of administration, and indications

6-Thioguanine is a purine analogue that belongs to a class of chemotherapy drugs know as anti-metabolites. It is a metabolite of azathiopurine and is structurally and functionally related to 6-mercaptopurine (GlaskoSmithKline 2004). 6-Thioguanine exerts cytotoxic effects by multiple mechanisms (Sahasranaman *et al.* 2008). The triphosphate metabolite of 6-thioguanine incorporates into nucleotide sequences in place of the endogenous guanine, which causes cell cycle arrest and cell death. Metabolites of 6-thioguanine also inhibit the enzymes responsible for the production of guanine, thus reducing its availability for DNA and RNA synthesis. 6-Thioguanine is administered orally and is indicated for acute non-lymphoblastic leukemia (also called acute myelogenous leukemia). It has also been used in treating the chronic phase of chronic myelogeneous leukemia (GlaskoSmithKline 2004).

5.4.2   Evidence of placental and breast milk transport

Placental transfer, but not breast milk transport, is reported to occur following direct administration of 6-thioguanine in humans. de Boer et al. 2005 (de Boer *et al.* 2005) detected 6-thioguanine nucleotides in the red blood cells of the umbilical cord blood at delivery following 3 times per week maternal exposure to 6-thioguanine. Expressed as picomoles/8×10^8 red blood cells, the values at birth were 494 in the mother and 41 in the infant. At one month, the value for the mother was 442 and below the limit of detection in the infant. Regarding breast milk transfer of 6-thioguanine, Gardiner et al. (Gardiner *et al.* 2006) reported that breast milk transfer of this drug was low based on an analysis of its metabolites in breast milk and the associated infants' blood samples. Metabolites of 6-thioguanine were not detected in the blood of the infants, although detectable levels of the drug were present in the breast milk offour mothers treated with daily oral doses of azathiopurine (Gardiner *et al.* 2006).

5.4.3   Laboratory animal developmental toxicity

Teratogenic effects have been reported in rat fetuses exposed to 6-thioguanine during organogenesis (GlaskoSmithKline 2004). Pregnant rats administered the drug at 5 times the recommended human dose **[dose not provided]** yielded litters in which 13% of the surviving placentas did not contain embryos and 19% of the [surviving] offspring were malformed or had stunted growth. Malformations observed in the rat fetuses included: cranial defects and general skeletal hypoplasia (including incomplete development of the limbs) as well as hydrocephalus, ventral hernia and situs inversus (GlaskoSmithKline 2004). Teratogenic effects or inhibited growth was observed following intravenous injection of pregnant rats treated with thioguanine at 10 mg/kg on the 4th and 5th or 11th and 12th days of gestation (Thiersch 1957). Malformations included: general edema and anasarca, stunting of the skeleton, cranial defects with and without hydrocephalus, incomplete development of the fore and hind limbs as well as ventral hernia, situs inversus, general edema and anasarca (Thiersch 1957).

5.4.4   Human gestational exposure and effects

6-Thioguanine is classified as FDA Pregnancy Category D. There were 46 patients administered 6-thioguanine during pregnancy identified from 20 case reports, 9 case series, 1 retrospective case series, 2 retrospective surveys, and 1 retrospective cohort study (Appendix C Table 3). Among these 46 patients, 6-thioguanine was used to treat acute leukemia (type not specified, n=1 case), acute myelogenous (n= 37 cases), acute promyelogenous leukemia (n=4 cases), and acute lymphocytic leukemia (n=2 cases). It was also used to treat one patient with both acute myelogenous and acute lymphocytic leukemia and one case of chronic granulocytic leukemia in blast crisis. At total of 49

singleton pregnancies were exposed to 6-thioguanine due to three patients having two pregnancies each (Maurer *et al.* 1971, Plows 1982, Schafer 1981). 6-Thioguanine was administered during the 1st trimester in 7 pregnancies and in the 2nd and/or 3rd trimester only in 43 pregnancies.

Fetal loss occurred in 11 pregnancies following in utero exposure to 6-thioguanine. Spontaneous abortion occurred in one pregnancy 20 days following 1st trimester exposure and co-treatment with daunorubicin, cytarabine and vincristine; no fetal autopsy data were reported (Zuazu *et al.* 1991). Post-mortem fetal evaluation of an induced abortion revealed no evidence of congenital malformations following 1st trimester exposure and co-exposure to cytarabine in the 1st trimester, and vincristine and rubidomycin **[daunorubicin]** in the 2nd trimester (Lilleyman *et al.* 1977). Normal chromosomes were detected in another induced abortus following exposure during the period of conception and 1st trimester and co-exposure to cytarabine (Maurer *et al.* 1971). Fetal autopsy data were not reported for a third induced abortion following exposure during the period of conception and 1st trimester {Zemlickis, 1992 #576}. Autopsy revealed a normal fetus of an induced abortion following 2nd trimester exposure and co-exposure to hydroxyurea, daunorubicin, cytarabine, vincristine (Doney *et al.* 1979); the fetus also had a slightly enlarged spleen. Abnormal chromosomes were observed in another induced abortus exposed in the 2nd trimester and co-exposed to cytarabine (Maurer *et al.* 1971). No congenital malformations were observed in four intrauterine fetal deaths occurring following 2nd trimester exposure and co-exposure to: cytarabine (Plows 1982), cytarabine and daunorubicin (O'Donnell *et al.* 1979, Volkenandt *et al.* 1987), or cytarabine and doxorubicin (Zemlickis *et al.* 1992). One of the normal stillborn fetuses had bruising and petechiae (broken capillaries under the skin) over multiple areas (Zemlickis *et al.* 1992).

Of the 39 live-born infants exposed to 6-thioguanine during pregnancy, four infants had major malformations and one infant had a minor malformation. Major malformations occurred in two infants exposed during the 1st trimester. One infant was born with multiple skeletal defects and a small ostium secundum-type atrial septal defect; the mother was administered 6-thioguanine and cytarabine in the 1st trimester following exposure to cytarabine, daunorubicin and doxorubicin around the period of conception (Artlich *et al.* 1994). The infant's skeletal malformations included: choanal stenosis, braciocephaly, hypoplasia of several cranial structures and premature closure of cranial sutures as well as bilateral 4-fingered hands with hypoplastic thumbs and bilateral absent radii. Another infant had distal limb defects following exposure during the period of conception through pregnancy and co-treatment with cytarabine (Schafer 1981). The infant's malformations included: the absence of the medial two digits of each foot, the absence of the distal phalanges of both thumbs, and a hypoplastic remnant of the right thumb. Major malformations were observed in two infants with exposure to 6-thioguanine in the 2nd and/or 3rd trimester only. An infant was born with six toes on his right foot, which was likely due to his family's history of polydactyly (Volkenandt *et al.* 1987); this infant was exposed in the 3rd trimester and co-treated with cytarabine and daunorubicin. Down syndrome was diagnosed in one newborn exposed during the 2nd and 3rd trimester and co-exposed to cytarabine and daunorubicin (Roy *et al.* 1989). Congenital adherence of the iris to the cornea, a minor malformation, was diagnosed in an infant at age 2 years (Reynoso *et al.* 1987).

A variety of pregnancy complications and health effects were observed following in utero exposure to 6-thioguanine. Two fetuses experienced intrauterine growth restriction (D'Emilio *et al.* 1989) or poor fetal growth (Roy *et al.* 1989), and polyhydramnios was observed in one pregnancy (Artlich *et al.* 1994). Fetal distress was reported in one pregnancy {Veneri, 1996 #665}. Preeclampsia was treated and resolved in another pregnancy (Bartsch *et al.* 1988). Two pregnancies had preterm spontaneous rupture of membranes {Volkenandt, 1987 #442}{Udink ten Cate, 2009 #434} and five pregnancies had spontaneous

preterm labor {Doney, 1979 #215}{Reynoso, 1987 #372}{Taylor, 1980 #648}{Tobias, 1980 #546}. Of the 36 pregnancies with individual gestational age at delivery, early preterm delivery (<34 weeks) was reported for 9 newborns (25%), late preterm delivery (34-36 weeks) was reported for 10 (27.8%) and 17 newborns were delivered at term (47.2%). None of the newborns were reported to be small for gestational age. Four newborns were treated for respiratory distress (Artlich *et al.* 1994, Bartsch *et al.* 1988, Requena *et al.* 1995, Veneri *et al.* 1996). A mild meningeal hemorrhage was observed in one infant, who also had respiratory distress syndrome (Veneri *et al.* 1996). One premature infant had decreased levels of sodium (hyponatremic), calcium (hypocalcemic), glucose (hypoglycemic) and increased levels of potassium (hyperkalemic), which resolved after 7 months (Doney *et al.* 1979). Two infants had jaundice (Au-Yong *et al.* 1972) (Taylor and Blom 1980) and 3 infants had transient myelosuppression, including thrombocytopenia (Reynoso *et al.* 1987, Taylor and Blom 1980) and thrombocytopenia with leucopenia and neutropenia (Udink ten Cate *et al.* 2009). Low hemoglobin was reported in one infant (Gulati *et al.* 1986). Follow-up evaluations were reported for 32 children at ages ranging from 1 month to 4 years. Normal growth and development was observed in all, but two children. At age 13.5 months, one child was below the 3rd percentile in growth, although his neurodevelopment was normal (Doney *et al.* 1979). At 26 months, another child was below the 10th percentile in body weight and had a constant cold; his immune tests and blood profile were normal (Gulati *et al.* 1986). Another child was normal at age 3 years, following multiple upper respiratory infections at 6 months and diagnosis of adherence of the iris to the cornea at age 2 years (Reynoso *et al.* 1987).

5.4.5 *Summary of pregnancy outcomes for 6-thioguanine*

In utero exposure to 6-thioguanine was documented for 49 singleton pregnancies (49 conceptuses). Of the 7 pregnancies exposed to 6-thioguanine in the 1st trimester, major malformations were observed in two infants. One infant had multiple cranial and limb defects and a small ostium secumdum-type atrial septal defect (Artlich *et al.* 1994). A second infant had distal limb defects in both his feet and hands (Schafer 1981). In addition, fetal loss occurred in 4 pregnancies following 1st trimester exposure: one spontaneous abortion without fetal autopsy data (Zuazu *et al.* 1991), two induced abortions with normal fetuses (Lilleyman *et al.* 1977, Maurer *et al.* 1971) and induced abortion without fetal autopsy data {Zemlickis, 1992 #576}. The occurrence of major malformations following 1st trimester to 6-thioguanine was 33.3% (2/6 conceptuses); however, there were too few reported pregnancy outcomes to make an accurate estimate. Of the 43 pregnancies exposed to 6-thioguanine in the 2nd and/or 3rd trimesters only, major malformations were observed in two infants: Down syndrome (Roy *et al.* 1989) and polydactyly (Volkenandt *et al.* 1987). The infant with polydactyly had a family history of polydactyly (Volkenandt *et al.* 1987). One infant with 3rd trimester exposure to 6-thioguanine had a minor malformation: congenital adherence of the iris to the cornea (Reynoso *et al.* 1987). Fetal loss was reported in 6 pregnancies, including: two induced abortions (Doney *et al.* 1979, Maurer *et al.* 1971) and four cases of intrauterine fetal demise (Doney *et al.* 1979, Volkenandt *et al.* 1987, Zemlickis *et al.* 1992); none of the fetuses had congenital malformations. The total occurrence of major malformations following exposure to 6-thioguanine in the 2nd and/or 3rd trimester only was 4.7% (2/43 conceptuses).

Pregnancy complications following exposure to 6-thioguanine in utero included: inhibited fetal growth (n=2 pregnancies) (D'Emilio *et al.* 1989, Roy *et al.* 1989), polyhydramnios (n=1 pregnancy) (Artlich *et al.* 1994), fetal distress (n=1 pregnancy) {Veneri, 1996 #665}, preeclampsia (n=1 pregnancy), preterm spontaneous rupture of membranes (n=2 pregnancies) and spontaneous preterm labor (n=5 pregnancies). Of the 36 pregnancies with individual gestational age at delivery, preterm delivery (<37 weeks) was reported for 19 newborns. None of the newborns were reported to be small for gestational age. Common infant health effects included: transient myelosuppression (n=3 infants), jaundice (n=2

infants), and breathing difficulties (n=4 infants). Follow-up examinations at ages 1 month to 4 years reported normal growth and development in all but two infants. At 13 months, one infant had growth below the 3rd percentile; however, his neurodevelopment was normal. At 26 months, another infant had normal growth, but its body weight was less than the 10th percentile and it had constant colds.

In conclusion, the total occurrence of major malformations in 6-thioguanine-exposed pregnancies was 8.2% (4/49 conceptuses). The occurrence of major malformations following exposure to 6-thioguanine during the 1st trimester (2/6 conceptuses) was higher than the prevalence of birth defects in the general population (33.3 ± 37.7% versus 3%). The occurrence of major malformations following exposure to 6-thioguanine in the 2nd and/or 3rd trimester only (2/43 conceptuses) was similar to the prevalence of birth defects in the general population (4.7 ± 6.3% versus 3%). It is not likely that either of these malformations, Down syndrome or polydactyly, could be attributed to 6-thioguanine exposure in the 2nd and/or 3rd trimester only. Therefore, the occurrence of major malformations possibly attributed to 6-thioguanine exposure in the 2nd and/or 3rd trimester only was 0% (0/43 conceptuses).

5.5 ACTINOMYCIN D

5.5.1 Mechanism of action, route of administration, and indications

Actinomycin D is a cytotoxic antibiotic produced by Streptomyces parvullus. It elicits cytotoxic effects by binding DNA and inhibiting RNA synthesis (Lundbeck Inc 2012). Actinomycin D is administered intravenously as a single agent or as part of a combination chemotherapy regimen. It is indicated for Wilms tumor, childhood rhabdomyosarcoma, Ewing sarcoma and metastatic, nonseminomatous testicular cancer (Lundbeck Inc 2012). It is also used as palliative treatment for locally recurrent and locoregional solid malignancies.

5.5.2 Evidence of placental and breast milk transport

It is not know if actinomycin D is transferred to the fetus via the placenta. Breast milk transfer of actinomycin D in humans is also unknown (Lundbeck Inc 2012). Actinomycin D was detected in the embryo by radioautograph **[presumably following maternal exposure in the rat]** (reviewed by (Shepard and Lemire 2004).

5.5.3 Laboratory animal developmental toxicity

Actinomycin D is reported to be embryotoxic and teratogenic in the rat, rabbit and hamster at doses of 50 to 100 µg/kg (approximately 0.5 to 2 times greater than the maximum daily human dose per surface area) (Lundbeck Inc 2012). As summarized in Shepard et al. (Shepard and Lemire 2004), administration of 25 to 100 µg/kg bw of actinomycin D on the 10th day of gestation in the rat induced various degrees of craniorachischisis, defects of the nervous system and branchial arch malformations; actinomycin D administered after gestation day 10 did not induce embryonic defects. Injections of actinomycin D (0.0625 to 0.25 µg) into the yolk sac of white leghorn chick embryos during the second and third days of incubation induced anomalous development of the axial skeleton (Pierro 1961). Abnormalities of the tail were also observed following exposure to 0.0625 µg actinomycin D per egg. Actinomycin D was teratogenic to hamster embryos when administered in doses of 200 or 300 µg/kg bw prior to implantation (Elis and DiPaolo 1970). The most common malformations reported were omphalocele, micrognathia or agnathia, microocphaly, exencephaly, hydrocephalus, spina bifida, and several malformations of the extremeties, such as amelia and phocomelia, usually involving the forelimbs.

5.5.4 Human gestational exposure and effects

Actinomycin D is classified as FDA Category D. There were 12 published cases of patients treated with actinomycin D during pregnancy identified from 11 case reports and 1 registry survey (Appendix C Table 4). Among these 12 patients, actinomycin D was used to treat the following cancers: ovarian cancer (n=4 cases), Ewing sarcoma (n=2 cases), rhabdomyosarcoma (n=3 cases), Wilms tumor (n=1 case), and choriocarcinoma of the uterus (n=1 case) or vagina (n=1 case). A total of 12 pregnancies were exposed to actinomycin D, including one twin pregnancy for a total of 13 conceptuses (Freedman *et al.* 1962). Actinomycin D was administered only in the 2nd and/or 3rd trimesters to all reported pregnancies; no pregnancies were exposed in the 1st trimester. Fetal loss did not occur in the reported pregnancies exposed to actinomycin D. Of the 13 infants exposed in utero to actinomycin D, none of the infants had major malformations.

Pregnancy complications and infant health effects were reported for some pregnancies exposed to actinomycin D. Spontaneous preterm labor was reported for three pregnancies {Kim, 1989 #134}{Martin, 1997 #277}{Brudie, 2011 #1094}. Another pregnancy reported complications of

anhydramnios and fetal growth retriction at four weeks after chemotherapy administration (Fernandez *et al.* 1989). Of the 11 infants with data on gestational age at delivery, early preterm delivery (<34 weeks) was reported for 5 infants, late preterm delivery (34 to 36 weeks) was reported for 3 infants and 3 infants were delivered at term. None of the newborns were reported to be small for gestational age. There was one death of an infant gestationally exposed to actinomycin D (Fernandez *et al.* 1989); this infant was also exposed in utero to vincristine and ifosfamide. The infant was born at 29 weeks of gestation with a bilateral intraventricular cerebral hemorrhages and a hematoma in the left occipital lobe. She experienced anuria and died at 7 days of age. Autopsy revealed cerebral hemorrhaging attributed to prematurity, but no renal abnormlaties (Fernandez *et al.* 1989). Other infant health issues included one infant with respiratory distress (Corapcioglu *et al.* 2004) and another infant with mild respiratory distress who also required intravenous calcium (Haerr and Pratt 1985).

Follow-up evaluations were reported for 8 children ranging in age from 3 months to 5.3 years. Normal growth and development was reported for all children.

5.5.5   *Summary of pregnancy outcome for actinomycin D*

Exposure to actinomycin D is documented for 12 pregnancies and 13 conceptuses, including one twin pregnancy. All pregnancies were exposed in the 2nd and/or 3rd trimester. There were no fetal losses reported following actinomycin D exposure and no major or minor malformations were observed in any of the infants. Pregnancy complications of anhydramnios and fetal growth restriction were observed in one pregnancy (Fernandez *et al.* 1989). None of the newborns were reported to be small for gestational age. This infant was delivered preterm and suffered from a bilateral intraventricular cerebral hemorrhages and a left occipital hematoma. The infant also experienced anuria and died at 7 days. Autopsy revealed cerebral hemorrhaging attributed to prematurity and no renal abnormalities. Preterm deliveries were reported for 8 of 11 infants with data on gestational age at delivery. Normal growth and development was reported for all 8 children with follow-up information at ages ranging from 3 months to 5.3 years.

In conclusion, the total occurrence of major malformations in actinomycin D-exposed pregnancies was 0% (0/13 conceptuses). However, this value is based on a very small number of conceptuses and may not accurate reflect the risk of major malformations following gestational exposure to this cancer chemotherapeutic agent.

5.6   ALL-*TRANS* RETINOIC ACID

5.6.1   *Mechanism of action, route of administration, and indications*

All-*trans* retinoic acid (ATRA, tretinoin) is a chemical related to retinol (vitamin A). All-*trans* retinoic acid is an antineoplastic agent, which acts to induce cytodifferentiation and decrease proliferation of cancerous cells. All-*trans* retinoic acid is administered orally in the treatment of acute promyelocytic leukemia (APL). The exact mechanism of action is not known, but the pathology of APL is due to the highly proliferative immature cells, and all-*trans* retinoic acid induces these cells to differentiate into functional cells, which helps to alleviate the disease (Roche 2008).

5.6.2   *Evidence of placental and breast milk transport*

Placental transfer of all-*trans* retinoic acid occurs in humans and lactational transfer may occur. In a review, Nau et al. (Nau 2001) reported that all-*trans* retinoic acid had extensive placental transport and a relatively short half-life (1 hour) in humans. In one infant, all-*trans* retinoic acid was not detectable in the umbilical cord blood at birth; however, low levels of the metabolites isotretinoin (0.437 ng/mL) and 4-oxo-isotretinoin (1.324 ng/mL) were present (Lipovsky *et al.* 1996). In a case series of three patients, Taikitani et al. (Takitani *et al.* 2005) reported that all-*trans* retinoic acid administered to one mother prior to delivery was detected in maternal blood (26 ng/mL) at 6 hours, and umbilical cord blood (8 ng/mL) at 9 hours post-treatment. In the remaining two cases, levels of all-*trans* retinoic acid and its metabolites were not detected in either umbilical cord blood or neonatal peripheral blood. The authors' suggest that the lack of detection may be due to later sampling times of umbilical cord blood, following administration of the drug to the mother, or individual **[metabolic]** differences. Lactational transport of all-*trans* retinoic acid has not been reported. However, lactational transfer of etretin has been observed; etretin is a second generation retinoid drug administered orally to treat psoriasis (reviewed in (Pilkington and Brogden 1992)).

5.6.3   *Laboratory animal developmental toxicity*

All-*trans* retinoic acid is embryolethal and teratogenic in mice, rats, hamsters, rabbits and monkeys. All-*trans* retinoic acid caused fetal resorptions and a decrease in live fetuses in all animals studied (Roche 2008). For example, embryolethality was increased in a dose-related manner following 5 mg (22%), 10 mg (50%) and 20 mg/kg (100%) oral administration of all-*trans* retinoic acid in the cynomolgus monkey on gestation days 10-24, which is equivalent to 2 times, 4 times and 8 times the human dose per surface area (Hendrickx and Hummler 1992). In rodents, gross external, soft tissue and skeletal alterations occurred at doses higher than 0.7 mg/kg/day in mice, 2 mg/kg/day in rats, and 7 mg/kg/day in hamsters (Roche 2008). All-*trans* retinoic acid induced craniofacial defects, such as ear defects, mandibular hypoplasia and cleft palate, in fetal cynomolgus monkeys whose mothers were administered oral doses of 10 mg/kg/d on gestation days 10-24 (Hendrickx and Hummler 1992). No malformations were reported at 5 mg/kg; however, one fetus out of seven exhibited intrauterine growth retardation (Hendrickx and Hummler 1992). Retinoic acid (10 mg/kg) administered orally to pregnant pigtail monkeys on gestation days 20 to 44 resulted in a high frequency of craniofacial and musculoskeletal malformations (Fantel *et al.* 1977). Craniofacial anomalies included ear tags, enlarged gingival, cleft palate or abnormalities of the shape of the skull. The most common musculoskeletal malformation reported in pigtail monkey was missing postaxial phalanges of the foot (Fantel *et al.* 1977).

5.6.4 Human gestational exposure and effects

All-*trans* retinoic acid is classified as FDA Pregnancy Category D. There were 28 published cases of patients treated with all-*trans* retinoic acid during pregnancy (29 conceptuses, including one set of twins) identified from 17 case reports, 5 case series, and 1 retrospective survey (Appendix C Table 5). In these patients, the drug was used to treat acute promyelogenous leukemia (n=23 cases) and acute myelogenous leukemia (n=5 cases). A total of 28 pregnancies with 29 conceptuses (including one twin pregnancy (Stentoft *et al.* 1994)) were exposed to all-*trans* retinoic acid. All-*trans* retinoic acid was administered in the 1st trimester in 5 pregnancies and in the 2nd and/or 3rd trimester only in 23 pregnancies (24 conceptuses due to a twin pregnancy). Fetal loss occurred in three singleton pregnancies. One spontaneous abortion, one induced abortion, and one intrauterine fetal death occurred in a pregnancy exposed during the 1st trimester and co-exposed to daunorubicin and cytarabine (Chelghoum *et al.* 2005); no fetal autopsy data were reported.

Of 26 live-born infants exposed in utero to all-*trans* retinoic acid, four infants had malformations and two of these infants had major malformations. In one pregnancy, Potter syndrome (bilateral renal agenesis and oligohydramnios) was diagnosed prior to the administration of all-*trans* retinoic acid in the 3rd trimester (Sham 1996); this infant died 30 minutes after birth. Another infant had two small secundum atrial septal defects at birth, which were accompanied by moderate dilation of the right atrium and right ventricle, and a small patent ductus arteriosus following exposure in the 2nd and 3rd trimester and co-exposure to idarubicin (Siu *et al.* 2002). At age 1.5 months, the infant had normal growth and no signs of congestive heart failure because the ventricular hypertrophy resolved, the ductus arteriosus closed, and, although there remained persistence of the small secundum atrial septal defects, the atrial septal defects did not significantly impact blood flow through the heart. Patent ductus arteriosus, a minor malformation, was observed in two additional infants: one infant was exposed in the 2nd and 3rd trimester and co-exposed to idarubicin (Carradice *et al.* 2002) and the other infant was exposed in the 3rd trimester with no co-treatments (Takitani *et al.* 2005).

There were a variety of pregnancy complications and infant health effects reported with in utero exposure to all-*trans* retinoic acid. Fetal ascites, oligohydramnios as well as intrauterine growth restriction due to placental insufficiency occurred in one pregnancy (Carradice *et al.* 2002). As mentioned previously, one pregnancy had oligohydramnios associated with bilateral renal agenesis diagnosed prior to treatment with all-*trans* retinoic acid (Sham 1996). Fetal growth retardation was reported in a second infant (Takitani *et al.* 2005, Terada *et al.* 1997). Fetal distress occurred in one pregnancy (Nakamura *et al.* 1995). Fetal arrhythmia occurred in two pregnancies (Leong *et al.* 2000), and one case was accompanied by abnormal systolic motion of the mitral valve {Takitani, 2005 #525}(Terada *et al.* 1997). Other pregnancy complications included: preeclampsia (n=1 pregnancy) {Siu, 2002 #410}, premature rupture of membranes (n=1 pregnancy) {Carradice, 2002 #187} and spontaneous preterm labor (n=4 pregnancies) {Consoli, 2004 #203}{Dilek, 2006 #212}{Incerpi, 1997 #626}{Sham, 1996 #627}. Of the 25 pregnancies with age at delivery data, early preterm delivery (<34 weeks) was reported for 14 pregnancies (15 infants) (56%), late preterm delivery was reported for 8 pregnancies (32%), and three infants were delivered at term (12%). None of the 26 infants were small for gestational age. Health issues reported for these infants included jaundice (n=4 infants) (Ganzitti *et al.* 2010, Incerpi *et al.* 1997, Simone *et al.* 1995, Valappil *et al.* 2007) and respiratory difficulties (n=12 infants) (Carradice *et al.* 2002, Delgado-Lamas and Garces-Ruiz 2000, Dilek *et al.* 2006, Ganzitti *et al.* 2010, Simone *et al.* 1995, Siu *et al.* 2002, Stentoft *et al.* 1994, Takitani *et al.* 2005, Valappil *et al.* 2007, Watanabe *et al.* 1995). A second neonate died at age day 1 after developing respiratory distress (Dilek *et al.* 2006); this early preterm infant had normal hematological values and was exposed in the 2nd and 3rd trimesters and co-exposed to daunorubicin and cytarabine. Another infant with breathing difficulties suffered from

pulmonary hypoplasia and bilateral pneumothorax (Carradice *et al.* 2002). Small bilateral subependymal hemorrhages were reported for one infant with jaundice (Incerpi *et al.* 1997). Cardiac arrhythmia led to cardiac arrest in one infant, who was successfully resuscitated and made satisfactory progress (Harrison *et al.* 1994). Cardiac arrhythmia and premature atrial contractions were observed in another infant, who suffered from arrhythmia and abnormal systolic motion of the mitral values in utero (Takitani *et al.* 2005, Terada *et al.* 1997); the symptoms disappeared in 1 day. Follow-up evaluations were available for 19 infants ranging in age from 1.5 months to 4 years. Normal growth and development were reported for all but one child. One infant, who was diagnosed with pulmonary hypoplasia at birth, continued to require nasal oxygen and had poor overall growth at age 6 months (Carradice *et al.* 2002).

Some retinoid drugs used to treat conditions other than cancer are documented to induce spontaneous abortion as well as fetal abnormalities in humans (Lammer *et al.* 1985, Rizzo *et al.* 1991). The defects reported following prenatal exposure to other retinoid drugs include: craniofacial malformations, limb reduction and other skeletal defects; abnormalities of the ear, thymus and circulatory system; and, in some cases, lower IQ scores.

5.6.5   *Summary of pregnancy outcomes for all-trans retinoic acid*

In utero exposure to all-*trans* retinoic acid was documented for 28 pregnancies with 29 conceptuses, including one set of twins. Major malformations occurred in two infants exposed in utero to all-*trans* retinoic acid. Of the five singleton pregnancies exposed during the 1st trimester, there were no conceptuses with major malformations. Fetal loss occurred in 3 pregnancies following 1st trimester exposure: one spontaneous abortion, one induced abortion and one intrauterine fetal death; no fetal autopsy data were provided. Thus, the total occurrence of major malformations following exposure to all-*trans* retinoic acid during the 1st trimester was 0% (0/5 conceptuses). Of the 23 pregnancies (24 conceptuses) exposed to all-*trans* retinoic acid in the 2nd and/or 3rd trimester only, major malformations were observed in two infants. One infant was diagnosed with Potter syndrome, which includes bilateral renal agenesis and oligohydramnios, in the womb prior to 3rd trimester exposure; thus, the renal agenesis was not caused by chemotherapy exposure (Sham 1996). Two small secundum atrial septal defects were observed in an infant exposed in the 2nd and 3rd trimester to all-*trans* retinoic acid and idarubicin (Siu *et al.* 2002). The atrial septal defects persisted at age 1.5 months, but did not significantly alter normal blood flow, and thus, the infant had normal growth and development with no signs of congestive heart failure (Siu *et al.* 2002). Two infants had minor malformations: patent ductus arteriosus (Carradice *et al.* 2002, Takitani *et al.* 2005). Thus, the total occurrence of major malformations following exposure to all-*trans* retinoic acid in the 2nd and/or 3rd trimester only was 6.7% (2/29 conceptuses).

Pregnancy complications following in utero exposure to all-*trans* retinoic acid, included fetal ascites and oligohydramnios (n=1 pregnancy) (Carradice *et al.* 2002), oligohydramnios associated with Potter syndrome (n=1 pregnancy) (Sham 1996), inhibited fetal growth (n=2 pregnancies) (Carradice *et al.* 2002, Terada *et al.* 1997), and fetal arrhythmia or fetal distress (n=3 pregnancies) (Leong *et al.* 2000, Nakamura *et al.* 1995, Terada *et al.* 1997). Of the 25 pregnancies with age at delivery data, preterm delivery was reported for 22 pregnancies. None of the 26 infants were small for gestational age. Health effects observed in the newborns included: respiratory distress (n=12 infants), jaundice (n=4 infants), as well as cardiac arrhythmia (n=2 infants) and premature atrial contractions (n=1 infant). One premature infant developed respiratory distress and died after day 1 (Dilek *et al.* 2006). Follow-up examinations on 19 children of ages ranging from 1.5 months to 4 years noted normal growth and development in all but one child. One infant, who was diagnosed with pulmonary hypoplasia at birth, had poor overall growth at age 6 months, and continued to require nasal oxygen (Carradice *et al.* 2002).

In conclusion, the total occurrence of major malformations in all-*trans* retinoic acid was 6.9% (2/29 conceptuses). The occurrence of major malformations following exposure to all-*trans* retinoic acid during the 1st trimester (0/5 conceptuses) was less than the prevalence of birth defects in the general population (0% versus 3%); however, there were too few published cases to make an accurate estimate. The occurrence of major malformations following exposure to all-*trans* retinoic acid in the 2nd and/or 3rd trimester only (2/24 conceptuses) was slightly greater than double the prevalence of birth defects in the general population (8.3 ± 11.1%). It is unlikely that either of the major malformations (Potter syndrome or atrial septal defects) was caused by exposure to *all-trans* retinoic acid during the 2nd and/or 3rd trimester only, especially the infant with Potters syndrome which was diagnosed prenatally prior to chemotherapy administration. Therefore, the revised occurrence of major malformations possibly attributed to exposure to all-*trans* retinoic acid in the 2nd and/or 3rd trimester only, or at any time during pregnancy, was 0%.

5.7   BLEOMYCIN

5.7.1   Mechanism of action, route of administration, and indications

Bleomycin is a mixture of glycosidic antibodies isolated from the bacterium *Streptomyces verticillus*. It inhibits DNA synthesis by causing DNA strand breaks through the generation of free radicals. It also inhibits the ligase enzyme that repairs DNA strand breaks (Ono *et al.* 1976).   Bleomycin is indicated for Hodgkin and non-Hodgkin lymphomas, squamous cell carcinomas, testicular cancer, and malignant pleural effusion (Bristol-Myers Squibb 2010).

5.7.2   Evidence of placental and breast milk transport

It is not known if bleomycin is transferred to the fetus via the placenta. Breast milk transfer of bleomycin in humans is also unknown (Bristol-Myers Squibb 2010).

5.7.3   Laboratory animal developmental toxicity

Bleomycin is reported to induce teratogenic effects in rats, but not in rabbits (Bristol-Myers Squibb 2010). In rats, administration of intraperitoneal doses of 1.5 mg/kg/day (~1.6 times the recommended human dose on a unit/m^2 basis) on days 6 to 15 of gestation caused skeletal malformations, shortened the brachiocephalic artery as well as the hydroureter. Bleomycin was not teratogenic in rabbits, but induced abortions at intravenous doses of 1.2 mg/kg/day (~2.4 times the recommended human dose on a unit/m^2 basis) given on gestation days 6 to 18. Teratogenic effects of bleomycin are also described in the peer-reviewed literature. As reviewed in Shepard and Lemire (Shepard and Lemire 2004), bleomycin inhibited fetal growth, caused embryolethality, and induced limb and tail defects in rats treated intraperitoneally at doses of 0.005 -1 mg/kg or 3-5 mg/kg during organogenesis.

5.7.4   Human gestational exposure and effects

Bleomycin is FDA Pregnancy Category D. There were 92 patients administered bleomycin during pregnancy identified from 22 case reports, 8 case series, 1 retrospective case series, 1 retrospective cohort study, 2 retrospective surveys, and 1 registry survey (Appendix C Table 6). Among these patients, bleomycin was used to treat Hodgkin lymphoma (n=48 cases), non-Hodgkin lymphoma (n=20 cases), Burkitt lymphoma (n=1 case), ovarian cancer (n=18 cases) and one case each of Ewing sarcoma, adenocarcinoma (primary cancer not identified), and cervical cancer. Cancer type was not specified in two cases. There were a total of 93 pregnancies with 95 conceptuses exposed to bleomycin due to one patient having two pregnancies (Dilek *et al.* 2006) and two set of twins (Cardonick *et al.* 2010, Nantel *et al.* 1990). Bleomycin was administered during the 1st trimester in 15 pregnancies and in the 2nd and/or 3rd trimester only in 78 pregnancies (including two set of twins); the timing of exposure was not specified for two singleton pregnancies. Fetal loss occurred in three pregnancies. One induced abortion revealed a fetus without congenital malformations, but with toxic degenerative changes in the liver and kidneys (Peres *et al.* 2001); this fetus was exposed in the 1st trimester and co-treated with nitrogen mustard, vincristine, procarbazine, doxorubicin, vinblastine, and dacarbazine. Another pregnancy ended by induced abortion following 2nd trimester exposure (d'Incalci *et al.* 1983) and intrauterine fetal death occurred following 2nd and 3rd trimester (Dilek *et al.* 2006); both cases were co-treated with doxorubicin, vinblastine, and dacarbazine; no fetal autopsy data were reported.

Of 92 live-born infants (88 singletons and two set of twins), congenital malformations were reported in 8 newborns exposed in utero to bleomycin. One infant exposed during the 1st trimester had a major malformation: a floating thumb malformation on the left hand, which included partial agenesis of a

metacarpal and hypoplasia of two phalanges on the left hand (Dilek *et al.* 2006); this infant was co-exposed to doxorubicin, vinblastine and dacarbazine. Major malformations occurred in four infants exposed to bleomycin in the 2nd and/or 3rd trimester only. Syndactyly of the 4th and 5th fingers was reported in one infant with 2nd and 3rd trimester exposure and co-exposure to doxorubicin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Another infant had bilateral syndactyly of digits II and III following exposure in the 2nd and 3rd trimesters and co-exposure to doxorubicin, vinblastine and dacarbazine, nitrogen mustard, vincristine and procarbazine (Van Calsteren *et al.* 2010). Ventriculomegaly occurred prenatally three weeks following exposure in the 2nd trimester to a combination of bleomycin, etoposide and cisplatin (Elit *et al.* 1999); at birth, this infant had ventriculomegaly and cerebral atrophy (Elit *et al.* 1999). Another infant had a spontaneous mutation for neurofibromatosis and genetic hearing loss (his parents were carriers) (Cardonick *et al.* 2010); this infant was exposed during the 2nd and 3rd trimesters and co-exposed to cisplatin and etoposide. Minor malformations were observed in three infants following in utero exposure to bleomycin. One newborn had plagiocephaly following 2nd and 3rd trimester exposure and co-exposure to doxorubicin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Pectus excavatum was observed in another infant with exposure in the 2nd and 3rd trimesters (Van Calsteren *et al.* 2010); this infant was co-exposed to doxorubicin, vinblastine, dacarbazine, nitrogen mustard, vincristine and procarbazine. Mild glandular hypospadias (considered a first degree hypospadias) was reported in an infant exposed during the 2nd trimester and co-exposed to etoposide and cisplatin (Ghaemmaghami *et al.* 2009).

Pregnancy complications and health effects were observed in infants exposed to bleomycin in utero. An inhibition of fetal growth was observed in six pregnancies, reported as intrauterine growth restriction (n=2 pregnancies) (Benjapibal *et al.* 2010, Motegi *et al.* 2007), fetal growth retardation (n=1 pregnancies) (Lambert *et al.* 1991), small for gestational age (n=2 pregnancies) (Fadilah *et al.* 2006, Han *et al.* 2005), and an estimated fetal body weight in the <5th percentile (n=1 pregnancies) (Ghaemmaghami *et al.* 2009). Oligohydramnios or a reduction in amniotic fluid occurred in two pregnancies (Ghaemmaghami *et al.* 2009, Motegi *et al.* 2007). Other pregnancy complications included: pregnancy-induced hypertension (n=1 case {Motegi, 2007 #308}, preeclampsia (n=4 cases) {Anselmo, 1999 #44}{Benjapibal, 2010 #841}{Horbelt, 1994 #537}{Lambert, 1991 #248}, premature rupture of membranes (n=1 case) {Ghaemmaghami, 2006 #77}, and spontaneous preterm labor (n=4 cases, including one case which subsided) {Moore, 1991 #718}{Nantel, 1990 #317}{Ortega, 1977 #335}{Raffles, 1989 #535}. Of 60 pregnancies reporting age at delivery, early pre-term delivery (<34 weeks) occurred in 8 pregnancies (13.3%), late pre-term delivery (34-36 weeks) occurred in 16 pregnancies (26.7%), and 36 newborns were delivered at term (60%). Two infants were identified as small for gestational age by the authors (Cardonick *et al.* 2010, Dilek *et al.* 2006). Respiratory issues, ranging from transient tachypnea to severe respiratory distress and pneumothorax, were observed in 5 newborns (Elit *et al.* 1999, Haerr and Pratt 1985, Malhotra and Sood 2000, Malone *et al.* 1986, Raffles *et al.* 1989). Hypoglycemia was reported for three infants (Cardonick *et al.* 2010), hyperbilirubinemia in one infant (Lambert *et al.* 1991), and another newborn was treated with intravenous calcium (Haerr and Pratt 1985). Transient myelosuppression occurred in two infants, including anemia (n=1 infant) (Horbelt *et al.* 1994) and leucopenia with neutropenia at day 3 (Raffles *et al.* 1989). The infant with leucopenia also experienced hair loss at day 10. Of the 71 infants with follow-up evaluations, normal development observed in all children ranging in age from 6 months to 16 years with the exception of two children. Motor/language delays were observed in the child with genetic hearing loss at 63.3 months (Cardonick *et al.* 2010). One child had sensorineural hearing loss, but normal neurodevelopmental progress at 1 year (Raffles *et al.* 1989). Another child had normal physical and neurological development by 26 months after suffering from intussusception at 7.5 months (Han *et al.* 2005).

5.7.5 *Summary of pregnancy outcomes for bleomycin*

In utero exposure to bleomycin was documented for 93 pregnancies, including two twin pregnancies, for a total of 95 conceptuses. Of the 15 pregnancies exposed during the 1st trimester, only one newborn had a major malformation: a floating thumb malformation on the left hand (i.e. partial agenesis of a metacarpal and hypoplasia of two phalanges) (Dilek *et al.* 2006). In addition, there was one induced abortion of a normal fetus following 1st trimester exposure. The total occurrence of major malformations following exposure to bleomycin in the 1st trimester was 6.7% (1/15 conceptuses). Of the 76 pregnancies (78 conceptuses) exposed to bleomycin in the 2nd and/or 3rd trimester only, major malformations were observed in four newborns. The major malformations included: syndactyly of the 4th and 5th fingers (n=1 infant) (Cardonick *et al.* 2010), bilateral syndactyly of digits II and III (n=1 infant) (Van Calsteren *et al.* 2010), a spontaneous mutation for neurofibromatosis in an infant with genetic hearing loss (his parents were carriers) (Cardonick *et al.* 2010), and cerebral atrophy in another infant diagnosed with ventriculomegaly in utero and at birth following chemotherapy exposure (Elit *et al.* 1999). Minor malformations were reported for three infants exposed in the 2nd or 2nd and 3rd trimesters to bleomycin: plagiocephaly (Cardonick *et al.* 2010), pectus excavatum (Van Calsteren *et al.* 2010), and mild glandular hypospadias (Ghaemmaghami *et al.* 2009), respectively. In addition, there was one induced abortion and one intrauterine fetal death following exposure in the 2nd (d'Incalci *et al.* 1983) and 2nd and 3rd trimesters (Dilek *et al.* 2006), respectively; no fetal autopsy data were reported. The total occurrence of major malformations following bleomycin exposure in the 2nd and/or 3rd trimester was 5.1% (4/78 conceptuses). Timing of exposure was not reported for two singleton pregnancies yielding normal infants.

Several pregnancy complications and health effects were observed following exposure to bleomycin during pregnancy, including an inhibition of fetal growth (n= 6 pregnancies) (Benjapibal *et al.* 2010, Fadilah *et al.* 2006, Ghaemmaghami *et al.* 2009, Han *et al.* 2005, Lambert *et al.* 1991, Motegi *et al.* 2007). Oligohydramnios occurred in two pregnancies (Ghaemmaghami *et al.* 2009, Motegi *et al.* 2007). Other pregnancy complications included: pregnancy-induced hypertension (n=1 case), preeclampsia (n=4 cases), premature rupture of membranes (n=1 case), and spontaneous preterm labor (n=4 cases, including one case which subsided). Of 60 pregnancies reporting age at delivery, preterm delivery occurred in 24 pregnancies. Two were identified as small for gestation age by the authors (Cardonick *et al.* 2010, Dilek *et al.* 2006). Health effects in newborns included: respiratory issues (n=5 infants), hypoglycemia (n=3 infants), transient myelosuppression (n=2 infants), hyperbilirubinemia (n=1 infant), and one newborn required intravenous calcium. Follow-up evaluations on 71 infants ranging in age from 6 months to 16 years reported normal health and development in all but two children. Motor/language delays were observed in the child with genetic hearing loss at 63.3 months (Cardonick *et al.* 2010) and another child had sensorineural hearing loss, but normal neurodevelopmental progress at 1 year (Raffles *et al.* 1989).

In conclusion, the total occurrence of major malformations in bleomycin-exposed pregnancies was 5.3% (5/95 conceptuses). The occurrence of major malformations following exposure to bleomycin during the 1st trimester (1/15 conceptuses) was higher than the prevalence of birth defects in the general population (6.7 ± 12.6% versus 3%). The occurrence of major malformations following exposure to bleomycin in the 2nd and/or 3rd trimester only (4/78 conceptuses) was not different than the prevalence of birth defects in the general population (5.1 ± 4.9% versus 3%). However, the two cases of syndactyly and the neurofibromatosis mutation are not likely the result of 2nd and/or 3rd trimester only exposure to bleomycin. Therefore, the revised occurrence of major malformations following exposure to bleomycin in the 2nd and/or 3rd trimester only is 1.3 ± 2.5% (1/78 conceptuses).

5.8   BUSULFAN

5.8.1   *Mechanism of action, route of administration, and indications*

Busulfan is an antineoplastic alkylating agent with particular toxicity for the bone marrow. Busulfan inhibits cell division by interactions with DNA and thiol groups on proteins (reviewed in (Wiebe and Sipila 1994)) and it is thought to induce cytotoxicity via DNA damage (BioPharma 2007). Busulfan can be administered by intravenous injection (BioPharma 2007) or orally (GlaxoSmithKline 2003). Busulfan is 55% protein-bound, which may explain the high distribution of busulfan into most tissues, plasma and cerebral spinal fluid (CSF) (Hassan *et al.* 1989). For example, similar steady state concentrations of busulfan were detected in plasma and cerebrospinal fluid of non-pregnant adult females being treated for acute myeloblastic leukemia (831-1480 ng/mL in plasma and 559-1180 ng/mL in CSF) (Hassan *et al.* 1989). Busulfan is indicated for chronic myelogenous leukemia (also called chronic myeloid, myelocytic, or granulocytic leukemia) (BioPharma 2007).

5.8.2   *Evidence of placental transfer and presence in breast milk*

Placental transport and breast milk transfer of busulfan in humans is unknown. It has been hypothesized that busulfan may occur in breast milk, based on the reported rapid and efficient transfer of busulfan across the blood brain barrier (Wiebe and Sipila 1994).

5.8.3   *Laboratory animal developmental toxicity*

Busulfan is teratogenic in rats, rabbits and mice inducing musculoskeletal defects and alterations in fetal body weight gain and body size (BioPharma 2007). In particular, intraperitoneal injections of busulfan at 10 mg/kg on gestation days 12-14 induced microencephaly and microphthalmia as well as reduced body weight and small body size in Wistar Hannover GALAS rat fetuses. Growth retardation and skeletal abnormalities were also observed in fetuses of Wistar rats treated intraperitoneally with 18-34 mg busulfan /kg body weight on gestation day 12 (Murphy *et al.* 1958). Gross malformations included: webbing of the forepaws and rear paws, tail malformations (85%), cleft palate and skeletal abnormalities of the ribs, sternum and scapula. Forelimb anomalies occurred in rat fetuses exposed to a single oral administration of 20 mg busulfan/kg to pregnant WKAH/Hkm rats on gestation days 10, 10.5 or 11 (Kato *et al.* 1990). Germ cell dysgenesis has been reported following in utero exposure to similar doses of busulfan in both rats (Heller and Jones 1964) and mice (Jansz and Pomerantz 1985). Busulfan is also teratogenic in birds. Busulfan exposure impaired hatchability in Japenese quail, and the surviving offspring had gonads that lacked germ cells (Hallett and Wentworth 1991). Busulfan induced limb and trunk defects in Rhode Island Red chick embryos in a dose response manner following a 48-hour incubation at doses ranging from 1 to 500 μg busulfan (Aige-Gil and Simkiss 1991).

5.8.4   *Human gestational exposure and effects*

Busulfan is classified as FDA Pregnancy Category D. There were 30 published cases treated with busulfan during pregnancy identified from 14 case reports, 5 case series, 1 retrospective case series, 2 retrospective cohort studies, and 1 retrospective survey (Appendix C Table 7). Among these patients, busulfan was used to treat two types of leukemia: chronic myelogenous (also called chronic granulocytic; n=29 cases) and acute granulocytic (n=1 case). A total of 31 singleton pregnancies (31 conceptuses) were exposed to busulfan, including one patient having two pregnancies (Lee *et al.* 1962). Busulfan was administered during the 1st trimester in 20 pregnancies and 2nd and/or 3rd trimester only in 5 pregnancies. Timing of exposure was not specified for 6 pregnancies. Fetal loss occurred in three pregnancies. A spontaneous abortion occurred at 1 month of gestation following exposure to busulfan

and radiation therapy **[exact timing of exposure not specified, but presumed to be 1st trimester]** (Lee *et al.* 1962); no fetal autopsy data were provided. Histological analysis revealed myeloschisis (cleft spinal cord) in an embryo following an induced abortion at 6 weeks of gestation (Abramovici *et al.* 1978); the pregnancy had been exposed during the period of conception and the 1st trimester with no co-treatments. A second induced abortion terminated a pregnancy at 16 weeks following 1st trimester exposure; no fetal autopsy data were reported (Zuazu *et al.* 1991).

Of the 28 live-born infants exposed to busulfan in utero, major malformations were observed in three infants. Two of the infants with major malformations were exposed during the 1st trimester. One newborn had cleft palate, bilateral microphthalmia and bilateral corneal opacities as well as poorly differentiated genitalia (Diamond *et al.* 1960); this infant was exposed in the 1st, 2nd and 3rd trimesters to busulfan and was co-treated with radiation therapy around the time of conception, and exposed to 6-mercaptopurine in the 1st and 3rd trimesters. This infant died at age 10 weeks, and the autopsy revealed disseminated cytomegaly, hypoplasia of the ovaries and the apparent absence of thyroid and parathyroid glands (Diamond *et al.* 1960). Another infant required surgery at age 2 months to remedy pyloric stenosis (Earll and May 1965); this infant had been exposed to busulfan during the 1st, 2nd and 3rd trimesters. One infant exposed to busulfan in the 2nd and 3rd trimesters was reported to have congenital absence of the right kidney and right ureter, and hydronephrosis of the left kidney and dilation of the left ureter (Boros and Reynolds 1977).

There are relatively few pregnancy complications and health issues reported for pregnancies exposed to busulfan during cancer treatment. Spontaneous preterm labor was reported in two pregnancies {Lee, 1962 #600}{Ozumba, 1992 #547}. Of the 21 pregnancies with age at delivery data, early preterm delivery (<34 weeks) was reported for one pregnancy (5%), late preterm delivery (34-36 weeks) was reported for 4 pregnancies (20%), and 16 pregnancies were delivered at term (75%). None of the newborns were reported to be small for gestational age. A "premature appearance" was reported for a normal infant, who was delivered at term (White 1962). A second neonatal death occurred at age 30 days due to an acute staphylococcus infection (Ruiz Reyes and Tamayo Perez 1961).

Follow-up evaluations were available on 22 infants at ages ranging from 5 weeks to 11 years. Normal growth and development were observed in all children, except one child. At 4 and 19 months, the child with an absent right kidney had a normal score on the Denver Developmental Screening Tests, but continued to have height and weight two standard deviations below the mean for her age at 19 months (Boros and Reynolds 1977).

5.8.5 *Summary of pregnancy outcomes for busulfan*

In utero exposure to busulfan is documented for 31 singleton pregnancies (31 conceptuses). Of the 20 pregnancies exposed to busulfan during the 1st trimester, major malformations occurred in three pregnancies. One newborn had cleft palate as well as bilateral microphthalmia, bilateral corneal opacities, and poorly differentiated genitalia following exposure beginning in the 1st trimester and co-exposure to radiation therapy around the time of conception (Diamond *et al.* 1960). This infant died at age 10 weeks, and the autopsy revealed disseminated cytomegaly, underdevelopment of the ovaries and the apparent absence of thyroid and parathyroid glands (Diamond *et al.* 1960). Pyloric stenosis, requiring surgical correction at age 2 months, was reported in an infant exposed during the 1st, 2nd and 3rd trimesters (Earll and May 1965). In addition, myeloschisis (cleft spinal cord) was reported in an induced abortus following exposure during conception and 1st trimester (Abramovici *et al.* 1978). No fetal data were provided for a spontaneous abortion occurring after **[1st trimester]** exposure and co-treatment with radiation therapy (Lee *et al.* 1962) and a second induced abortion performed following

1st trimester exposure (Zuazu *et al.* 1991). The total occurrence of major malformations following exposure to busulfan during the 1st trimester was 15% (3/20 conceptuses). Of the 5 infants exposed to busulfan in the 2nd and/or 3rd trimesters only, major malformations were observed in one infant: congenital absence of a right kidney and right ureter as well as hydronephrosis of the left kidney and a dilated left ureter (Boros and Reynolds 1977). The total occurrence for major malformations following exposure to busulfan in the 2nd and/or 3rd trimester was 20% (1/5 conceptuses). The timing of exposure was not specified for 6 pregnancies. A second neonatal death of a normal infant occurred at age 30 days due to an acute staphylococcus infection (Ruiz Reyes and Tamayo Perez 1961).

Regarding pregnancy complications and infant health effects, there were two cases of spontaneous preterm labor. Of the 21 pregnancies with age at delivery data, preterm delivery was reported for five pregnancies. None of the newborns were reported to be small for gestational age. Follow-up evaluations of 22 infants at ages ranging from 5 weeks to 11 years reported normal growth and development in all but one child who remained two standard deviations below the mean height and weight for her age at 19 months, despite normal neurodevelopmental progress (Boros and Reynolds 1977).

In conclusion, the total occurrence of major malformations in busulfan-exposed pregnancies was 12.9% (4/31 conceptuses). The occurrence of major malformations following exposure to busulfan in the 1st trimester (3/20 conceptuses) was greater than the prevalence of birth defects in the general population (15.0 ± 15.6% versus 3%). The occurrence of major malformations following exposure to busulfan in the 2nd and/or 3rd trimester only (1/5 conceptuses) was also higher than the prevalence of birth defects in the general population (20.0 ± 35.1% versus 3%). However, it is unlikely that the absence of right kidney and ureter resulted from busulfan exposure in the 2nd and/or 3rd trimesters. Therefore, a revised occurrence of malformations possibly caused by busulfan in the 2nd and/or 3rd trimester only was 0%.

5.9 CARBOPLATIN

5.9.1 Mechanism of action, route of administration, and Indications

Carboplatin is an organoplatinum compound in the class of alkylating agents that possess anti-neoplastic activity. Carboplatin binds to DNA producing predominately interstrand versus intrastrand cross-links that lead to DNA breakage and it not cell cycle specific (Bedford Laboratories 2004). Carboplatin is administered intravenously on a body surface area (mg/m^2) basis. Carboplatin is indicated for ovarian cancer (Bedford Laboratories 2004).

5.9.2 Evidence of placental transfer and presence in breast milk

There is evidence that carboplatin and similar platinum-derivatives (e.g., cisplatin) can cross the placenta in humans, although transfer of carboplatin in breast milk is not known. Platinum DNA adducts were detected in the maternal blood and placental tissue of a patient administered cisplatin and cyclophosphamide during the 2nd and 3rd trimester and subsequently treated with carboplatin and cyclophosphamide in the 3rd trimester of pregnancy (Henderson *et al.* 1993). In another study, platinum DNA adducts were detected in both maternal blood at gestation week 30 and in cord blood at delivery (at gestation week 37) of a cancer patient treated with carboplatin (400 mg/m^2 every 4 weeks); the first dose was administered at 22 weeks gestation and the last dose was administered nine weeks prior to delivery [~26 weeks gestation] (Koc *et al.* 1994). Levels of platinum adducts were similar at delivery in maternal and fetal lymphocyte samples (14.5 pg/µg versus 14.1 pg/µg DNA adducts in maternal versus umbilical cord blood, respectively). Furthermore, placental transport of carboplatin has been reported for baboons and mice. Fetal plasma levels of total platinum averaged 58% of maternal plasma levels when serially sampled over a 24-hour period following a single intravenous dose of carboplatin alone or with other chemotherapy agents to pregnant baboons (n=7 baboons) at a median gestational age of 129 days (Van Calsteren *et al.* 2010). In studies of mice, Van Calsteren et al. (Van Calsteren *et al.* 2010) report that total platinum easily crossed the placenta with the fetal blood concentration being 117% +/- 38.9% (n=6) of the maternal blood concentration at 90-minutes following a single intravenous dose of carboplatin with other chemotherapy agents. Finally, the possibility of maternal transfer of carboplatin to the infant via breastfeeding is not known, however the relatively low molecular weight of carboplatin suggests that it could be found in breast milk.

5.9.3 Laboratory animal developmental toxicity

Carboplatin induced embryolethal and teratogenic effects in rat fetuses when administered during the early period of organogenesis. Kai et al. (Kai *et al.* 1989) reported that carboplatin induced a significant increase in percent of empty implantation sites in rat dams and congenital malformations in fetal rats following intravenous administration of the drug to pregnant dams at a dose of 6 mg/kg/d on days 6 to 9 of gestation versus controls (Kai *et al.* 1989), while there was no significant difference between carboplatin-treated groups and controls dosed on gestation days 7 to 10. The congenital malformations produced by carboplatin included: gastroschisis, dilation of cerebral ventricles, cleft sternum, fused ribs, and malformed thoracic vertebra. Delayed ossification was observed in rat fetuses treated during both administration periods (gestation days 6-9 or 7-10), which the authors suggested may be caused by fetal growth retardation (Kai *et al.* 1989). As reviewed in Shepard et al. (Shepard 1979), carboplatin decreased fetal weight and induced maternal toxicity, but did not induce teratogenic effects in rat fetuses, when administered intravenously to rat dams at 4 mg/kg/d on gestation days 7 to 17 of gestation.

5.9.4   Human gestational exposure and effects

Carboplatin is classified as FDA Pregnancy Category D. There were 17 published cases treated with carboplatin during pregnancy identified from 12 case reports, 1 case series, and 1 registry survey (Appendix C Table 8). Among these patients, carboplatin was used to treat cancers of the ovary (n=12 cases), lung (n=2 cases), breast (n=1 case), central nervous system (n=1 case), and cervix (n=1 case). A total of 17 singleton pregnancies (17 conceptuses) were exposed to carboplatin, and all pregnancies were exposed in the 2nd and/or 3rd trimester. Carboplatin was not administered during the 1st trimester in any case. There was only one major malformation reported following in utero exposure to carboplatin. Gastroschisis, a congenital fissure in the abdominal wall, was observed in a fetus following spontaneous abortion at gestation week 19 (Cardonick *et al.* 2010); this fetus had been exposed in the 2nd trimester only. There were 16 liveborn infants following exposure to carboplatin.

There were relatively few pregnancy complications or infant health effects following in utero exposure to carboplatin. Anhydramnios and intrauterine growth restriction was observed in a pregnancy that was co-treated with docetaxel and trastuzumab in the second and third trimesters {Gottschalk, 2011 #1328}. Spontaneous preterm labor and preeclampsia occurred in one pregnancy each {Henderson, 1993 #533}{Azim, 2009 #63}. Of the 13 pregnancies reporting age at delivery, early preterm delivery (<34 weeks) occurred for 5 pregnancies (41.7%), late preterm delivery (34-36 weeks) occurred for 7 pregnancies (58.3%), and 1 pregnancy (8.3%) was delivered at term. One newborn was reported as small for gestational age (Cardonick *et al.* 2010). Anemia and breathing difficulties were reported for two newborns (Gurumurthy *et al.* 2009, Hubalek *et al.* 2007). One of the infants, who was born at 28 weeks of gestation, required surfactant treatment and was placed on a respirator for 29 days followed by oxygen treatment until 8 months of age (Gurumurthy *et al.* 2009); she also developed sepsis at age 36 days, from which she recovered well. Follow-up examinations were reported for 14 children at ages ranging from 5 months to 4 years; age at follow-up was not specified for one child. Normal growth and development were reported for all the children, except one child who had motor/language delay at 1 year of age (Cardonick *et al.* 2010).

5.9.5   Summary of pregnancy outcomes for carboplatin

In utero exposure to carboplatin was documented for 17 singleton pregnancies (17 conceptuses). None of the infants were exposed in the 1st trimester. Of the 17 pregnancies exposed in the 2nd and/or 3rd trimester, a major malformation was noted in one fetus. Gastroschisis was reported in a fetus from a spontaneous abortion at gestation week 19 (Cardonick *et al.* 2010). The occurrence of major malformations following exposure to carboplatin during 2nd and/or 3rd trimester only is 5.9% (1/17 conceptuses). Timing of exposure was not specified in one pregnancy yielding a normal infant.

Complications were observed in 3 pregnancies: anhydramnios and intrauterine growth restriction in a pregnancy co-exposed to trastuzumab {Gottschalk, 2011 #1328}, preeclampsia {Henderson, 1993 #533}, and preterm spontaneous labor {Azim, 2009 #63}. Of the 13 pregnancies reporting age at delivery, preterm delivery (<37 weeks) occurred in 12 pregnancies. One infant was identified as small for gestational age by the authors (Cardonick *et al.* 2010). Two newborns had both anemia and breathing difficulties, and one of these infants also had sepsis at day 36. Normal growth and development were reported for 14 of 15 children at ages ranging from 5 months to 4 years; age at follow-up was not specified for one child. One child had a motor/language delay at 1 year of age (Cardonick *et al.* 2010).

In conclusion the total occurrence of major malformations in carboplatin-exposed pregnancies was 5.9% (1/17 conceptuses). There were no published reports of pregnancies exposed to carboplatin during the

1st trimester. The occurrence of major malformations following exposure in the 2nd and/or 3rd trimester (1/17 conceptuses) was twice as high as the prevalence of birth defects in the general population (5.9 ± 11.2% versus 3%). The single malformation, gastroschisis, was not likely the result of carboplatin exposure in the 2nd trimester. Therefore, the revised occurrence of major malformations following exposure to carboplatin in the 2nd and/or 3rd trimester only was 0%.

5.10 CISPLATIN

5.10.1 Mechanism of action, route of administration, and indications

Cisplatin, an inorganic compound, is a *cis*-isomer of diammine dichloroplatinum. Cisplatin induces interstrand and intrastrand crosslinks in DNA, which inhibits the growth of cancer cells. Its action is not cell-cycle specific. Cisplatin is administered on a body surface area (mg/m^2) basis intravenously (IV) (Bristol-Myers Squibb 2010) or by intraperitoneal injection (Markman 2009). Cisplatin is indicated for the treatment of metastatic testicular tumors, metastatic ovarian tumors, and advanced bladder cancer (Bristol-Myers Squibb 2010). It is also used in the treatment of other types of cancers, including head and neck cancer, cancer of the esophagus, small cell and non-small cell lung cancer, non-Hodgkin lymphoma and choriocarcinoma (Leslie 2002).

5.10.2 Evidence of placental and breast milk transport

Transplacental transport of cisplatin has been reported in at least one study, while evidence for breast milk transport of the drug is currently not clear. In a twin pregnancy, Marnitz et al. (Marnitz *et al.* 2009) reported that cisplatin levels in the amniotic fluid were one-tenth of maternal serum levels (106.7 versus 1148.8 µg/L, respectively) when sampled 30 minutes following IV administration of cisplatin in the 3rd trimester. At birth at 32 weeks gestation, cisplatin levels in the umbilical cord bloods of the twins were 57.1 and 61.2 µg/L, which was approximately one-third of the amniotic fluid levels (data not provided). Following a C-section birth at 28 weeks gestation, nearly equivalent levels of cisplatin were detected in maternal blood and umbilical cord blood of a patient treated with cisplatin every 5 days of a 3-week cycle (1.10 and 0.82 µm/L [330 µg/L and 246 µg/L assuming a molecular weight of cisplatin of 300] in maternal and umbilical cord blood, respectively) (Elit *et al.* 1999); the timing of the last dose of cisplatin prior to birth was not stated. Arango et al. (Arango *et al.* 1994) reported cisplatin levels of 40 µg/mL [mg/L] in an infant's blood at birth, three days post-administration of cisplatin to the mother [this value is 1000-fold higher than two other studies reported above]. Most recently, Marnitz et al. (Marnitz *et al.* 2010) reported detectable levels of cisplatin in maternal serum, amniotic fluid and umbilical cord artery serum at birth for 7 patients. The cisplatin concentrations in umbilical cord artery blood samples were 31-65% that of maternal serum (15-162 µg/L versus 22-234 µg/L, respectively), while amniotic fluid levels (5-33 µg/L) were 13-42% of maternal levels. Platinum DNA adducts were detected in maternal blood and placental tissue of a patient administered cisplatin and cyclophosphamide during the 2nd and 3rd trimester, followed by carboplatin and cyclophosphamide during the 3rd trimester of pregnancy (Henderson *et al.* 1993); however, there was insufficient DNA from fetal amniotic cells and cord blood to measure adducts with maximum sensitivity. Cis-platin adducts were absent from infant blood at 3 and 12 months (Henderson *et al.* 1993). Transplacental transport of cisplatin has been reported in mice (Kopf-Maier and Merker 1983) and patas monkeys (Shamkhani *et al.* 1994).

The published literature on maternal transfer of cisplatin to the infant via breastfeeding is not consistent. Two studies report platinum in breast milk. de Vries et al. (de Vries *et al.* 1989) detected platinum levels of 0.9 mg/L in breast milk and 0.8 mg/L in maternal plasma (approximately a 1:1 ratio) in a woman 30 minutes prior to her 3rd daily dose of cisplatin at 30 mg/m^2 (co-treatment with etoposide and bleomycin) intravenously, following a C-section at 33 weeks gestation. In another study, levels of platinum in breast milk were, at minimum, one-tenth of plasma levels throughout the 18 hours of sampling of a patient administered cisplatin at 60 mg/m^2 (or 100 mg total dose) and cyclophosphamide intravenously per cycle; for example, platinum levels were approximately 0.25 versus 2.8 ng/mL [µg/L; estimated from Figure 1] in breast milk versus peripheral blood 30 minutes after completion of cisplatin administration (Ben-Baruch *et al.* 1992). In contrast, Egan et al. (Egan *et al.* 1985) reported that levels of

platinum reached a maximum value of 2.99 μg/mL [mg/L] in plasma samples versus undetectable platinum levels in breast milk samples from a patient, who was 7 months postpartum, administered cisplatin (130 mg total dose) in combination with doxorubicin.

5.10.3 Laboratory animal developmental toxicity

Cisplatin is reported to be highly embryotoxic in several laboratory animal species; however, teratogenic effects occur at a lesser frequency. Keller et al. (Keller and Aggarwal 1983) report that the embryonic LD$_{50}$s were 1.0 to 2.9 mg cisplatin/kg bw/d in the rat and 5.2 mg cisplatin/kg bw/d in the mouse during the period of organogenesis; theses doses are below the estimated human dose of 6 mg/kg bw/day. Other studies also reported dose-dependent increases in fetal resorptions during organogenesis, but not after organogenesis, in the mouse (Kopf-Maier *et al.* 1985), rat (Muranaka *et al.* 1995) as well as the rabbit, where significantly greater rates of fetal mortality were reported for rabbits exposed in utero to ≥0.125 mg cisplatin/kg bw/d during organogenesis. Fetal body weights were also reduced by cisplatin exposure in mice and rats at comparable doses to their effects on fetal mortality (Kopf-Maier *et al.* 1985, Lazar *et al.* 1979, Muranaka *et al.* 1995). While Muranaka et al. (Muranaka *et al.* 1995) reported the greatest decrease in fetal body weights by cisplatin occurred during organogenesis in rats, other studies in rats and rabbits report fetal weight decreases regardless of the timing of cisplatin exposure (Kopf-Maier *et al.* 1985, Shepard and Lemire 2004) . Consistent with body weight reductions, transplacental exposure to cisplatin during organogenesis causes growth retardation in rabbits (reviewed in (Shepard and Lemire 2004)) and delayed skeletal ossification in mice (Kopf-Maier *et al.* 1985). Transplacental exposure to cisplatin was less likely to induce malformations than to induce fetal mortality in rats and mice (Keller and Aggarwal 1983, Kopf-Maier and Merker 1983, Muranaka *et al.* 1995), and malformations were not observed in the rabbits exposed to 0.125 to 5 mg cisplatin/kg bw/d (Shepard and Lemire 2004). Fetal malformations that occurred following tranplacental cisplatin exposure included: malformations of the digits and tail in rats (Muranaka *et al.* 1995), minor skeletal malformations in mice (e.g. supernumerary ribs, vertebral malformations (Lazar *et al.* 1979), hydrocephaly in rats (Kopf-Maier *et al.* 1985), as well as bilateral microphthalmia in White Leghorn chicks (Narbaitz and Marino 1988) and anophthalmia and microphthalmia in rats (Muranaka *et al.* 1995). Narbaitz and Marino ((Narbaitz and Marino 1988)) suggested the cisplatin-induced microphthalmia was caused by a primary lesion of the ciliary epithelium, which decreased pressure and thus expansion of the eye during development. The incidence of skeletal malformations and microphthalmia were attributed to sensitivity of the period of organogenesis to cisplatin. In contrast, the slight signs of hydrocephaly (determined by histopathology) and changes in the neuroepithelium of the brain (e.g. a reduction in mitotic activity and an increase in necrosis) were observed after, but not during, the period of organogenesis in the mouse (Kopf-Maier *et al.* 1985, Kopf-Maier and Merker 1983). Köpf-Maier et al. ((Kopf-Maier *et al.* 1985, Kopf-Maier and Merker 1983)) suggest that there may be less placental transfer of cisplatin during organogenesis in the mouse than at later stages of fetal development.

5.10.4 Human gestational exposure and effects

Cisplatin is classified as FDA Pregnancy Category D. There were 99 published cases of patients treated with cisplatin during pregnancy identified from 44 case reports, 13 case series, 2 retrospective cohort studies, 1 retrospective survey, and 1 registry survey (Appendix C Table 9). Among these 99 patients, cisplatin was used to treat cancers of the ovary (n=42 cases), cervix (n=40 cases), lung (n=6 cases), pancreas (n=1 case) and urethra (n=1 case) as well as melanoma (n=3 cases), non-Hodgkin lymphoma (n=2 cases), adenocarcinoma of the liver (primary tumor not identified; n=1 case), adenoid cystic carcinoma (n=1 case), Hodgkin lymphoma (n=1 case), and neuroblastoma (n=1 case). A total of 99 pregnancies (101 conceptuses) were exposed to cisplatin, including two twin pregnancies (Cardonick *et*

al. 2010, Marnitz *et al.* 2010). Cisplatin was administered during the 1st trimester in 4 cases (4 conceptuses) and the 2nd and/or 3rd trimester only in 95 cases (97 conceptuses). Fetal loss occurred in three singleton pregnancies. Following hysterectomy at gestation week 13, histological examination of the fetus revealed normal organs with the exception of a large giant cell in the testes; the giant cell was possibly a megakaryocyte (Jacobs *et al.* 1980); the pregnancy was exposed to cisplatin beginning at gestation week 10. One intrauterine fetal death occurred at gestation week 26 following exposure during the 2nd trimester and co-treatment with etoposide (Peres *et al.* 2001); the fetus had no malformations. A spontaneous abortion occurred at gestation week 22 following 2nd trimester exposure (Gambino *et al.* 2011); no fetal autopsy data were provided.

Of the 98 live-born infants exposed in utero to cisplatin, malformations were observed in four infants. Malformations were not observed in any of the four conceptuses exposed during the 1st trimester. Major malformations were reported in three infants exposed in utero to cisplatin in the 2nd and/or 3rd trimester only. In one infant, ventriculomegaly was diagnosed prenatally one week after initiation of cisplatin administration in the 2nd trimester, and was also observed at birth with cerebral atrophy (Elit *et al.* 1999); the pregnancy was co-treated with etoposide and bleomycin. A second infant with 2nd trimester exposure suffered from ventriculomegaly, which was diagnosed prior to chemotherapy and appeared to worsen during chemotherapy exposure (Rouzi *et al.* 2009); this infant died 5 days after birth from congenital malformations detected prior to chemotherapy exposure. One infant had a spontaneous mutation for neurofibromatosis and genetic hearing loss (both parents were carriers) (Cardonick *et al.* 2010); this infant was exposed in the 2nd and 3rd trimester and co-treated with etoposide, and bleomycin. Two of these major malformations were not likely caused by chemotherapy administered in the 2nd and/or 3rd trimester: ventriculomegaly diagnosed prior to chemotherapy (Rouzi *et al.* 2009) and the neurofibromatosis mutation (Cardonick *et al.* 2010). One infant had a mild hypospadias, considered a first degree hypospadias and a minor malformation, following exposure in the 3rd trimester and co-treated with etoposide, and bleomycin (Ghaemmaghami *et al.* 2009). In addition, one infant was diagnosed with micropthalmia with severe hypermetropia, not considered a congenital malformation by the CDC, at age 1 year (Li *et al.* 2007); this infant was exposed in the 1st and 2nd trimesters and with co-exposure to carmustine, dacarbazine, and tamoxifen during the 1st and 2nd trimesters.

A variety of pregnancy complications and infant health effects were observed following in utero exposure to cisplatin. Alterations in amniotic fluid levels were observed in five pregnancies, including polyhydramnios (Bayhan *et al.* 1999), oligohydramnios or a marked reduction in amniotic fluid (Buller *et al.* 1992, Ghaemmaghami *et al.* 2009), and anhydramnios (Motegi *et al.* 2007). An inhibition of fetal growth was observed in 7 fetuses, including intrauterine growth restriction (Arango *et al.* 1994, Buller *et al.* 1992, Gottschalk *et al.* 2009, Motegi *et al.* 2007), small for gestational age fetus (Benjapibal *et al.* 2010, Han *et al.* 2005), and fetal body weight <5th percentile (Ghaemmaghami *et al.* 2009). Preeclampsia occurred in three pregnancies {Benham, 2008 #157}{Henderson, 1993 #533;Horbelt, 1994 #537}, pregnancy-induced hypertension was repored in one pregnancy {Raghunath, 2006 #662}, premature rupture of the membranes occurred in four pregnancies, including two cases that also had spontaneous preterm labor {Gambino, 2011 #890}{Ghaemmaghami, 2006 #77}{Huang, 2004 #112}{King, 1991 #137}. Spontaneous preterm labor occurred in three additional pregnancies, including two pregnancies in which it resolved with treatment {Raffles, 1989 #535}{Karam, 2007 #127}{Li, 2011 #962}. One pregnancy was terminated by C-section at gestation week 30 due to maternal tonic-clonic seizures induced by brain metastases (Garcia-Gonzalez *et al.* 2008). Of the 76 pregnancies reporting age at delivery, early preterm birth (<34 weeks) was observed for 30 pregnancies (41.1%), late preterm delivery (34 weeks to 36 weeks 6 days) was reported for 30 pregnancies (39.5%) and 16 pregnancies

were delivered at term (21.1%).   Small for gestational age was reported for two newborns (Abellar *et al.* 2009, Cardonick *et al.* 2010). Tachycardia was observed in one newborn {King, 1991 #137}. Respiratory difficulties were reported in 13 newborns {Bader, 2007 #65}{Bayhan, 1999 #663}{Boyd, 2009 #169}{Elit, 1999 #534}{Garcia-Gonzalez, 2008 #70}{King, 1991 #137}{Malhotra, 2000 #660;Malone, 1986 #270}{Rabaiotti, 2010 #831;Robova, 2007 #596}{Marnitz, 2010 #978}{Fruscio, 2012 #1335}. Anemia was observed in 5 infants (Gambino *et al.* 2011, Horbelt *et al.* 1994, Peres *et al.* 2001, Rabaiotti *et al.* 2010, Robova *et al.* 2007). Another infant with anemia had profound leucopenia with neutropenia by day 3, which resolved by 13 days of age, and alopecia at 10 days of age (Raffles *et al.* 1989). Another infant had decreased white blood cells and platelets at 10 days of age, which resolved by 3 weeks of age (Janne *et al.* 2001). Other transient newborn health effects included: hypoglycemia (Boyd *et al.* 2009), a mild elevation in creatinine that normalized by 8 days of age (Karam *et al.* 2007), and jaundice (Peres *et al.* 2001). One infant had an intraventricular hemorrhage, and was discharged from the hospital healthy after 40 days {Fruscio, 2012 #1335}.

Follow-up data were available for 68 offspring ranging in age from 20 days to 11 years with normal growth and development reported for all but three children. Hearing loss was reported for two children: moderate sensorineural hearing loss at 1 year old (Raffles *et al.* 1989), and genetic hearing loss as well as a spontaneous mutation for neurofibromatosis (Cardonick *et al.* 2010). One child, with a normal twin, had Aspergers syndrome and delays in school at 11 years of age (Cardonick *et al.* 2010). Another child with normal growth and development at 26 months of age had suffered from intussusception (blockage of intestine due to telescoping of intestine) at age 7.5 months.

5.10.5 Summary of pregnancy outcomes for cisplatin

In utero exposure to cisplatin is documented for 99 pregnancies with 101 conceptuses (included two sets of twins). Major malformations were observed in 3 conceptuses exposed in utero to cisplatin. None of the four pregnancies exposed to cisplatin in the 1st trimester resulted in a major malformation. Microphthalamia, a minor malformation, was diagnosed in one child exposed during the 1st and 2nd trimesters (Li *et al.* 2007). In addition, a normal fetus was observed via histological examination following a hysterectomy at gestation week 13 (Jacobs *et al.* 1980); the pregnancy was exposed during the 1st trimester. The total occurrence of major malformations following 1st trimester exposure to cisplatin was 0% (0/4 conceptuses). Of the 95 pregnancies (97 conceptuses due to two sets of twins) with exposure during the 2nd and/or 3rd trimester only, major malformations possibly attributable to cisplatin occurred in one infant. One infant had ventriculomegaly (first observed prenatally one week following exposure to cisplatin and co-treatments) and cerebral atrophy following 2nd trimester exposure (Elit *et al.* 1999). Two other infants had major malformations: spontaneous mutation for neurofibromatosis as well as genetic hearing loss (both parents were carriers) following 2nd and 3rd trimester exposure (n=1 infant) (Cardonick *et al.* 2010) and ventriculomegaly with other congenital malformations that were observed prior to administration of cisplatin and co-treatments in the 2nd trimester (n=1 infant) (Rouzi *et al.* 2009). Mild hypospadias, a minor malformation, was reported in an infant with 3rd trimester exposure (Ghaemmaghami *et al.* 2009). In addition, two pregnancies ended in fetal death following 2nd trimester exposure: a spontaneous abortion at 22 weeks with no fetal autopsy data (Gambino *et al.* 2011) and the intrauterine death of a fetus without malformations (Peres *et al.* 2001). The occurrence of major malformations possibly attributable to 2nd and/or 3rd trimester exposure to cisplatin was 1.1% (1/89 conceptuses). Timing of in utero exposure to cisplatin was not specified for one pregnancy yielding a normal infant.

Pregnancy complications and health effects observed following in utero exposure to cisplatin included: polyhydramnios (n=1 case), reduced or absent amniotic fluid (n=5 cases), inhibited fetal growth (n=7

fetuses), transient myelosuppression (n=7 infants), respiratory difficulties (n=13 infants) and one infant each with hypoglycemia, elevated creatinine, tachycardia, and jaundice. Of the 76 pregnancies reporting age at delivery, preterm birth occurred in 60 pregnancies. Small for gestational age was reported for two newborns (Abellar *et al.* 2009, Cardonick *et al.* 2010). Follow-up examinations on 68 children at ages ranging from a 20 days to a 11 years found no adverse developmental effects, with the exception of three children. Hearing loss was reported for two children; moderate sensorineural hearing loss in a 1 year old infant, genetic hearing loss as well as a spontaneous mutation for neurofibromatosis in another child, and an 11 year old child, with a normal twin, had Aspergers syndrome and delays in school.

In conclusion, the total occurrence of major malformations in cisplatin-exposed pregnancies was 3.0% (3/101 conceptuses). No major malformations were observed in the 4 conceptuses exposed to cisplatin in the 1st trimester. Major malformations were observed in three of 101 conceptuses exposed in the 2nd and/or 3rd trimester, which was comparable to the prevalence of major malformations in the general population (3.0 ± 3.3% versus 3%). Of these three major malformations, two malformations were unlikely to have been the result of 2nd and/or 3rd trimester exposure: ventriculomegaly and other birth defects detected prior to chemotherapy administration (Rouzi *et al.* 2009) and a mutation for neurofibromatosis (Cardonick *et al.* 2010). Therefore, the revised occurrence of major malformation possibly attributed to exposure to cisplatin in the 2nd and/or 3rd trimester exposure was 1.0 ± 1.9 (1/101 conceptuses).

5.11 CYCLOPHOSPHAMIDE

5.11.1 Mechanism of action, route of administration, and indications

Cyclophosphamide is an anti-neoplastic alkylating agent that is chemically similar to the nitrogen mustards (Baxter 2009). It is biotransformed in the liver to metabolites that crosslink with DNA to inhibit the growth of rapidly dividing cancer cells. Cyclophosphamide may be administered orally or by intravenous injection. Cyclophosphamide is indicated for several cancer types including breast cancer, ovarian cancer, neuroblastoma, retinoblastoma and multiple myeloma. It is also indicated for leukemia (chronic lymphocytic leukemia, chronic granulocytic leukemia, acute myelogenous and monocytic leukemia, and acute lymphoblastic leukemia) as well as Hodgkin lymphoma and non-Hodgkin lymphoma (malignant lymphoma, lymphocytic lymphoma, mixed cell type lymphoma, histiocytic lymphoma, Burkitt lymphoma, and mycosis fungoides) (Baxter 2009). It is often used in combination with other cancer chemotherapeutic agents.

5.11.2 Evidence of placental and breast milk transport

Placental transport of cyclophosphamide in humans may occur and the drug is found in human breast milk. In a case report, D'Incalci et al. (D'Incalci *et al.* 1982) reported that the amniotic fluid level of cyclophosphamide was approximately 25% (2.1 µg/mL) of the drug concentration in maternal plasma at one hour post-administration of the last IV dose of 400 mg/m^2 prior to C-section delivery of the infant. Transplacental transfer of cyclophosphamide has also been documented in baboons. Using a pregnant baboon model, Van Calsteren et al. (Van Calsteren *et al.* 2010) determined the placental transfer of cyclophosphamide to the fetus. Fetal and maternal plasma levels of cyclophosphamide were comparable at two hours following intravenous administration of the drug to 3 pregnant baboons (Van Calsteren *et al.* 2010). Cyclophosphamide was also detected in the amniotic fluid and the cerebral spinal fluid of the fetus and mother. However, fetal plasma and cerebral spinal fluid levels of the metabolite 4-hydroxy-cyclophosphamide were only about 25.1 ± 6.3% (n=3) and 63% (n=1) of maternal levels, respectively. At 24 hours post-treatment, cyclophosphamide and the metabolite were undetectable in fetal and maternal plasma (Van Calsteren *et al.* 2010).

Cyclophosphamide is found in human milk and can cause myelosuppression in the human infant. Cyclophosphamide was present in breast milk at 1, 3, 5 and 6 hours after an intravenous dose of 500 mg to a woman with generalized lymphosarcoma, who was 8 months postpartum and lactating (Wiernik and Duncan 1971). Myelosuppression was observed in two infants whose mothers continued breastfeeding while being treated with cyclophosphamide. A patient with Burkitt lymphoma, would not stop breast feeding following treatment with cyclophosphamide during pregnancy and again during lactation beginning at postnatal day 20 (Durodola 1979). The infant's leukocyte and platelet counts were rapidly depressed over 3 daily doses of cyclophosphamide to the mother with leukocyte and platelet counts falling from pretreatment values of 4,800/mm^3 and 270,000/mm^3 to 3,200/mm^3 and 47,000/mm^3, respectively (Durodola 1979). The mother died at postnatal day 23 (the day of the 3rd dose) and no follow-up data were available for the infant. Amato and Niblett 1977 (Amato and Niblett 1977) reported transient neutropenia in an infant who was breast-fed while the mother was undergoing weekly administration of 800 mg of cyclophosphamide as well as 2 mg vincristine for lymphocytic lymphoma. The American Academy of Pediatrics Committee on Drugs considers cyclophosphamide one of the drugs "that may interfere with cellular metabolism of the nursing infant" (American Academy of Pediatrics 2001).

5.11.3   Laboratory animal developmental toxicity

Cyclophosphamide induced birth defects and embryotoxicity in all animal species tested. The teratogenic effects observed in animal experiments included facial clefts, limb reduction, and eye defects. Chaube et al. (Chaube *et al.* 1968) administered cyclophosphamide by intraperitoneal injection at 7 to 10 mg/kg to pregnant Wistar rats on the 11th or the 12th day of gestation and reported skeletal malformations in their fetuses including retarded or clubbed legs, ectrodactyly, polydactyly, syndactyly, brachydactyly of the paws, absent or malformed (short or kinky) tails, and encephalocele or exencephaly. Gibson and Becker (Gibson and Becker 1968) administered single intraperitoneal injection of cyclophosphamide at 5, 10 or 20 mg/kg to pregnant Swiss Webster mice on gestation 9 through 14. They reported an increased numbers of resorptions and a variety of gross and skeletal teratogenic effects in the mouse fetuses following a single injection of 20 mg/kg/day on gestation days 9, 10, 11, 12 or 14 (Gibson and Becker 1968). The skeletal malformations included: cleft palate, exencephaly, kinky tail, polydactyly, syndactyly, ectrodactyly, adactyly, fusion of the long bones, curvature of the long bones, and missing ribs and the soft tissue malformations included: open eyes, aphakia, microphakia, hydronephrosis, and hydrocephalus. In contrast, an increase in resorptions and inhibited growth but no gross malformations were induced by doses of 5 and 10 mg/kg (Gibson and Becker 1968). In the rabbit, cyclophosphamide is both embryotoxic and teratogenic with the embryotoxic effects occurring following exposure during the early periods of embryonic development and teratogenic effects occurring following exposure in the later periods of organogenesis (Fritz and Hess 1971). A single intravenous injection of 30 mg cyclophosphamide/kg administered to pregnant rabbits induced: malformations in ventral neural tube closure in 10% of the fetuses (gestation day 7 exposure), cleft palate and malformations of jaws and lips in 30% of the fetuses (gestation day 11 exposure), oligodactyly (gestation day 12 exposure) and brachydactyly (gestation days 12 or 13 exposure) (Fritz and Hess 1971). These malformations are occurring during stages of increased embryonic nutrition, which is further illustrated by a decrease in average weight of fetuses exhibiting malformations (Fritz and Hess 1971).

In the primate, cyclophosphamide is both embryotoxic and teratogenic. Administration of cyclophosphamide (10 mg/kg) to pregnant Rhesus monkeys on gestation days 27 and 29 resulted in cleft lip and/or cleft palate, and exophthalmos in 6 of 10 offspring. In addition, one offspring had a kinky tail and another had partially fused eyelids and skeletal anomalies, including: fused ribs, missing ulna, missing several carpal bones and ectrosyndactyly of the left hand. Administration of cyclophosphamide (10 mg/kg) on gestation days 32-40 resulted in craniofacial dysmorphia (i.e., underdeveloped midfacial bones, highly arched closed palate) and/or either meningoencephalocele or persistent anterior fontanel (8 of 8 offspring) (McClure *et al.* 1979). Embryotoxicity occurred with exposure to higher doses of cyclophosphamide (20 mg/kg) or for a long duration (10 days of gestation) (McClure *et al.* 1979).

5.11.4   Human gestational exposure and effects

Cyclophosphamide is classified as FDA Pregnancy Category D. There were 405 published cases of patients treated with cyclophosphamide during pregnancy identified from 82 case reports, 14 case series, 4 retrospective case series, 10 retrospective surveys, 1 registry survey and 2 retrospective cohort studies (Appendix C Table 10). Among these patients, cyclophosphamide was used to treat breast cancer (n=268 cases), ovarian cancer (n=14 cases), uterine cancer (choriocarcinoma) (n=1 case), sarcoma (n=3 cases), Ewing sarcoma (n=3 cases), rhabdosarcoma (n=2 cases), undifferentiated sarcoma (n=1 case), adenoid cystic carcinoma (n=1 case), and vaginal (neuroendocrine) carcinoma (n=1 case). Cyclophosphamide was also used to treat hematological cancers including: acute lymphocytic leukemia (n=23 cases), acute myeloid leukemia (n=3 cases), multiple myeloma (n=1 case), Hodgkin lymphoma (n=9 cases), non-Hodgkin lymphoma (n=55 cases), Burkitt lymphoma (n=11 cases), large B-cell

lymphoma (n=1 case), B-cell lymphoma (n=2 case), T-cell leukemia/lymphoma (n=1 case), and subcutaneous panniculitis-like T-cell lymphoma (n=1 case).   In addition, cancer type was not specified in 4 cases. A total of 405 pregnancies and 408 conceptuses were exposed to cyclophosphamide due to three sets of twins {Lycette, 2006 #265;Nantel, 1990 #317;Reynoso, 1987 #372}. Cyclophosphamide was administered during the 1st trimester in 45 cases (46 conceptuses due to one set of twins {Reynoso, 1987 #372}) and the 2nd and/or 3rd trimester only in 360 cases (362 conceptuses due to two sets of twins {Lycette, 2006 #265;Nantel, 1990 #317}). The total number of cases exposed in the 2nd and/or 3rd trimester included 47 singleton pregnancies from two studies that did not specify individual timing of exposure during gestation, but were likely exposed during the 2nd and/or 3rd trimester. The gestational age at initiation of chemotherapy for the two studies ranged from 11-34 weeks (median 23 weeks) for 40 cases (Hahn *et al.* 2006) and 12-33 weeks (mean = 24 weeks) for 7 cases (Jameel and Jamil 2007).

Fetal loss occurred in 19 pregnancies exposed to cyclophosphamide, including four spontaneous abortions, seven induced abortions, and two intrauterine fetal death occurring following 1st trimester exposure. Spontaneous abortion occurred in four pregnancies following 1st trimester exposure and co-treatment with 5-fluorouracil and epirubicin (Giacalone *et al.* 1999) or 5-fluorouracil and methotrexate (Zemlickis *et al.* 1992), or exposure during the period of conception and 1st trimester with co-exposure to 5-fluorouracil and methotrexate (Ring *et al.* 2005) or co-exposure to vincristine (Zuazu *et al.* 1991). No fetal autopsy data were reported for any of the spontaneous abortions. Skeletal malformations were observed in the fetal autopsies of two induced abortions following exposure to cyclophosphamide in the 1st and 2nd trimesters. One fetus had syndactyly of the 1st and 2nd fingers of both hands, clinodactyly of the 5th finger, and syndactyly of the 4th and the 5th metatarsal bones of both feet among other skeletal malformations (Leyder *et al.* 2010). This pregnancy was also co-exposed to radiation therapy, 5-fluorouracil, and epirubicin in the 1st trimester and 5-fluorouracil and methotrexate in the 2nd trimester (Leyder *et al.* 2010). The second fetus terminated by induced abortion was missing the phalanges in both feet and had only a single left coronary artery (Toledo *et al.* 1971); co-treatments included radiation therapy in the 1st trimester. No fetal autopsy data were reported for the remaining 5 induced abortions performed in the 1st trimester (Chelghoum *et al.* 2005, Zuazu *et al.* 1991). Intrauterine fetal death occurred in one pregnancy exposed during the 1st trimester: polydactyly was observed in one stillborn exposed during the 1st trimester and co-treated with 6-mercaptopurine (Mulvihill *et al.* 1987). A second fetal death occurred at gestation week 25 after 1st trimester exposure and co-exposure to 5-fluorouracil and methotrexate {Peres, 2001 #354}.

Of the fetal losses occurring following exposure to cyclophosphamide in the 2nd and/or 3rd trimester only, there was one spontaneous abortion, two induced abortions, and three intrauterine fetal deaths. One spontaneous abortion occurred at 22 weeks gestation following exposure in the 2nd trimester and co-exposure to vincristine, doxorubicin, and dacarbazine (Jameel and Jamil 2007); no fetal autopsy data were reported. Autopsy following an induced abortion revealed a normal fetus following 2nd trimester exposure and co-exposed to methotrexate, intrathecally (Armitage *et al.* 1977). No fetal autopsy data were reported for other pregnancy terminated by induced abortion following 2nd trimester exposure (Zemlickis *et al.* 1992). Intrauterine fetal death occurred in three cases with exposure in the 2nd and/or 3rd trimester only. A normal fetus at autopsy was reported for a stillborn exposed during the 2nd and 3rd trimesters and co-exposed to doxorubicin, vincristine, and rituximab (Cardonick *et al.* 2010). Another pregnancy ending in stillbirth had experienced oligohydramnios and early intrauterine fetal growth restriction prior to death (Peterson *et al.* 2010). This pregnancy was exposed during the 2nd trimester and co-exposed to vincristine, doxorubicin, ifosfamide, etoposide, cytarabine, and rituximab; no autopsy data were provided. Finally, no fetal autopsy data were reported for the remaining stillborn, who was exposed during the 2nd trimester and co-exposed to epirubicin (Giacalone *et al.* 1999).

There were 386 live infants born following in utero exposure to cyclophosphamide, including 3 sets of twins. Congenital malformations were observed in 18 newborns, 9 infants with major malformations and 9 with minor malformations. Major malformations were observed in 4 infants exposed to cyclophosphamide during the 1st trimester. One infant exposed to cyclophosphamide during the 1st, 2nd and 3rd trimesters was born with cranial malformations (i.e., groove extending to the uvula on each side of the midline of the hard palate and a flattened nasal ridge), bilateral absence of one toe, 1st and 4th toes were larger than the middle toes, and his feet were wider at the heels and tapered to the toes (Greenberg and Tanaka 1964). The infant also had a small skin tag on the anterior mid-abdomen, a slightly hypoplastic middle phalanx of the fifth finger, and bilateral inguinal hernia sacs (Greenberg and Tanaka 1964). An imperforate anus and rectovaginal fistula were reported in an infant with 1st and 2nd trimester exposure and co-exposure to doxorubicin and cobalt therapy (Murray *et al.* 1984). Another infant suffered from microencephaly, bilateral ventriculomegaly and colpocephaly, a flat nasal bridge and high arched palate, and multiple skeletal malformations of the hands, including bilateral syndactyly of the 1st and 2nd fingers, and a cleft between the 2nd and 3rd (Paskulin *et al.* 2005). The infant was exposed during the period of conception and the 1st and 2nd trimester and co-exposed to doxorubicin and 5-fluorouracil (Paskulin *et al.* 2005). A male infant from a twin pregnancy was born with Madelung deformity of the right arm (i.e., an absent thumb, club hand, paraxial hemimelia), esophageal atresia, anomalous inferior vena cava, undescended testes and an extra pair of collecting systems for the kidneys (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). The female twin infant was normal and the pregnancy was exposed during the period of conception, 1st, 2nd and 3rd trimesters with no co-treatments (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). Inguinal hernia, a minor malformation, occurred in an infant exposed during the 1st and 2nd trimesters and co-exposed to 5-fluorouracil and methotrexate (Giannakopoulou *et al.* 2000).

Malformations were observed in 13 infants exposed to cyclophosphamide in the 2nd and/or 3rd trimester only. Major malformations were observed in 5 infants. In a registry survey, Cardonick et al. (Cardonick *et al.* 2010) reported the occurrence of three major malformations: pyloric stenosis (n=1 infant) following 2nd and 3rd trimester exposure and co-exposure to doxorubicin, then docetaxel; a small main pulmonary fistula (n=1 infant) following 2nd and 3rd trimester exposure and co-exposure to doxorubicin; and clubfoot as well as a left eye hemangioma (n=1 infant) following 2nd and 3rd trimester exposure and co-exposure to epirubicin. Down syndrome was reported in one infant and clubfoot in another following 2nd and/or 3rd trimester exposure and co-exposure to 5-fluorouracil and doxorubicin (Hahn *et al.* 2006). Minor malformations were reported in 8 infants exposed to cyclophosphamide in the 2nd and/or 3rd trimester only. Bilateral ureteral reflux was reported in an infant exposed in the 2nd and/or 3rd trimester exposure and co-exposed to 5-fluorouracil and doxorubicin (Hahn *et al.* 2006). A retrospective survey by Van Calsteren et al. (Van Calsteren *et al.* 2010) reported three infants with minor malformations following 2nd and 3rd trimester: hip subluxation in an infant co-exposed to doxorubicin, bilateral protuberance on phalanx 5 in an infant co-exposed to 5-fluorouracil and epirubicin, and double cartilage rings in both ears in an infant co-exposed to 5-fluorouracil, doxorubicin and radiation therapy. Hemangiomas were reported in two infants exposed to cyclophosphamide in the 2nd and 3rd trimesters and co-treated with vincristine, methotrexate, daunorubicin, asparaginase, and 6-mercaptopurine (Van Calsteren *et al.* 2010); and during the 2nd and/or 3rd trimester and co-exposed to either 5-fluorouracil and methotrexate or doxorubicin or epirubicin (Ring *et al.* 2005). Two infants had minor malformations that subsided over time. Suspected holoprosencephaly was diagnosed in a newborn exposed during the 2nd and 3rd trimesters and co-treated with doxorubicin and cytarabine (Cardonick *et al.* 2010). At age 2.6 years, this infant was normal with prominent lateral ventricles (Cardonick *et al.* 2010). Another infant had mild hydrocephalus, which was diagnosed prenatally three weeks after exposure to cyclophosphamide and doxorubicin in the 2nd trimester, and treated with

docetaxel beginning at gestation week 26 and into the 3rd trimester (Potluri *et al.* 2006). This case of mild hydrocephalus regressed spontaneously over several months. In addition, infant death occurred in 3 cases. One newborn died at age 8 days and the autopsy revealed no malformations (Giacalone *et al.* 1999). One infant died of septicemia at age 21 days (Aviles and Niz 1988). One infant, who had thrombocytopenia at birth, died at 13 months due to a severe autoimmune disorder (Cardonick *et al.* 2010).

A variety of pregnancy complications and infant health issues occurred following in utero exposure to cyclophosphamide. Polyhydramnios was observed in one pregnancy (Bayhan *et al.* 1999). There were three cases with oligohydramnios {Shieh, 2011 #1065}{Hansen, 2001 #105}{Meyer-Wittkopf, 2001 #293} and two cases reporting a reduction in amniotic fluid (Cordoba *et al.* 2010){Peterson, 2008 #1099}. Intrauterine growth retardation was observed in four pregnancies (Cordoba *et al.* 2010, Lambert *et al.* 1991, Peterson *et al.* 2010), including one case where intrauterine growth restriction was due to placental insufficiency (Ring *et al.* 2005). Fetal distress occurred in one pregnancy (Ali *et al.* 2009) and an abnormal cardiotocogram and low biophysical profile score occurred in another (Mavrommatis *et al.* 1998). Spontaneous preterm labor was reported in 24 cases , including a case that had "signs of premature delivery" (Andreadis *et al.* 2004) as well as and four cases with transient spontaneous preterm labor {Berrebi, 1983 #697}{Berry, 1999 #484}{Decker, 2006 #403}{Durodola, 1979 #218}{Giannakopoulou, 2000 #84}{Hansen, 2001 #105}{Huang, 2004 #112}{Kim, 1989 #134}{King, 1991 #137}{Martin, 1997 #277}{Meador, 1987 #283}{Meyer-Wittkopf, 2001 #293}{Moore, 1991 #718}{Nantel, 1990 #317}{Reynoso, 1987 #372}{Ring, 2005 #373}{Sharma, 2009 #391}{Webb, 1980 #906;Weed, 1979 #578}{Lycette, 2006 #265;Ortega, 1977 #335}{Brudie, 2011 #1094}. Preeclampsia occurred in 6 cases {Berry, 1999 #484}{Gonzalez-Angulo, 2004 #90}{Henderson, 1993 #533}{Kuerer, 2002 #495}{Lambert, 1991 #248}{Chakravarty, 2011 #860}, maternal hypotension occurred in one case {Turchi, 1988 #433}, and eclamptic seizures occurred in one case {Muller, 1996 #1332}. Spontaneous preterm rupture of membranes occurred in 9 cases {Ali, 2009 #709}{Bayhan, 1999 #663}{Ginopoulos, 2004 #668}{Huang, 2004 #112}{King, 1991 #137}{Meador, 1987 #283}{Okun, 1979 #691}{Udink ten Cate, 2009 #434}{Webb, 1980 #906}. Of the 151 pregnancies with data on age at delivery, early preterm delivery (<34 weeks) was reported for 36 pregnancies (23.8%), late preterm delivery (34-36 weeks) was reported for 50 pregnancies (33.1%), and 65 pregnancies were delivered at term (43.0%). One retrospective survey reported a premature infant, but no gestational age at delivery was provided and it was not include in the preterm tally (Chelghoum *et al.* 2005). Small for gestational age was reported for 12 newborns {Magloire, 2006 #268}{Berry, 1999 #484;Cardonick, 2010 #7;Dilek, 2006 #212;Giacalone, 1999 #78}.

Respiratory difficulties were reported for 37 infants for effects ranging from respiratory distress (n=18 infants) (Achtari and Hohlfeld 2000, Ali *et al.* 2009, Berrebi *et al.* 1983, Berry *et al.* 1999, Cardonick *et al.* 2010, Cordeiro *et al.* 2009, Giacalone *et al.* 1999, Giannakopoulou *et al.* 2000, Ginopoulos *et al.* 2004, Haerr and Pratt 1985, Kerr 2005, King *et al.* 1991, Lam 2006, Mavrommatis *et al.* 1998, Ring *et al.* 2005), transient tachypnea (n=7) (Berry *et al.* 1999, Cardonick *et al.* 2010)), breathing difficulties (n=11 (Hahn *et al.* 2006)), and oxygen required due to meconium aspiration (n=1 infant) (Hansen *et al.* 2001). A total of 19 newborns were diagnosed with transient myelosupression, including: anemia (Cardonick *et al.* 2010, Udink ten Cate *et al.* 2009, Zuazu *et al.* 1991){Aviles, 1988 #772}, leucopenia (Berry *et al.* 1999, Cardonick *et al.* 2010, Giacalone *et al.* 1999, Khurshid and Saleem 1978, Udink ten Cate *et al.* 2009){Garcia, 1999 #69}, an absence or decrease of B-cells (Chakravarty *et al.* 2011, Decker *et al.* 2006, Friedrichs *et al.* 2006), neutropenia (Cardonick *et al.* 2010, Giacalone *et al.* 1999, Hahn *et al.* 2006, Udink ten Cate *et al.* 2009), thrombocytopenia (Cardonick *et al.* 2010, Hahn *et al.* 2006, Udink ten Cate *et al.* 2009), and severe myelosuppression (Okun *et al.* 1979). Hyperbilirubinemia or jaundice were reported for 12 infants (Cardonick *et al.* 2010, Dreicer and Love 1991, Hansen *et al.* 2001, Kerr 2005, Lambert *et*

al. 1991). One infant had tachycardia {King, 1991 #137}, and two newborns were treated for acute cardiac failure (Achtari and Hohlfeld 2000), including one infant who also had slight cardiomegaly, an enlarge spleen, a petechial rash and was hydropic (Okun *et al.* 1979). The other infant had a ventricular hemorrhage and was treated for necrotizing enterocolitis (Achtari and Hohlfeld 2000). Another infant had a subarachnoid hemorrhage (Hahn *et al.* 2006). Meconium aspiration syndrome was reported for two infants (Cardonick *et al.* 2010, Hansen *et al.* 2001) and gastroesophageal reflux or difficulty in feeding occurred in three other infants (Cardonick *et al.* 2010). One newborn was hypoglycemic (Kerr 2005) and another required intravenous calcium (Haerr and Pratt 1985). One infant had abnormal serum protein electrophoretic patterns and high gamma globulin levels at birth (Lergier *et al.* 1974); the infant had normal serum protein electrophoretic results at age 28 months. Chromosomal breakage and a ring chromosome were observed in an otherwise normal newborn (Schleuning and Clemm 1987). The remaining health effects included: omphalitis (Cordeiro *et al.* 2009), urinary tract infection (Udink ten Cate *et al.* 2009), sepsis (Cardonick *et al.* 2010), hair loss (Berry *et al.* 1999), and necrotizing enterocolitis that was successfully treated {Garcia, 1999 #69}.

Follow up evaluations were available for 282 infants at ages ranging from 6 weeks to 22 years, including 4 children for which age at follow up was not specified {Huang, 2004 #112}{Khurshid, 1978 #818}{Murray, 1984 #503}{Ohara, 2000 #653}. Normal health and development were reported for all with the exception of 8 children. Delays in development were noted for 5 children, including one with Down syndrome (Hahn *et al.* 2006), two with developmental delay (Cardonick *et al.* 2010, Lam 2006), one with motor development delay (Paskulin *et al.* 2005), and one child with learning problems at 11 years (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). The child with learning problems at age 11 years was treated for papillary thyroid cancer at this age, followed by surgery to correct undescended testicles at 13 years, and had a ruptured neuroblastoma in his adrenal gland at age 14 years, and metastatic thyroid cancer at age 16 years; he also had severe anemia at ages 2 to 4 years. At age 17 years, he was free of thyroid cancer (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). His twin sister had normal growth and development. She had surgery to correct strabismus (cross-eyedness) at age 9 and was healthy at age 22 years (Zemlickis *et al.* 1993). Another child, who had hypocapnia as a newborn, was diagnosed with periventricular leukomalacia at age 2 months and had developmental delay (Cardonick *et al.* 2010). Speech delay was diagnosed in two other children (Cardonick *et al.* 2010). Other health problems included: otitis media (n=3 children), mild hearing loss with recurrent otitis media (n=1 child), reactive airway disease (n=2 children), selective IgA deficiency not requiring treatment, and one child with gastroesophageal reflux, eczema, and sinusitis (Cardonick *et al.* 2010).

5.11.5 *Summary of pregnancy outcomes for cyclophosphamide*

In utero exposure to cyclophosphamide was documented for 405 pregnancies for a total of 408 conceptuses, including three sets of twins. Of the 45 pregnancies (46 conceptuses due to 1 set of twins) exposed to cyclophosphamide during the 1st trimester, major malformations were observed in four live-born infants and three pregnancies ending in fetal loss. One infant was born with cranial malformations (i.e., groove extending to the uvula on each side of the midline of the hard palate and a flattened nasal ridge), bilateral absence of one toe, 1st and 4th toes that were larger than the middle toes, feet that were wider at the heels and tapered to the toes, as well as a small skin tag on the anterior mid-abdomen, a slightly hypoplastic middle phalanx of the fifth finger, and bilateral inguinal hernia sacs (Greenberg and Tanaka 1964). An imperforate anus and rectovaginal fistula were reported in another infant (Murray *et al.* 1984). An infant suffered from microencephaly, bilateral ventriculomegaly and colpocephaly, a flat nasal bridge and high arched palate, and multiple skeletal malformations of the hands, including bilateral syndactyly of the 1st and 2nd fingers, and a cleft between the 2nd and 3rd (Paskulin *et al.* 2005). A male infant from a twin pregnancy was born with Madelung's deformity of the right arm, esophageal

atresia, anomalous inferior vena cava, undescended testes and an extra pair of collecting systems for the kidneys (Zemlickis *et al.* 1993); the female twin sibling had no malformations. Inguinal hernia, a minor malformation, occurred in one infant exposed during the 1st trimester (Giannakopoulou *et al.* 2000). Skeletal malformations were observed in the fetal autopsies of two induced abortions following exposure during the 1st trimester: one fetus had bilateral syndactyly of the 1st and 2nd fingers, clinodactyly of the 5th finger, and bilateral syndactyly of the 4th and 5th metatarsal bones among other skeletal malformations (Leyder *et al.* 2010), and the other fetus was missing the phalanges in both feet and had only a single left coronary artery (Toledo *et al.* 1971). Polydactyly was observed in the one case of intrauterine fetal death following 1st trimester exposure (Mulvihill *et al.* 1987). No fetal autopsy data were reported for the remaining 5 induced abortions (Chelghoum *et al.* 2005, Zuazu *et al.* 1991), 4 spontaneous abortions (Giacalone *et al.* 1999, Ring *et al.* 2005, Zemlickis *et al.* 1992, Zuazu *et al.* 1991), and one intrauterine fetal death {Peres, 2001 #354} of pregnancies that were exposed during the 1st trimester. A total occurrence of major malformations following 1st trimester exposure to cyclophosphamide was 15.2% (7/46 conceptuses).

Of the 360 pregnancies (362 conceptuses, including two sets of twins) exposed to cyclophosphamide during the 2nd and/or 3rd trimester only, major malformations were observed in five infants. Cardonick et al. (Cardonick *et al.* 2010) reported the occurrence of pyloric stenosis (n=1 infant), a small main pulmonary fistula (n=1 infant), and clubfoot (n=1 infant). Down syndrome (n=1 infant) and clubfoot (n=1 infant) were reported in a case series by Hahn et al. (Hahn *et al.* 2006). Minor malformations were observed in 8 infants exposed in the 2nd and/or 3rd trimester only. One infant each had bilateral ureteral reflux (Hahn *et al.* 2006), hip subluxation, bilateral protuberance on phalanx 5, and double cartilage rings in both ears (Van Calsteren *et al.* 2010). Two infants had hemangiomas (Ring *et al.* 2005, Van Calsteren *et al.* 2010). Two minor malformations resolved over time. One newborn was diagnosed with suspected holoprosencephaly (Cardonick *et al.* 2010); however, at age 2.6 years, the child had prominent lateral ventricles but was otherwise normal. One infant had mild hydrocephalus, which was diagnosed prenatally three weeks after exposure to chemotherapy, and regressed over several months (Potluri *et al.* 2006). In addition, a normal fetus was observed in the autopsy of an induced abortion occurring following 2nd trimester exposure (Armitage *et al.* 1977). No fetal autopsy data were reported for the spontaneous abortion (Jameel and Jamil 2007) and a second induced abortion (Zemlickis *et al.* 1992) occurring after exposure in the 2nd and/or 3rd trimester only. There were three stillbirths following 2nd and/or 3rd trimester exposure: one normal fetus at autopsy (Cardonick *et al.* 2010) and two stillbirths with no autopsy data reported (Giacalone *et al.* 1999, Peterson *et al.* 2010). A total occurrence of major malformations following exposure to cyclophosphamide in the 2nd and/or 3rd trimester only was 1.4% (5/353 conceptuses).

The most frequently occurring pregnancy complications observed following cyclophosphamide exposure during pregnancy included: oligohydramnios or a reduction in amniotic fluid (n=5 pregnancies) and intrauterine growth retardation (n=4 pregnancies). Preterm birth was reported for 86 of 151 pregnancies with gestational age at delivery data. Small for gestational age was reported for 12 newborns {Magloire, 2006 #268}{Berry, 1999 #484;Cardonick, 2010 #7;Dilek, 2006 #212;Giacalone, 1999 #78}. One infant had tachycardia {King, 1991 #137} and two infants were treated for cardiac failure {Achtari, 2000 #30;Okun, 1979 #691}. Common infant health effects observed following cyclophosphamide exposure during pregnancy included: respiratory difficulties (n=37 infants), transient myelosuppression (n=19 infants), and jaundice/hyperbilirubinemia (n=12 infants). In addition, there were three infant deaths: one newborn died at age 8 days of unidentified causes (Giacalone *et al.* 1999), one infant died of septicemia at age 21 days (Aviles and Niz 1988) and a third infant, who had thrombocytopenia at birth, died due to severe autoimmune disorder at age 13 months (Cardonick *et al.*

2010). Follow-up examinations of 282 children at ages ranging from 6 weeks to 22 years reported normal growth and development in all but 8 children. Delays in development were noted for 5 children, including one with Down syndrome (Cardonick *et al.* 2010, Hahn *et al.* 2006, Lam 2006, Paskulin *et al.* 2005, Zemlickis *et al.* 1993). One child with learning problems at age 11 years was treated was also treated for papillary thyroid, followed by surgery to correct undescended testicles at 13 years, treated for a ruptured neuroblastoma in his adrenal gland at age 14 years and metastatic thyroid cancer at age 16 years of which he had suffered two reoccurrences by age 22 {Reynoso, 1987 #372}(Zemlickis *et al.* 1993); his female twin sibling was normal. Another child with developmental delay was diagnosed with periventricular leukomalacia at age 2 months and was improving with occupational and physical therapy (Cardonick *et al.* 2010). Other follow-up health issues included: speech delay (n=2 children), ear infections (n=4 children, including one with mild hearing loss), reactive airway disease (n=2 children), selective IgA deficiency not requiring treatment, and one child with gastroesophageal reflux, eczema, and sinusitis (Cardonick *et al.* 2010).

In conclusion, the total occurrence of major malformations in cyclophosphamide-exposed pregnancies was 2.9% (12/408 conceptuses). Exposure to cyclophosphamide in the 1st trimester induced a 5-fold higher prevalence of major malformations (7/46 conceptuses) than the prevalence in the general population (15.2 ± 10.4% versus 3%). The occurrence of major malformations following exposure to cyclophosphamide in the 2nd and/or 3rd trimester only (5/360 conceptuses) was similar to the prevalence of birth defects in the general population (1.4 ± 1.2% versus 3%). At least two of these major malformations, Down syndrome and the pulmonary artery fistula, were unlikely to have resulted from chemotherapy exposure in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations following exposure to cyclophosphamide in the 2nd and/or 3rd trimester only was 0.8 ± 0.9% (3/360 conceptuses).

5.12 CYTARABINE (Cytosine arabinoside)

5.12.1 Mechanism of action, route of administration, and indications

Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells during the S-phase. Intracellularly, cytarabine is converted to the active metabolite cytarabine-5'-triphosphate (ara-CTP). Its primary mechanism of action is thought to be through inhibition of DNA polymerase. It is also incorporated into DNA and RNA, impairing synthesis and function. Cytarabine is administered by intravenous, subcutaneous or intrathecal (directly into cerebrospinal fluid) injection. Cytarabine is indicated for acute lymphocytic leukemia, acute non-lymphocytic leukemia and the blast phase of chronic myelogenous leukemia. Intrathecal injection of cytarabine is indicated in the treatment and prophylaxis of meningeal leukemia (Hospira 2008).

5.12.2 Evidence of placental and breast milk transport

There are no published reports of placental or breast milk transfer of cytarabine in humans. However, Van Calsteren et al. (Van Calsteren *et al.* 2010) reported that, in a mouse model, cytarabine crosses the placenta. Pregnant dams were administered 100 mg/kg cytarabine by injection in the tail vein. Ninety minutes later fetuses were collected. At this single time point, maternal plasma contained 19.0 ng/mL cytarabine while fetal plasma contained 9.2 ng/mL. Likewise, no published animal studies of the presence of cytarabine in breast milk were located.

5.12.3 Laboratory animal developmental toxicity

According to the manufacturer product label, cytarabine is teratogenic in mice, inducing cleft palate, phocomelia, deformed appendages, and skeletal abnormalities at doses ≥2 mg/kg/day administered intraperitoneally during organogenesis (about 0.2 times the recommended human dose on mg/m^2 basis) (SkyePharma 2006). In rats, cytarabine induced deformed appendages when 20 mg/kg was administered as a single intraperitoneally dose on day 12 of gestation (about 4 times the recommended human dose on mg/m^2 basis). In rats administered single intraperitoneally doses of 50 mg/kg (about 10 times the recommended human dose on mg/m^2 basis) on day 14 of gestation, reduced prenatal and postnatal brain size and permanent impairment of learning ability were observed. When administered to mice during the period of organogenesis, embryotoxicity was characterized by decreased fetal weight at 0.5 mg/kg/day (about 0.05 times the recommended human dose on mg/m^2 basis), and increased early and late resorptions. Decreased live litter sizes at 8 mg/kg/day were observed (approximately equal to the recommended human dose on mg/m^2 basis) (SkyePharma 2006).

In other studies, cytarabine has been shown to induce teratogenic effects in mice, rats, and chicks, including skeletal defects, cleft palate, cerebellar hypoplasia, microcytic renal changes, and retinal dysplasia. Percy et al. (Percy 1975) reports that treatment of pregnant ICR Swiss mice and Spraque-Dawley rats by subcutaneous injection of 12.5, 25 or 50 mg/kg/day cytosine arabinoside on 3 consecutive days, beginning GD 16 in mice and GD 18 in rats, resulted in segmental cerebellar hypoplasia and focal microcyctic renal cortical dysplasia in both rats and mice as well as retinal dysplasia in rats exposed to 50 mg/kg /day cytosine arabinoside. As reviewed in Shepard et al. (Shepard and Lemire 2004), rats administered oral doses of cytarabine on days 7-17 with doses up to 10 mg/kg and found fetal toxicity and digital defects. No effects were observed at the 1.6 mg/kg dose. Also summarized in Shepard et al. (Shepard and Lemire 2004), cleft palate and skeletal defects were observed in the fetuses of rats and mice administered cytarabine intravenously to pregnant dams at doses ranging from 1.5 to 15 mg/kg on gestation days 7-12 in the mouse and 15-60 mg **[not specified if doses were on a mg/kg basis]** on gestation day 9-14 in the rat. Pregnant CD-1 (ICR) mice treated with a

single intraperitoneal injection of cytarabine at 5 mg/kg on gestation day 11 resulted in fetal malformations, including oligodactyly in forelimbs and polydactyly in hindlimbs (Endo *et al.* 1987). Digit malformations occurred in offspring following a single intraperitoneal dose of cytarabine at 2.5, 5 or 10 mg/kg to pregnant Jc1:ICR mice on gestation day 9.5 or 10.5 (Goto and Endo 1987). Swiss mice treated with an intraperitoneal injection on gestation days 6-15 with doses of 0, 0.5, 2 and 8 mg cytarabine/kg/day resulted in decreased fetal body weight at 8 mg/kg/day and increased cleft palate, renoureteral agenesis or hypoplasia and poly- or oligodactyly at 2 mg/kg/day dose (Ortega *et al.* 1991). Intraperitoneal treatment of Wistar rats with cytarabine at 50 mg/kg on gestation day 12 resulted in 8% resorptions and 7% of the survivors having malformations, including: brachydactyly, ectrodactyly, syndactyly, polydactyly, and kinky tail. Treatment on gestation day 10 resulted in 6% resorptions and only 5% of survivors had malformations, which included fused ribs and heart defects (Ritter 1984). In addition, pregnant Wistar rats treated with a single intraperitoneal injection of a dose range of cytarabine (20-800 mg/kg) on gestation day 11 or 12, induced malformations including: cleft palate, retarded/clubbed fore or rear leg and missing or short fingers and toes (Chaube *et al.* 1968). Various skeletal changes of the forepaw and hindpaw occurred in the offspring of pregnant Jcl:ICR mice treated with a single intraperitoneal dose of 5 mg cytarabine/kg on gestation day 10.5, including: forelimb oligodactyly (46%), hindlimb oligodactyly (25%), hindlimb polydactyly (10%) and anomalies of the carpal and tarsal bones (i.e., fusion, absence and deformation) (Rahman *et al.* 1994). Finally, development of the chick embryo was inhibited by an injection of 0.025 mg cytarbine/egg on Day 4 of incubation. Surviving embryos were stunted and had abnormalities of the facial coloboma, absence of the pelvic skeleton and other bone deletions, corneal cysts and feather inhibition. Embryos exposed to cytarabine later in development, day 8 of incubation, exhibited less severe abnormalities, including: feather disturbances, weight inhibition and cerebellar atrophy (Karnofsky and Lacon 1966).

5.12.4 *Human gestational exposure and effects*

Cytarabine is classified as FDA Pregnancy Category D. There were 148 patients treated for cancer using cytarabine identified from 45 case reports, 18 case series, 4 retrospective case series, 5 retrospective surveys, 2 retrospective cohort study and 1 retrospective survey (Appendix C Table 11). Among these patients, cytarabine was primarily used to treat acute myelogenous leukemia (also called acute granulocytic leukemia; n=101 cases) as well as acute promyelogenous leukemia (n=7 cases), erthyroleukemia (n=1 case), acute lymphocytic leukemia (n=16 cases), and acute leukemia (type not specified; n=4 cases). In addition, cytarabine was used to treat chronic myelogenous leukemia (also called chronic granulocytic leukemia; n=4 cases), Hodgkin lymphoma (n=1 case), non-Hodgkin lymphoma (n=9 cases), Burkitt lymphoma (n=2 cases), and cancer of the breast (n=1 case), cervix (n=1 case) and lung (n=1 case). A total of 148 singleton pregnancies (151 conceptuses) were exposed to cytarabine; three patients had two pregnancies each (Aviles and Niz 1988, Scherf and Price 1996). Cytarabine was administered during the 1st trimester in 32 pregnancies, and in the 2nd and/or 3rd trimester in 118 pregnancies. The timing of exposure was not specified for 1 pregnancy.

Fetal loss occurred in 35 pregnancies following in utero exposure to cytarabine, including 5 spontaneous abortions, 7 induced abortions, 1 intrauterine fetal death and 1 maternal death following exposure in the 1st trimester. Of the spontaneous abortions, 5 pregnancies ended following 1st trimester exposure and co-treatment with: daunorubicin only (n=1 pregnancy) (Zuazu *et al.* 1991), daunorubicin and all-trans retinoic acid (n=1 pregnancy) or daunorubicin and mitoxantrone (n=1 pregnancy) (Chelghoum *et al.* 2005), or with vincristine and doxorubicin (n=1 pregnancy) (Awidi *et al.* 1983) or vincristine and 6-thioguanine (n=1 pregnancy) (Zuazu *et al.* 1991). No fetal autopsy data were available for these five spontaneous abortions. Induced abortion terminated 7 pregnancies following exposure during the 1st trimester. Autopsy revealed a normal fetus from an induced abortion following 1st and 2nd trimester

exposure and co-exposure to daunorubicin, vincristine and 6-thioguanine (Lilleyman *et al.* 1977). Normal chromosomes were observed in an induced abortus that was exposed during the period of conception and 1st trimester and co-exposed to 6-thioguanine (Maurer *et al.* 1971). No fetal data were provided for the remaining 5 induced abortions following 1st trimester exposure (Chelghoum *et al.* 2005){Zemlickis, 1992 #576}. Intrauterine fetal demise occurred in one pregnancy following exposure in the 1st trimester and co-treated with daunorubicin and all-*trans* retinoic acid (Chelghoum *et al.* 2005); no fetal data were provided. Maternal death at 23 weeks gestation revealed a normal fetus following exposure in the 1st and 2nd trimesters and co-exposure to daunorubicin, vincristine, and 6-mercaptopurine (Feliu *et al.* 1988).

There were 20 cases of fetal loss following exposure in the 2nd and/or 3rd trimester only, including 1 spontaneous abortion, 7 induced abortions, 11 intrauterine fetal deaths and 1 maternal and fetal death. Only one spontaneous abortion occurred following 2nd trimester exposure (Ali *et al.* 2003); the pregnancy was co-exposed to daunorubicin and no fetal data were reported. Gross evaluation of an induced abortus revealed a normal fetus with an enlarged spleen following 2nd trimester exposure and co-exposure to daunorubicin, vincristine, 6-thioguanine and hydroxyurea (Doney *et al.* 1979). Abnormal chromosomes were observed in an induced abortus exposed in the 2nd trimester and co-exposed to 6-thioguanine (Maurer *et al.* 1971). No fetal data were provided for the remaining five induced abortions (Chelghoum *et al.* 2005). Normal fetuses were observed following intrauterine fetal death in 7 pregnancies exposed in utero to cytarabine, including: 2nd trimester exposure and co-exposure to daunorubicin (Ali *et al.* 2003), 2nd trimester exposure and co-treatment with 6-thioguanine (Plows 1982), 2nd trimester exposure and co-exposure to daunorubicin and 6-thioguanine (Volkenandt *et al.* 1987), exposure in the 2nd and 3rd trimesters and co-exposure to daunorubicin and 6-thioguanine(O'Donnell *et al.* 1979), and 3rd trimester exposure and co-exposure to daunorubicin, 6-thioguanine and vincristine (Zuazu *et al.* 1991). Normal fetuses were observed in two other intrauterine fetal deaths: one pregnancy exposed 2nd and 3rd trimester and co-exposed to daunorubicin, mitoxantrone, and idarubicin (Reynoso and Huerta 1994). Another intrauterine death of normal fetus with brusing and petechia in multiple areas followed exposure in the 2nd trimester and co-exposure to 6-thioguanine and doxorubicin {Zemlickis, 1992 #576}. One intrauterine fetal death was preceded by oligohydramnios and early intrauterine growth restriction following 2nd trimester exposure and co-exposure to cyclphosphamide, doxorubicin, ifosfamide, etoposide, vincristine, and rituximab (Peterson *et al.* 2010); no fetal autopsy data were reported. No fetal autopsy data were reported for the three remaining intrauterine fetal deaths following: 2nd trimester exposure and co-treatment with daunorubicin (Greenlund *et al.* 2001), 2nd trimester exposure and co-treatment with daunorubicin, vincristine, asparaginase, and methotrexate (intrathecal) (Molkenboer *et al.* 2005), and 2nd and 3rd trimester exposure and co-exposure to fludarabine and idarubicin (Paşa *et al.* 2009). Ten of the 11 intrauterine fetal deaths followed 2nd and/or 3rd only trimester exposure of cytarabine plus an anthracycline antibiotic (8 with daunorubicin, 1 with idarubicin, and 1 with doxorubicin), with the exception of one conceptus exposed to cytarabine and idarubicin in which timing of exposure was not specified (Peres *et al.* 2001).] One maternal and fetal death occurred at approximately gestation week 24 following 2nd trimester exposure; no fetal autopsy data were provided {Greenlund, 2001 #93} and one intrauterine fetal death occurred in another pregnancy co-exposed to daunorubicin and idarubicin for which timing of exposure was not specified; the fetus was normal (Peres *et al.* 2001).

Of the 116 live-born infants, malformations were observed in 10 infants exposed in utero to cytarabine. Major malformations were reported in 8 newborns. One newborn had multiple cranial and skeletal defects and a small ostium secundum atrial septal defect (Artlich *et al.* 1994); the infant was exposed during the period of conception and 1st trimester; co-treatments included daunorubicin, 6-thioguanine,

and doxorubicin around the period of conception and 6-thioguanine in the 1st trimester. The skeletal malformations included: choanal stenosis, brachiocephaly, hypoplasia of several cranial structures and premature closure of cranial sutures as well as bilateral 4-fingered hands with hypoplastic thumbs and bilateral absent radii. Another newborn had an atrial septal defect and bilateral loss of the radius and 5th digit following exposure during the period of conception and 1st trimester and co-exposure to vincristine and doxorubicin (Ebert *et al.* 1997). Distal limb defects were reported in an infant following exposure during the period of conception through pregnancy and co-treated with 6-thioguanine (Schafer 1981). The malformations included: the absence of the medial two digits of each foot, the absence of the distal phalanges of both thumbs, and a hypoplastic remnant of the right thumb (Schafer 1981). Multiple skeletal defects occurred in another infant following exposure during the period of conception and the 1st trimester (Wagner *et al.* 1980). The malformations included: bilateral microtia and atresia of the auditory canals, right hand had a lobster claw with only 3 digits, each leg had a malformed femur and only one bone in the lower leg (instead of two), and each foot was composed of an os calcis and only two lateral metatarsals (Wagner *et al.* 1980). Four additional infants had major malformations following 2nd and/or 3rd trimester exposure. A ventricular septal defect, requiring surgery at 5 months, was observed in a newborn that also had a shallow sacral dimple, short digits and limbs, dysplastic fingernails, and a prominent frontal skull with macrognathia (Niedermeier *et al.* 2005); this infant was exposed in the 2nd trimester and co-exposed to idarubicin. Down syndrome was diagnosed in a newborn exposed the 2nd and 3rd trimesters and co-exposed to daunorubicin (Roy *et al.* 1989). Polydactyly occurred in an infant with a family history of this condition; this infant had six toes on his right foot and was exposed in the 3rd trimester and co-treated with daunorubicin and 6-thioguanine (Volkenandt *et al.* 1987). Hypospadias occurred in a newborn exposed in the 3rd trimester and co-treated with daunorubicin (De Carolis *et al.* 2006). Minor malformations were observed in two infants. Congenital adherence of the iris to the cornea was diagnosed in a 2-year old infant, who had been exposed in the 3rd trimester and co-treated with daunorubicin and 6-thioguanine (Reynoso *et al.* 1987). One infant suffered from bilateral hydronephrosis and dilation of the proximal ureter of the left kidney (Garcia *et al.* 1999); this infant was exposed in the 2nd and 3rd trimesters and co-exposed to daunorubicin and mitoxantrone. One additional health anomaly was observed: chromosomal breakage and a ring chromosome in an otherwise normal infant (Schleuning and Clemm 1987).

A variety of pregnancy complications and infant health effects were reported following in utero exposure to cytarabine. Polyhydramnios occurred in one pregnancy (Artlich *et al.* 1994). Oligohydramnios occurred in four pregnancies (Garcia *et al.* 1999, Hansen *et al.* 2001, Matsuo *et al.* 2004, Peres *et al.* 2001, Peterson *et al.* 2010) and two pregnancies experienceda reduction in amniotic fluid (Scherf and Price 1996){Peterson, 2008 #1099}. Ten pregnancies reported inhibited fetal growth following chemotherapy administration, including intrauterine fetal growth restriction (Baumgartner *et al.* 2009, Claahsen *et al.* 1998, D'Emilio *et al.* 1989, Garcia *et al.* 1999, Hsu *et al.* 1995, Peres *et al.* 2001, Peterson *et al.* 2010), poor fetal growth (Murray *et al.* 1994) and a cessation of fetal growth (Roy *et al.* 1989, Scherf and Price 1996). **[Murray et al. (Murray *et al.* 1994) and Scherf et al. (Scherf and Price 1996) appear to be the same case, but are considered as two separate case reports in this evaluation.]** Fetal cardiac effects were observed in 2 pregnancies, including cardiomyopathy (Baumgartner *et al.* 2009) and fetal tachycardia (Garcia *et al.* 1999). Transient cerebral ventriculomegaly occurred in one fetus experiencing cardiomyopathy (Baumgartner *et al.* 2009). In addition, fetal distress was reported in 4 pregnancies {Claahsen, 1998 #197;Hsu, 1995 #111}{Veneri, 1996 #665;Yucebilgin, 2004 #459}. Other pregnancy complications included: preeclampsia (n=2 cases) {Bartsch, 1988 #615}{Potluri, 2006 #361}, premature rupture of membranes (n=2 cases) {Udink ten Cate, 2009 #434;Volkenandt, 1987 #442}, and spontaneous preterm labor (n=9 cases) {Doney, 1979 #215}{Fassas, 1984 #231}{Hansen, 2001 #105}{Reynoso, 1987 #372}{Taylor, 1980 #648;Tobias, 1980 #546}{Yucebilgin, 2004 #459}. Labor was

induced in one case because patient was seriously ill (Roy *et al.* 1989). Of the 99 pregnancies reporting age at delivery, 25 pregnancies were delivered early preterm (<34 weeks; 25.3%), 29 pregnancies were delivered late preterm (34-36 weeks; 29.3%), and 45 pregnancies were delivered at term (45.5%). In addition, one retrospective survey reported that three infants were premature; **[however the authors did not provide individual age at delivery data, so this case was not included in the tally]** (Chelghoum *et al.* 2005). No newborns were reported to be small for gestational age. Breathing difficulties occurred in 12 newborns (Baumgartner *et al.* 2009, De Carolis *et al.* 2006, Delgado-Lamas and Garces-Ruiz 2000, Dilek *et al.* 2006, Garcia *et al.* 1999, Lam 2006, Murray *et al.* 1994, Scherf and Price 1996, Veneri *et al.* 1996), including one infant with respiratory distress due to choanal stenosis and pneumothorax (Artlich *et al.* 1994) and another infant with bilateral pneumothorax and seizures (Cantini and Yanes 1984). One infant also had cyanosis of the extremities (Niedermeier *et al.* 2005). One infant born at 28 weeks of gestation developed respiratory distress and died at age 1 day (Dilek *et al.* 2006). Transient myelosuppression was reported in 12 newborns {Aviles, 1988 #772}(Aviles *et al.* 1991, Baumgartner *et al.* 2009, Doney *et al.* 1979, Garcia *et al.* 1999, Hsu *et al.* 1995, Matsuo *et al.* 2004, Murray *et al.* 1994, Peres *et al.* 2001, Scherf and Price 1996, Udink ten Cate *et al.* 2009). One infant had polycythemia (Dara *et al.* 1981), another had low hemoglobin (Gulati *et al.* 1986) and 4 infants had jaundice (Dara *et al.* 1981, Hansen *et al.* 2001, Peres *et al.* 2001){Au-Yong, 1972 #780}. Two infants suffered from meconium aspiration (Hansen *et al.* 2001, Yucebilgin *et al.* 2004), and the amniotic fluid was meconium-stained in the delivery of another infant (Claahsen *et al.* 1998). Other health effects observed in newborns included: failure to thrive in an infant with a moderate meningeal hemorrhage, hyponatremia and hypoglycemia (n=1 infant) (Garcia *et al.* 1999), elevated creatinine and transient hepatopathy (n=1 infant) (Matsuo *et al.* 2004), and hypocalcemia (Doney *et al.* 1979). Neonatal death was reported for two additional infants: one infant died of septicemia at age 21 days and another infant died of gastroenteritis at 90 days of age (Aviles and Niz 1988).

Follow-up evaluations were available for 77 infants at ages from 5 months to 15 years. Normal growth and development were reported for all but two children {Requena, 1995 #369}{Chelghoum, 2005 #193}. One child each had mild developmental delay at age 1 year (Lam 2006), failure to thrive and finally gaining weight at age 3 months (Garcia *et al.* 1999), and body weight at <10th percentile at age 26 months with a constant cold (Gulati *et al.* 1986). Other children showed progress including: one child with expressive speech delay that was showing improvement with therapy (age, group mean = 62 ± 22 months) (Cardonick *et al.* 2010), another child recovered quickly from surgery to repair a ventricular septal defect (Niedermeier *et al.* 2005), and another infant at 6 months of age had no detectable hydrocephalus or heart problems following a prenatal diagnosis of ventriculomegaly and cardiomyopathy in utero following exposure to cytarabine and co-treatments (Baumgartner *et al.* 2009). In addition, one infant with a normal blood count at birth had elevated leukocyte counts and a differential count that was lymphocytic with occasional nucleated red blood cells at 3-4 months of age (Fassas *et al.* 1984); by 20 to 30 months of age, the child had normal blood counts.

5.12.5 *Summary of pregnancy outcomes for cytarabine*

In utero exposure to cytarabine was documented for 148 singleton pregnancies (151 conceptuses). Of the 32 pregnancies (32 conceptuses) exposed to cytarabine during the 1st trimester, four live-born infants had major malformations. Multiple cranial and skeletal defects and a small ostium secundum atrial septal defect occurred in an infant who was exposed during the period of conception and 1st trimester (Artlich *et al.* 1994). Another newborn had an atrial septal defect and bilateral loss of the radius and 5th digit following exposure during the period of conception and 1st trimester (Ebert *et al.* 1997). Malformations of the digits of the hands and feet were reported in an infant following exposure during the period of conception through pregnancy (Schafer 1981). A fourth live-born infant, who was

exposed during the period of conception and into the 1st trimester, had bilateral microtia and absence of the ear canals, deformed right hand with only three fingers, bilateral malformed femurs and only one bone in the lower leg (instead of two), and missing bones in each foot (Wagner *et al.* 1980). In addition, fetal loss occurred in 13 cases exposed during the 1st trimester to cytarabine. Spontaneous abortions were reported for five pregnancies and no fetal data were reported (Awidi *et al.* 1983, Chelghoum *et al.* 2005, Zuazu *et al.* 1991). Induced abortion terminated 7 pregnancies with exposure in the 1st trimester and no fetal data were provided for 5 of these pregnancies (Chelghoum *et al.* 2005){Zemlickis, 1992 #576}. One induced abortion had a normal fetus at autopsy (Lilleyman *et al.* 1977) and another induced abortion reported a fetus with normal chromosomes (Maurer *et al.* 1971). Intrauterine fetal demise occurred in one pregnancy following exposure in the 1st trimester and co-treated with daunorubicin and all-*trans* retinoic acid (Chelghoum *et al.* 2005); no fetal data were provided. A normal fetus was also reported in the case of maternal death at 23 weeks of gestation, following exposure in the 1st and 2nd trimesters (Feliu *et al.* 1988). A total occurrence of major malformations following exposure in the 1st trimester to cytarabine was 12.5% (4/32 conceptuses).

Of the 118 pregnancies (118 conceptuses) exposed in the 2nd and/or 3rd trimester only, major malformations were observed in four infants. One newborn had a ventricular septal defect, requiring surgery at 5 months, as well as a shallow sacral dimple, short digits and limbs, dysplastic fingernails, and a prominent frontal skull with macrognathia (Niedermeier *et al.* 2005). Hypospadias was diagnosed in a newborn exposed at gestation week 28 (De Carolis *et al.* 2006). Down syndrome occurred in one newborn with 2nd trimester exposure (Roy *et al.* 1989). Polydactyly on the right foot occurred in an infant with a family history of this condition (Volkenandt *et al.* 1987); thus, it is unlikely that the infant's exposure to chemotherapy in the 3rd trimester caused this malformation. Two infants had minor malformations: congenital adherence of the iris to the cornea (Reynoso *et al.* 1987) and bilateral hydronephrosis and dilation of the proximal ureter of the left kidney (Garcia *et al.* 1999). One additional health anomaly, not considered a malformation, occurred following 3rd trimester exposure: chromosomal abnormalities were reported in an otherwise normal infant (Schleuning and Clemm 1987). Fetal loss occurred in 20 cases exposed in the 2nd and/or 3rd trimesters only, including one spontaneous abortion (Ali *et al.* 2003), seven induced abortions and 11 intrauterine fetal deaths, and one maternal/fetal death. Fetal autopsy data for two induced abortions revealed a normal fetus (Doney *et al.* 1979) and a fetus with abnormal chromosomes (not considered a malformation) (Maurer *et al.* 1971). No fetal data were reported for the remaining five induced abortions (Chelghoum *et al.* 2005). Normal fetuses were reported in 7 of the 11 pregnancies ending in intrauterine fetal death following 2nd and/or 3rd trimester exposure (Ali *et al.* 2003, O'Donnell *et al.* 1979, Plows 1982, Reynoso and Huerta 1994, Volkenandt *et al.* 1987, Zuazu *et al.* 1991){Zemlickis, 1992 #576}. Oligohydramnios and early intrauterine growth restriction preceded the intrauterine fetal death in another pregnancy exposed in the 2nd trimester (Peterson *et al.* 2010); however, no fetal autopsy data were reported. No fetal data were provided for the remaining 3 intrauterine fetal deaths occurring in the 2nd and/or 3rd trimester (Greenlund *et al.* 2001, Molkenboer *et al.* 2005, Paşa *et al.* 2009). One maternal and fetal death occurred at approximately gestation week 24 following 2nd trimester exposure {Greenlund, 2001 #93}. A total occurrence of major malformations was 3.4% (4/118 conceptuses) for pregnancies exposed to cytarabrine in the 2nd and /or 3rd trimester only. In addition, timing of exposure was not specified for one intrauterine fetal death of a normal fetus (Peres *et al.* 2001).

There were a variety of pregnancy complications and infant health effects that occurred following in utero exposure to cytarabine. Pregnancy complications included: polyhydramnios (n=1 pregnancy) (Artlich *et al.* 1994), oligohydramnios or a reduction in amniotic fluid (n=6 pregnancies) (Garcia *et al.* 1999, Hansen *et al.* 2001, Matsuo *et al.* 2004, Peres *et al.* 2001, Peterson *et al.* 2010, Scherf and Price

1996), and inhibited fetal growth (n=10 pregnancies) (Baumgartner *et al.* 2009, Claahsen *et al.* 1998, D'Emilio *et al.* 1989, Garcia *et al.* 1999, Hsu *et al.* 1995, Murray *et al.* 1994, Peres *et al.* 2001, Peterson *et al.* 2010, Roy *et al.* 1989). Fetal cardiac effects were reported in 2 pregnancies (Garcia *et al.* 1999), including one with transient cerebral ventriculomegaly (Baumgartner *et al.* 2009). Fetal distress occurred in 4 pregnancies {Claahsen, 1998 #197;Yucebilgin, 2004 #459}{Hsu, 1995 #111}{Veneri, 1996 #665}. Other pregnancy complications included: preeclampsia (n=2 cases), premature rupture of membranes (n=2 cases), spontaneous preterm labor (n=9 cases), and induced labor due to poor health of mother (n=1 case) (Roy *et al.* 1989). Of the 99 pregnancies reporting age at delivery, 54 infants were delivered preterm. In addition, one retrospective survey reported a premature infant (age at delivery was not reported) (Chelghoum *et al.* 2005). No newborns were reported to be small for gestational age. Common infant health issues included: respiratory difficulties (n=12 infants), transient myelosuppression (n=12 infants), jaundice (n=3 infants), meconium aspiration (n=2 infants), and decreased nutrient levels (i.e., hypoglycemia and hypoatremia; n=2 infants). Infant death occurred in 3 cases due to: respiratory distress (Dilek *et al.* 2006), septicemia (Aviles and Niz 1988), or gastroenteritis (Aviles and Niz 1988). Follow-up evaluations on 77 infants at ages 5 months to 15 years revealed normal growth and development, with the exception of three children. These three children had: mild developmental delay at age 1 year (Lam 2006), failure to thrive and finally gaining weight at age 3 months (Garcia *et al.* 1999), and body weight at <10th percentile at age 26 months with a constant cold (Gulati *et al.* 1986).

In conclusion, the total occurrence of major malformations in cytarabine-exposed pregnancies was 5.3% (8/151 conceptuses). The occurrence of major malformations following 1st trimester exposure to cytarabine (4/32 conceptuses) was nearly four-times higher than the prevalence of birth defects in the general population (12.5 ± 11.5% versus 3%). The occurrence of major malformations following exposure to cytarabine in the 2nd and/or 3rd trimester only (4/118 conceptuses) was similar to the prevalence of birth defects in the general population (3.4 ± 3.3% versus 3%). However, it is unlikely that any of these four major malformations (i.e., ventricular septal defect, hypospadias, Down syndrome, and polydactyly in an infant with a family history of this condition) can be attributed to exposure to cytarabine in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations following exposure to cytarabine in the 2nd and/or 3rd trimester only is 0%. Of note, there was a high rate of occurrence of intrauterine fetal deaths following in utero exposure to cytarabine (8.6%; 13 intrauterine fetal deaths/151 total conceptuses). Twelve of 13 of the intrauterine fetal deaths occurred in pregnancies co-exposed to anthracycline antibiotics daunorubicin in combination therapies (n=8 conceptuses), doxorubicin (n=2 conceptuses), or idarubicin (n=2 conceptuses). As a reference point, the rate of stillbirths (spontaneous fetal loss at >20 weeks gestation) was 0.3 to 0.4% in the general United States population (MacDorman 2005).

5.13 DACARBAZINE

5.13.1 Mechanism of action, route of administration, and indications

Dacarbazine is an antineoplastic agent that appears to act by cross-linking DNA strands. The exact mechanism of dacarbazine is unknown, but it is thought to inhibit DNA synthesis by: acting as an alkylating agent, acting as a purine analog, and interacting with protein sulfhydryl groups. Dacarbazine is administered via intravenous injection. It is indicated for treatment of melanoma and as a second-line therapy for Hodgkin disease (Bedford Laboratories 2007).

5.13.2 Evidence of placental and breast milk transport

Placental and breast milk transport in humans is not known. Van Calsteren et al. (Van Calsteren *et al.* 2010) administered the combination therapy with doxorubicin, bleomycin, vinblastine and dacarbazine to pregnant baboons, then measured the concentration of the drugs in maternal and fetal serum. However, they did not report serum levels of dacarbazine levels (Van Calsteren *et al.* 2010). There are no published reports of breast milk transfer of dacarbazine in humans or animals.

5.13.3 Laboratory animal developmental toxicity

Dacarbazine has been shown to be embryolethal and teratogenic in laboratory animals. Dacarbazine is teratogenic when administered at 20 times the recommended human daily dose **[dose not indicated]** on day 12 of gestation (Bedford Laboratories 2007). In particular, dacarbazine induced malformations in rat fetuses in a dose-dependent manner when administered via intraperitoneal injection to pregnant CFN Wistar rats on gestation days 11 or 12 with a dose range of 100, 200, 400, 600, 800 or 1000 mg/kg) (Chaube 1973). Malformations of the forelimb, hindlimb, paws, tail (kinky and short), cleft palate, micrognathia, open eyes, encephalocele and microcephaly were observed in rat fetuses following a single injection of 400-1000 mg dacarbazine/kg on gestation day 12 to the rat dam. Administration of this dose range on gestational Days 9 or 10 induced embryotoxicity in the rat (Chaube 1973). Thompson et al. (Thompson *et al.* 1975) also observed that dacarbazine induced fetal malformations when administered during the period of organogenesis to pregnant Sprague-Dawley rats. Fetal skeletal anomalies, including skeletal delayed ossification and malformations, were observed at all dacarbazine dose levels evaluated (30, 50, and 70 mg/kg/day by intraperitoneal injection), whereas soft tissue anomalies involving the eye, cardiovascular system and abdominal wall occurred in fetuses exposed to the higher doses only (50 or 70 mg/kg) (Thompson *et al.* 1975). Neonatal survival rates were lowered when dacarbazine exposure (7.5, 15, or 30 mg/kg/day) occurred later in pregnancy and during the postpartum period (gestation day 15 through postnatal day 21) (Thompson *et al.* 1975). In the rabbit, dacarbazine was both abortifacient and teratogenic at 10 mg/kg (the highest dose tested) (Thompson *et al.* 1975). Skeletal defects involving bones of the extremities, pelvic girdle, palate and facies were reported for the 10 mg dacarbazine/kg dose group, while the lower doses (2.5 or 5 mg/kg/day) were reported to have no adverse effects (Thompson *et al.* 1975).

5.13.4 Human gestational exposure and effects

Dacarbazine is FDA Pregnancy Category C. There were 55 patients treated with dacarbazine identified from 8 case reports, 4 case series, 1 retrospective case series, 2 retrospective surveys, 1 retrospective cohort study, 1 retrospective cohort study and 1 registry survey (Appendix Table 12). Dacarbazine was used to treat Hodgkin lymphoma (n=44 cases), melanoma (n=9 cases), pancreas (n=1 case) and sarcoma (n=1 case). A total of 56 pregnancies (57 conceptuses) were exposed to dacarbazine, including two pregnancies of the same patient (Dilek *et al.* 2006) and one set of twins (Cardonick *et al.* 2010).

Dacarbazine was administered in the 1st trimester in 9 pregnancies, and in the 2nd and/or 3rd trimester only in 45 pregnancies (46 conceptuses due to one set of twins). The individual timing of exposure was not specified for two pregnancies from a case series where age at initiation of exposure was 12-33 weeks of gestation (mean=22 weeks) (Jameel and Jamil 2007); thus, it was assumed that these two pregnancies were likely exposed to dacarbazine in the 2nd and/or 3rd trimester only for a total of 47 pregnancies (48 conceptuses).

There were 5 cases of fetal demise, including 1 spontaneous abortion, 3 induced abortions and 1 intrauterine fetal death. Spontaneous abortion at gestation week 22 ended one pregnancy following 2nd trimester exposure and co-exposure to doxorubicin and cyclophosphamide (Jameel and Jamil 2007); no fetal autopsy data were provided. One pregnancy was ended by induced abortion of a gestation week 18 fetus without congenital malformations, but with toxic degenerative changes in the liver and kidneys (Peres *et al.* 2001); this fetus was exposed in the 1st trimester and co-treated with nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, and vinblastine. Induced abortion terminated two additional pregnancies following 2nd trimester exposure (d'Incalci *et al.* 1983) {Zemlickis, 1992 #576}; no fetal data were provided. Intrauterine fetal death occurred in the 8th month of pregnancy following 2nd and 3rd trimester exposure and co-exposure to bleomycin, doxorubicin and vinblastine (Dilek *et al.* 2006); no fetal data were reported.

Of the 51 live born infants exposed in utero to dacarbazine, three infants had malformations. Major malformations were observed in two infants. One infant had a floating thumb malformation on the left hand, involving the partial agenesis of a metacarpal and hypoplasia of two phalanges (Dilek *et al.* 2006); this infant was exposed in the 1st trimester and co-exposed to bleomycin, doxorubicin, and vinblastine. Another infant had syndactyly of the 4th and 5th fingers with exposure in the 2nd and 3rd trimesters and co-exposure to bleomycin, doxorubicin, and vinblastine (Cardonick *et al.* 2010). Plagiocephaly, a minor malformation, was reported in one infant also with exposure in the 2nd and 3rd trimesters and co-exposure to bleomycin, doxorubicin, and vinblastine. In addition, one infant had a health anomaly not considered a malformation: microphthalmia and severe hypermetropia, which was diagnosed at age 1 year (Li *et al.* 2007); the pregnancy was exposed in the 1st and 2nd trimesters and co-exposed to carmustine, cisplatin and tamoxifen (Li *et al.* 2007).

There were relatively few pregnancy complications and adverse health effects reported following exposure to dacarbazine in utero. Two pregnancies reported fetal growth restriction: intrauterine growth restriction after two courses of dacarbazine (Gottschalk *et al.* 2009) and a small for gestational age fetus (Fadilah *et al.* 2006). Of the 27 pregnancies reporting age at delivery, early preterm delivery (<34 weeks) was reported for 5 pregnancies (18.5%), late preterm delivery (34-36 weeks) was reported for 9 pregnancies (33.3%), and 13 pregnancies were delivered at term (48.1%). Small for gestational age was reported for one newborn (Dilek *et al.* 2006). Three infants were hypoglycemic (Cardonick *et al.* 2010). One preterm newborn suffered from hyaline membrane disease, bronchopulmonary dysplasia, a cytomegalovirus infection and necrotizing enterocolitis (Pages *et al.* 2009). Follow-up evaluations were reported for 37 infants ranging in age from 4 months to 16 years, including one child for whom age at follow-up was not specified. Normal health and development were observed in all of these children. Chronic bronchitis, recurrent otitis media, and asthma were reported for one child each (Cardonick *et al.* 2010).

5.13.5 *Summary of pregnancy outcomes for dacarbazine*

In utero exposure to dacarbazine was documented for 56 pregnancies (57 conceptuses due to one set of twins). Of the 9 pregnancies with 1st trimester exposure to dacarbazine, major malformations were

observed in one infant. One newborn had a floating thumb malformation, which consists of partial agenesis of a metacarpal bone and hypoplasia of two phalanges (Dilek *et al.* 2006). Induced abortion terminated two pregnancies following 1st trimester exposure, including one normal fetus (Peres *et al.* 2001) and another with no fetal autopsy data {Zemlickis, 1992 #576}. One newborn had a health anomaly following 1st trimester exposure: microphthalmia and severe hypermetropia (Li *et al.* 2007). The total occurrence of major malformations following 1st trimester exposure was 11.1 % (1/9 conceptuses); however, there were too few reported pregnancies to accurately estimate this value. There were 47 pregnancies (48 conceptuses due to one set of twins) exposed to dacarbazine in the 2nd and/or 3rd trimesters only, including two pregnancies without data on individual timing of exposure that were assumed to be 2nd and/or 3rd trimester based on a group range of age at initiation of exposure of 12-33 weeks of gestation (Jameel and Jamil 2007). A major malformation was observed in one infant with 2nd and 3rd trimester exposure: syndactyly of the 4th and 5th fingers (Cardonick *et al.* 2010). Plagiocephaly, a minor malformation, was observed in another infant (Cardonick *et al.* 2010) following 2nd and or/ 3rd trimester exposure. Fetal loss was reported for three pregnancies exposed in the 2nd and/or 3rd trimester only, including one spontaneous abortion (Jameel and Jamil 2007), one intrauterine fetal death (Dilek *et al.* 2006), and one induced abortion (d'Incalci *et al.* 1983); no fetal autopsy data were reported. The total occurrence of major malformations following exposure to dacarbazine in the 2nd and/or 3rd trimester only was 2.1% (1/48 conceptuses).

Pregnancy complications and infant health effects included only fetal growth restriction (n=2 pregnancies) (Fadilah *et al.* 2006, Gottschalk *et al.* 2009). Of the 27 pregnancies reporting age at delivery, preterm birth was reported for 14 pregnancies. Small for gestational age was reported for one newborn (Dilek *et al.* 2006). Hypoglycemia was observed in three newborns. One newborn had respiratory distress, bronchopulmonary dysplasia, a cytomegalovirus infection and necrotizing entercolitis (Pages *et al.* 2009). Follow-up examinations were reported for 37 children with normal growth and development reported at ages ranging from 4 months to 16 years.

In conclusion, the total occurrence of major malformations in dacarbazine-exposed pregnancies was 3.5% (2/57 conceptuses). The occurrence of major malformations following exposure to dacarbazine during the 1st trimester (1/9 conceptuses) was higher than the prevalence of birth defects in the general population (11.1 ± 20.5% versus 3%). The occurrence of major malformations following exposure in the 2nd and/or 3rd trimester only (1/48 conceptuses) was similar to the prevalence of birth defects in the general population (2.1 ± 4.0% versus 3%). This one case of syndactyly was unlikely to have resulted from chemotherapy exposure in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations possibly attributed to exposure to dacarbazine in the 2nd and/or 3rd trimester only is 0%.

5.14 DAUNORUBICIN

5.14.1 Mechanism of action, route of administration, and indications

Daunorubicin is an anthracycline cytotoxic agent that intercalates between DNA base pairs, inhibiting DNA synthesis and function (Bedford 2008).   Daunorubicin may also inhibit polymerase activity, affect gene expression, and produce free radical damage to DNA.   Daunorubicin in administered via intravenous injection and is indicated for acute non-lymphocytic leukemia (myelogenous, monocytic and erythroid) and acute lymphocytic leukemia. A liposome-encapsulated version of daunorubicin is indicated for advanced HIV-associated Karposi sarcoma (Gilead Sciences 2002).

5.14.2 Evidence of placental and breast milk transport

There is limited evidence of transplacental transport of daunorubicin and breast milk transfer of the drug is not known. Daunorubicin was detected in liver (0.015 ng/mL), kidney (0.021 ng/mL) and lung (0.02 ng/mL) tissues of a fetus who died at 29.5-30.5 weeks gestation (Germann *et al.* 2004); tissue samples were collected at one time point (48 hours + 5 days) after administration of the drug to the mother. There are no published cases of breast milk transfer of daunorubicin. However, it has a low molecular weight (540 for daunorubicin hydrochloride), which might facilitate its transport into milk.

5.14.3 Laboratory animal developmental toxicity

Information in the product label describes daunorubicin as embryotoxic and teratogenic in rabbits and rats (Gilead Sciences 2002). Pregnant rats administered daunorubicin at 0.05 mg/kg **[route not indicated]** (~1/100th of the maximal recommended human dose per body surface area) resulted in an increase of abortions and fetal abnormalities, including parieto-occipital cranioschisis, umbilical hernias, orrachischisis. In rats, an increased incidence of esophageal, cardiovascular and urogenital abnormalities as well as rib fusions occurred in fetuses of rat dams administered doses of 4 mg/kg/day (~1/2 of the maximal recommended human dose per body surface area). Effects of in utero exposure to daunorubicin in mice included decreased birth weight and post-delivery growth rate **[doses, route and exact timing of exposure not provided]**.   When treated with the liposome-encapsulated form of daunorubicin on gestation days 6-15, daunorubicin caused severe maternal toxicity and embryolethality at 2.0 mg/kg/day (~1/3rd of the recommend maximal human dose per body surface area) (Gilead Sciences 2002), and eye malformations (anophthalmia and micropthalmia) and incomplete ossification in rat fetuses at 0.3 mg/kg/day (~1/20th of the recommended maximal human dose per body surface area)(Gilead Sciences 2002).

Embryotoxic and teratogenic effects of daunorubicin are also described in the peer-reviewed literature. In a review by Shepard et al. (Shepard and Lemire 2004), malformations were observed in 45% of rat fetuses following administration of daunorubicin to pregnant rats at 1-3 mg/kg via intravenous injections on gestation day 7 or at 3 mg/kg via intraperitoneal injection for 3 days during organogenesis. The malformations included ocular anomalies, and defects of the heart, kidney and brain. The malformation rate was 16%, when 1 mg daunorubicin/kg was administered via intraperitoneal injection to the pregnant rat dam on gestation day 7-14 (Shepard and Lemire 2004). Daunorubicin did not cause teratogenic effects in Dutch Belted rabbits administered intraperitoneal injections of up to 0.6 mg/kg/day on days 6-18 of gestation (Thompson *et al.* 1978) or in the chick or fetal mouse exposed in utero to 1.25 mg/kg administered to their mothers during pregnancy (Shepard and Lemire 2004).

5.14.4 *Human gestational exposure and effects*

Daunorubicin is classified as FDA Pregnancy Category D. There were 105 patients treated with daunorubicin during pregnancy identified from 29 case reports, 18 case series, 1 retrospective case series, 6 retrospective surveys, 2 retrospective cohort study, and 1 registry survey (Appendix C Table 13). Among the 105 patients, daunorubicin was used to treat acute lymphocytic leukemia (n=24 cases), acute myelogeneous leukemia (n=66 cases), acute promyelogenous leukemia (n=8 cases), acute leukemia (type not specified; n=4 cases), chronic myelogenous leukemia (also called chronic granulocytic leukemia, n=2 cases), and one case in which cancer type was not specified. A total of 106 conceptuses were exposed to daunorubicin, including one twin pregnancy (Turchi and Villasis 1988). Daunorubicin was administered during the 1st trimester in 18 pregnancies and in the 2nd and/or 3rd trimester only in 82 pregnancies (83 conceptuses, including one set of twins). Timing of exposure was not specified for 5 pregnancies; however, it was assumed that one of these cases was likely exposed in the 2nd and/or 3rd trimester with the age of initiation of chemotherapy ranging from 12-33 weeks of gestation (mean = 24 weeks) (Jameel and Jamil 2007). Thus, the total pregnancies exposed only in the 2nd and/or 3rd trimester were calculated to be 83 cases (84 conceptuses) and timing of exposure was not specified for 4 cases.

Fetal loss was reported in 31 pregnancies exposed to daunorubucin. Spontaneous abortion occurred in four pregnancies exposed during the 1st trimester and co-exposed to: cytarabine (n=1 pregnancy) (Zuazu *et al.* 1991), cytarabine and all-trans retinoic acid (n=1 pregnancy) or cytarabine and mitoxantrone (n=1 pregnancy) (Chelghoum *et al.* 2005), or cytarabine, 6-thioguanine and vincristine (n=1 pregnancy) (Zuazu *et al.* 1991). Induced abortion terminated 8 pregnancies following 1st trimester exposure and no fetal autopsy data were available for any of these pregnancies {Chelghoum, 2005 #193;Molkenboer, 2005 #302;Zemlickis, 1992 #576}. One intrauterine fetal demise occurred following 1st trimester exposure and co-exposure to cytarabine and all-*trans* retinoic acid (Chelghoum *et al.* 2005); no fetal data were reported. In addition, a maternal and fetal death occurred following 1st and 2nd trimester exposure and co-treatment with cytarabine, vincristine and 6-mercaptopurine (Feliu *et al.* 1988); the fetus had no malformations.

Fetal loss occurred in 17 singleton pregnancies following 2nd and/or 3rd trimester only exposure to daunorubicin. One pregnancy ended in spontaneous abortion following 2nd trimester exposure and co-treatment with cytarabine (Ali *et al.* 2003). Normal fetuses were observed in two induced abortions following exposure in the 2nd trimester and co-exposure to: cytarabine, vincristine, hydroxyurea, and 6-thioguanine (Doney *et al.* 1979) or cytarabine, 6-thioguanine, and vincristine (Lilleyman *et al.* 1977). No fetal data were reported for the remaining three induced abortions (Chelghoum *et al.* 2005). Intrauterine fetal demise occurred in 9 pregnancies following exposure in the 2nd and/or 3rd trimester only exposure to daunorubicin and normal fetuses were observed in four cases. Intrauterine fetal death of a normal fetus was reported following 2nd trimester exposure and co-exposure to cytarabine (Ali *et al.* 2003). An intrauterine fetal death of a normal fetus was associated with maternal preeclamptic toxemia following 2nd trimester treatment and co-treatment with cytarabine and 6-thioguanine (O'Donnell *et al.* 1979). A normal fetus was reported following an intrauterine fetal death at 20 weeks of gestation (Volkenandt *et al.* 1987); this pregnancy was exposed in the 2nd trimester and co-exposed to cytarabine. A stillborn fetus had no obvious malformations following exposure in the 2nd trimester and co-exposure to idarubicin in the 3rd trimester and cytarabine and mitoxantrone in the 2nd and 3rd trimesters (Reynoso and Huerta 1994). No fetal data were provided for the remaining five pregnancies ending in intrauterine fetal death, including two pregnancies with 2nd trimester exposure and co-exposure to: cytarabine (Greenlund *et al.* 2001), and cytarabine, vincristine, asparaginase, and methotrexate (intrathecal) (Molkenboer *et al.* 2005). Another intrauterine death occurred following 2nd and/or 3rd trimester only exposure and co-treatment with vincristine (Jameel and Jamil 2007). Two intrauterine fetal deaths

occurred following 3rd trimester exposure with co-treatments: none (Germann *et al.* 2004), and cytarabine, 6-thioguanine, and vincristine (Zuazu *et al.* 1991). One maternal and fetal death occurred following exposure during the 5th month of gestation to daunorubicin only (Zuazu *et al.* 1991); no fetal data were reported. Another maternal and fetal death occurred following exposure during the 2nd trimester {Zemlickis, 1992 #576}; this pregnancy was co-exposed to vincristine and cytarabine.

Of the 75 live-born infants, malformations occurred in eight infants exposed in utero to daunorubicin. Four infants had major malformations. One infant had skeletal malformations of the distal limbs and cranium, and a cardiac defect following exposure during the period of conception and in the 1st trimester and co-exposed to cytarabine (Artlich *et al.* 1994); the malformations included: choanal stenosis, brachiocephaly, hypoplasia of several cranial structures, premature closure of cranial sutures, bilateral 4-fingered hands with hypoplastic thumbs, and a small ostium, secundum-type atrial defect. Major malformations reported following 2nd trimester exposure and co-exposure to cytarabine and 6-thioguanine included: polydactyly on one foot in an infant with a family history of polydactyly (Volkenandt *et al.* 1987), and Down syndrome in another infant (Roy *et al.* 1989). Hypospadias was reported in one newborn following exposure in the 3rd trimester and co-treatment with cytarabine (De Carolis *et al.* 2006). Three infants had minor malformations following in utero exposure to daunorubicin. A hemangioma was reported in an infant with 2nd and 3rd trimester (Van Calsteren *et al.* 2010); this infant was also co-treated with methotrexate, vincristine, cyclophosphamide, asparaginase, and 6-mercaptopurine. One infant suffered from bilateral hydronephrosis with dilation of the proximal ureter of the left kidney (Garcia *et al.* 1999); this infant was exposed in the 2nd trimester and co-exposed to cytarabine (2nd and 3rd trimesters) and mitoxantrone (3rd trimester). Congenital adherence of the lens to the cornea was diagnosed at age 2 in a child who was exposed in the 3rd trimester and co-exposed to cytarabine and 6-thioguanine (Reynoso *et al.* 1987).

There were several pregnancy complications and infant health effects observed following in utero exposure to daunorubicin. Intrauterine growth restriction was reported for 6 fetuses (Hsu *et al.* 1995, Matsuo *et al.* 2004, Morishita *et al.* 1994), including one fetus with poor growth (Roy *et al.* 1989), and two fetuses with a preterm cessation in fetal growth (Murray *et al.* 1994, Scherf and Price 1996). Polyhydramios occurred in one pregnancy (Artlich *et al.* 1994), while three other pregnancies experienced oligohydramnios (Hansen *et al.* 2001, Matsuo *et al.* 2004) or reduced amniotic fluid (Scherf and Price 1996). Fetal tachycardia was reported in one pregnancy {Garcia, 1999 #69}. Fetal distress occurred in 2 pregnancies {Ali, 2009 #709}{Hsu, 1995 #111}. Premature rupture of membranes occurred in 5 cases {Ali, 2009 #709}{Morishita, 1994 #306}{Okun, 1979 #691}{Udink ten Cate, 2009 #434}, including in one case likely caused by medical evaluation of the placenta (Volkenandt *et al.* 1987). Spontaneous preterm labor occurred in 7 cases {Doney, 1979 #215}{Hansen, 2001 #105}{Sanz, 1982 #380}{Tobias, 1980 #546}{Reynoso, 1987 #372}. Labor was induced because mother was seriously ill {Roy, 1989 #717}. As mentioned above, toxemia due to preeclampsia caused one intrauterine fetal death (O'Donnell *et al.* 1979). Of the 61 cases reporting gestational age at delivery, early preterm delivery (<34 weeks) was reported for 24 pregnancies (39.3%), late preterm delivery (34-36 weeks) was reported for 16 pregnancies (26.2%) and 21 pregnancies were delivered at term (34.4%). None of the newborns were reported to be small for gestational age. One newborn was treated for congestive heart failure, {Okun, 1979 #691}; this infant was also hydropic, and had an enlarged liver and spleen, slight cardiomegaly, and a petechial rash on her abdomen and extremities. Breathing difficulties occurred in eleven newborns (Ali *et al.* 2009, De Carolis *et al.* 2006, Dilek *et al.* 2006, Garcia *et al.* 1999, Hansen *et al.* 2001, Murray *et al.* 1994, Papantoniou *et al.* 2008, Scherf and Price 1996), including one infant with bilateral pneumothorax and seizures (Cantini and Yanes 1984). Respiratory distress was associated with choanal stenosis and pneumothorax in another infant (Artlich *et al.* 1994), and occurred with meconium

aspiration syndrome in another infant (Hansen *et al.* 2001). One infant with respiratory distress died of pulmonary hemorrhage on day 1 (Dilek *et al.* 2006). Transient myelosuppression was observed in 9 infants (Biener *et al.* 2009, Doney *et al.* 1979, Garcia *et al.* 1999, Hsu *et al.* 1995, Matsuo *et al.* 2004, Murray *et al.* 1994, Okun *et al.* 1979, Scherf and Price 1996, Udink ten Cate *et al.* 2009). Hyponatremia (sodium deficiency) and hypoglycemia were observed in two infants (Garcia *et al.* 1999), one of which also was hypocalemic (calcium deficient) and hyperkalemic (excess potassium in blood) (Doney *et al.* 1979). Other health effects included: jaundice (Hansen *et al.* 2001), hepatopathy and elevated creatine (Matsuo *et al.* 2004), and diarrhea and hypotonia (Turchi and Villasis 1988). Follow-up evaluations were available for 48 infants ranging in age from 2 months to 29 years. Normal growth and development were observed in all but two children. At 13 months, one child had normal fine motor skills and social development, but was underweight with slightly delayed motor milestones (Artlich *et al.* 1994). Failure to thrive was reported in another infant, who did not begin to gain weight until 3 months of age (Garcia *et al.* 1999). Of note, the newborn treated for cardiac arrest had normal growth and development at age 1 year.

5.14.5 Summary of pregnancy outcomes for daunorubicin

In utero exposure to daunorubicin was documented for 105 pregnancies, including one twin pregnancy, for a total of 106 conceptuses. Of the 18 pregnancies exposed to daunorubicin in the 1st trimester, one infant had a major malformation (Artlich *et al.* 1994); the malformations included hypoplastic thumbs on each hand, a variety of cranial defects and hypoplasia, and a small ostium, secundum-type atrial defect. Spontaneous abortion occurred in four pregnancies exposed during the 1st trimester (Chelghoum *et al.* 2005, Zuazu *et al.* 1991) and induced abortion terminated 8 pregnancies following 1st trimester exposure (Chelghoum *et al.* 2005, Molkenboer *et al.* 2005){Zemlickis, 1992 #576}; no fetal autopsy data were reported for these abortions. One intrauterine fetal demise occurred following 1st trimester exposure and co-exposure to cytarabine and all-*trans* retinoic acid (Chelghoum *et al.* 2005); no fetal data were reported. A normal fetus was observed in the maternal and fetal death that followed 1st and 2nd trimester exposure (Chelghoum *et al.* 2005). A total occurrence of major malformations following 1st trimester exposure to daunorubicin was 5.6% (1/18 conceptuses).

Major malformations were observed in three infants of 83 pregnancies (84 conceptuses, including one set of twins) with exposure to daunorubicin in the 2nd and/or 3rd trimester only. The total of 83 conceptuses included one case where the individual timing of exposure was not provided, but exposure occurred between 12-33 weeks of gestation (mean= 24 weeks) (Jameel and Jamil 2007). Hypospadias was reported in one infant with 3rd trimester exposure (De Carolis *et al.* 2006). An infant had polydactyly on the right foot and a family history of polydactyly {Volkenandt, 1987 #442). Down syndrome was diagnosed in another infant (Roy *et al.* 1989). Minor malformations were observed in three infants with exposure in the 2nd and/or 3rd trimester only, including: bilateral hydronephrosis and dilation of proximal ureter of left kidney (Garcia *et al.* 1999), congenital adherence of the lens to the cornea (n=1 infant) (Reynoso *et al.* 1987), and hemangioma (n=1 infant) (Van Calsteren *et al.* 2010). Fetal loss occurred in 17 singleton pregnancies following 2nd and/or 3rd trimester only exposure. Spontaneous abortion ended one pregnancy and no fetal data were provided (Ali *et al.* 2003). Normal fetuses were observed in two induced abortions following exposure in the 2nd trimester (Doney *et al.* 1979, Lilleyman *et al.* 1977), and no fetal data were provided for 3 additional induced abortions in the 2nd and/or 3rd trimester only. Intrauterine fetal demise occurred in 9 pregnancies following exposure in the 2nd and/or 3rd trimester only. Normal fetuses were observed in four cases of intrauterine fetal death (Ali *et al.* 2003, Reynoso and Huerta 1994, Volkenandt *et al.* 1987), including the intrauterine fetal death of a normal fetus associated with maternal preeclamptic toxemia following 2nd trimester treatment (O'Donnell *et al.* 1979). No fetal data were provided for the remaining five pregnancies ending in

intrauterine fetal death (Germann *et al.* 2004, Greenlund *et al.* 2001, Jameel and Jamil 2007, Molkenboer *et al.* 2005, Zuazu *et al.* 1991). Maternal and fetal death occurred in two pregnancies exposed to daunorubicin (Zuazu *et al.* 1991){Greenlund, 2001 #93}; no fetal data were reported. A total occurrence of major malformation following exposure to daunorubicin in the 2nd and 3rd trimester only was 3.7% (3/82 conceptuses). Timing of exposure was not provided for 4 singleton pregnancies yielding 4 normal infants (Aviles *et al.* 1991).

A variety of pregnancy complications and health effects were observed following in utero exposure to daunorubicin. Pregnancy complications included: intrauterine growth restriction or poor fetal growth (n=6 pregnancies) (Hsu *et al.* 1995, Matsuo *et al.* 2004, Morishita *et al.* 1994, Murray *et al.* 1994, Roy *et al.* 1989, Scherf and Price 1996), oligohydramnios or reduced amniotic fluid levels (n=3 pregnancies) (Hansen *et al.* 2001, Matsuo *et al.* 2004, Scherf and Price 1996), polyhydramnios (n=1 infant) (Artlich *et al.* 1994) as well as spontaneous preterm labor (n=7 pregnancies), premature rupture of membranes (n=5 pregnancies), and toxemia due to preeclampsia (n=1 pregnancy) (O'Donnell *et al.* 1979). In addition, fetal tachycardia was reported in one pregnancy {Garcia, 1999 #69} and fetal distress occurred in 2 pregnancies {Ali, 2009 #709}{Hsu, 1995 #111}. Of the 61 cases reporting gestational age at delivery, preterm delivery was reported for 40 pregnancies. None of the newborns were reported to be small for gestational age. One newborn was treated for congestive heart failure {Okun, 1979 #691}; this infant also was hydropic and had an enlarged liver and spleen, slight cardiomegaly, and a petechial rash. Common infant health issues were respiratory difficulties (n= 11 infants), and transient myelosuppression (n=9 infants). Follow-up evaluations performed on 48 children at ages ranging from 2 months to 29 years reported normal growth and development in all but two children. One 13 month-old girl was underweight and had slightly delayed motor milestones (Artlich *et al.* 1994). Failure to thrive was reported in another infant, who did not begin to gain weight until 3 months of age (Garcia *et al.* 1999).

In conclusion, the total occurrence of major malformations in daunorubicin-exposed pregnancies was 3.8% (4/106 conceptuses). The occurrence of major malformations following 1st trimester exposure (1/18 conceptuses) was slightly higher than the prevalence of birth defects in the general population (5.6 ± 10.6% versus 3%). The occurrence of major malformations following exposure in the 2nd and/or 3rd trimester only (3/84 conceptuses) was similar to the prevalence of major malformations in the general population (3.6 ± 4.0% versus 3%). None of these three malformations (Down syndrome, hypospadias, or polydactyly) were likely to have resulted from exposure to chemotherapy in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of malformations possibly attributed to exposure to daunorubicin in the 2nd and/or 3rd trimester only was 0% (0/84 conceptuses).

5.15 DOCETAXEL

5.15.1 Mechanism, route of administration, and indications

Docetaxel (also called Taxotere) is a semi-synthetic analog of paclitaxel, which is isolated from the needles of the European yew tree. Docetaxel binds to microtubules and promotes microtubulin assembly, which stabilizes the polymers against depolymerization. This action prevents cell division and leads to cell cycle arrest (Herbst and Khuri 2003). Docetaxel and paclitaxel have a mutual binding site, but there is evidence for distinct effects on microtubule dynamics (reviewed in (Herbst and Khuri 2003)). Docetaxel is administered intravenously. Docetaxel is indicated for the treatment of breast cancer, non-small cell lung cancer, gastric adenocarcinoma, squamous cell carcinoma of the head and neck cancer, and hormone-refractory prostate cancer (sanofi-aventis 2010).

5.15.2 Evidence of placental and breast milk transport

Placental transfer in humans is not known. It has been suggested that placental transport of the docetaxel is unlikely because it is a substrate for P-glycoprotein, a transporter protein, which is an efflux transporter for xenobiotics and hypothesized to serve as a protective mechanism against toxicity in the human placenta (Mir *et al.* 2008). In the baboon model, Van Calsteren et al. (Van Calsteren *et al.* 2010) reported that 100 mg/m^2 docetaxel administered intravenously to the mother was not detected in fetal plasma in the first 76 hours after drug infusion. Docetaxel was detected just above the lower limit of quantification in 3 of 10 amniotic fluid samples and fetal tissues contained 5%-50% of maternal tissue concentrations of docetaxel three hours after infusion. Levels in maternal and fetal tissues were equal after 24 and 76 hours (Van Calsteren *et al.* 2010). Maternal transfer of docetaxel to the infant via breast milk is not known (sanofi-aventis 2010).

5.15.3 Laboratory animal developmental toxicity

Docetaxel was reported to cause pregnancy loss as well as maternal toxicity when administered intravenously during organogenesis in rats and rabbits (Brunel *et al.* 1995, sanofi-aventis 2010). Intrauterine mortality, increased fetal resorptions, reduced fetal weights and delays in ossification are reported to occur at 0.3 mg/kg/d in rats and 3.0 mg/kg/d in rabbits when administered during the period of organogenesis (1/50 and 1/300, respectively, the daily maximum recommended human dose on a mg/m^2 basis). Docetaxel did not induce teratogenic effects in fetuses, even at the highest doses intravenously administered to rat (1.8 mg/m^2/d) or rabbit dams (1.2 mg/m^2/d) (abstract by (Brunel *et al.* 1995)).

5.15.4 Human gestational exposure and effects

Docetaxel is classified as FDA Pregnancy Category D. There were 20 published cases of patients treated with docetaxel during pregnancy identified from 7 case reports, 2 case series, 1 retrospective case series and 1 registry survey (Appendix C Table 14). Among these patients, docetaxel was used to treat cancers of the breast (n=18 cases), lung (n=1 case) and ovary (n=1 case). Docetaxel was administered during the 1st trimester in one patient, and in the 2nd and/or 3rd trimester in 19 patients. Of the 20 pregnancies, there were 20 conceptuses, and 20 live-born infants. Major malformations were observed in two newborns. Pyloric stenosis was reported in a newborn exposed in the 2nd and 3rd trimester and co-exposed to doxorubicin, cytarabine, and paclitaxel (Cardonick *et al.* 2010). Left-sided ventriculomegaly was diagnosed prenatally in a newborn prior to exposure in the 2nd trimester and co-treatment with cisplatin (Rouzi *et al.* 2009). Anhydramnios and increasing ventriculomegaly occurred with chemotherapy exposure, and this infant died at age 5 days due to multiple congenital malformations

that were observed prior to administration of chemotherapy (Rouzi *et al.* 2009). Two infants had minor malformations that resolved without treatment. Suspected holoprosencephaly was diagnosed in a newborn exposed during the 2nd and 3rd trimesters and co-treated with doxorubicin and cytarabine (Cardonick *et al.* 2010). At age 2.6 years, this infant was normal with prominent lateral ventricles (Cardonick *et al.* 2010). Another infant had mild hydrocephalus, which was diagnosed prenatally at approximately gestation week 17, three weeks after initiation of doxorubicin and cyclophosphamide, and prior administration of docetaxel only at gestation week 26 and in the 3rd trimester (Potluri *et al.* 2006). This case of mild hydrocephalus regressed spontaneously over several months.

Pregnancy complications and newborn health effects were reported in a few cases. Anhydramnios and increasing ventriculomegaly occurred in one pregnancy (Rouzi *et al.* 2009), and anhydramnios and intrauterine growth restriction occurred in two additional pregnancies that were co-exposed to trastuzumab in the 2nd and 3rd trimester {Gottschalk, 2011 #1328;Sekar, 2007 #389}. Preeclampsia was reported for one pregnancy (Potluri *et al.* 2006). Of the 14 pregnancies with individual age at delivery data, early preterm delivery (<34 weeks) was reported for 4 pregnancies (28.6%), late preterm delivery (34-36 weeks) was reported for 6 pregnancies (42.9%), and 4 pregnancies were delivered at term (28.6%). Small for gestational age was not reported for any of the newborns. One newborn had transient neutropenia (Cardonick *et al.* 2010). Follow-up evaluations were conducted on 13 children at ages ranging from 2.4 months to 2.6 years. Normal development was observed in all children. At age 2.6 years, the child with suspected holoprosencephaly at birth had prominent lateral ventricles, but was otherwise normal (Cardonick *et al.* 2010).

5.15.5 Summary of pregnancy outcomes for docetaxel

In utero exposure to docetaxel was documented for 20 singleton pregnancies. In the one pregnancy exposed in the 1st trimester, a healthy infant was born without congenital malformations. A total occurrence of major malformations following exposure to docetaxel during the 1st trimester was 0% (0/1 conceptuses). Of the 19 pregnancies exposed in the 2nd and/or 3rd trimester only, there were two infants with major malformations. Fetal ventriculomegaly, which was diagnosed prenatally and prior to chemotherapy exposure, increased with the administration of chemotherapy (Rouzi *et al.* 2009). The newborn died at age 5 days of congenital malformations identified prior to chemotherapy exposure (Rouzi *et al.* 2009). The second major malformation was pyloric stenosis in one infant with 2nd and 3rd trimester only exposure to docetaxel (Cardonick *et al.* 2010). Minor malformations were observed in two other newborns. One child was diagnosed with suspected holoprosencephaly at birth, but was developing normally at 2.6 years with prominent lateral ventricles (Cardonick *et al.* 2010). Mild hydrocephalus, diagnosed prenatally after exposure to doxorubicin and cyclophosphamide and prior to docetaxel exposure, resolved spontaneously over several months after birth (Potluri *et al.* 2006). A total occurrence of major malformations following exposure to docetaxel during the 2nd and/or 3rd trimesters was 5.5% (1/18 conceptuses).

Anhydramnios or oligohydramnios occurred in three pregnancies {Rouzi, 2009 #376}, including two pregnancies with intrauterine growth restriction that was co-exposed to trastuzumab in the 2nd and 3rd trimesters {Gottschalk, 2011 #1328;Sekar, 2007 #389}. Of the 14 pregnancies with individual age at delivery data, preterm birth was reported for 10 pregnancies. None of the newborns were reported to be small for gestational age. Transient myelosuppression was observed in only one infant. Follow-up evaluations on 13 infants at ages ranging from age 2.4 months to 2.6 years reported normal growth and development in all children.

In conclusion, the total occurrence of major malformations in docetaxel-exposed pregnancies was 10% (2/20 conceptuses). The occurrence of major malformations following exposure to docetaxel in the 1st trimester (0/1 conceptus) was lower than the prevalence of birth defects in the general population (0% versus 3%); however, there were too few published case reports to make an accurate estimate. The occurrence of major malformations following exposure to docetaxel in the 2nd and/or 3rd trimester only exposure (2/19 conceptuses) was higher than the prevalence of birth defects in the general population (10.5 ± 13.8% versus 3%). However, fetal ventriculomegaly diagnosed prior to initiation of chemotherapy was not caused by exposure to docetaxel in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations cause by exposure to docetaxel in the 2nd and/or 3rd trimester only was 5.3 ± 10.0% (1/19 conceptuses).

5.16 DOXORUBICIN

5.16.1 Mechanism of action, route of administration, and indications

Doxorubicin (doxorubicin hydrochloride; adriamycin) is an anthracycline antibiotic that intercalates between DNA base pairs inhibiting DNA and RNA synthesis. The cytoxic properties of doxorubicin are, in part, due to its interaction with the enzyme topoisomerase II to form DNA-cleavable complexes, as well as the generation of free radicals following the binding and reduction of doxorubicin at the cell surface, which are thought to be the possible mechanism for its cardiotoxicity. Doxorubicin is administered via intravenous injection. It is indicated for hematological cancers, including: acute lymphoblastic leukemia, acute myeloblastic leukemia, multiple myeloma, Hodgkin lymphoma, and malignant lymphoma. It is also indicated for cancers of the breast, ovary, stomach, thyroid gland, as well as Wilm tumor, neuroblastoma, soft tissue and bone sarcomas, transitional cell bladder cancer and bronchogenic carcinoma (Pharmacia & UpJohn Company 2010).

5.16.2 Evidence of placental and breast milk transport

Placental and breast milk transport of doxorubicin may occur in humans. Doxorubicin has been detected in tissues from a fetus aborted at gestation week 17 and a stillborn fetus of gestation age 31 weeks. Specifically, d'Incalci et al. (d'Incalci *et al.* 1983) reported detectable levels of doxorubicin in fetal liver, kidney and lung at 15 hours after dose administration in a fetus aborted at gestation week 17. Doxorubicin was not detected in amniotic fluid, or in brain, intestine or skeletal tissue (d'Incalci *et al.* 1983). A suspected doxorubicin metabolite was detected in many fetal tissues with highest levels reported in the fetal spleen at 60 hours post-dose, while the parent drug (doxorubicin) was not detected (Karp *et al.* 1983). Doxorubicin was also detected in umbilical cord tissue, but not in umbilical cord blood at 48 hours post-dose following a gestation week 34 delivery (Karp *et al.* 1983). Two additional reports did not find doxorubicin in the amniotic fluid in humans: at 96 hours post-dose administration at gestation week 35.5 (Barni *et al.* 1992) or at 4 and 16 hours post-dose administration at gestation week 20 (Roboz *et al.* 1979). Studies in mice and baboons report that there is a low rate of transfer of doxorubicin from maternal serum to the fetal serum. The transfer rate of doxorubicin from maternal to fetal serum was 5.1 % in mice at 90 minutes post-dose on gestation day 18.5 (Van Calsteren *et al.* 2010). A similarly low rate of maternal-fetal transfer of doxorubicin (7.5 %) was observed in baboons up to 3 hours post-dose (Van Calsteren *et al.* 2010). No doxorubicin was detected in fetal blood samples in baboons at 24 hours post-dose.

Doxorubicin and its major metabolite, doxorubicinol, were detected in the milk of at least one lactating patient (Egan *et al.* 1985). The amount of doxorubicin excreted in milk appears to be small with the peak serum concentrations of doxorubicin and its metabolite in the infant measuring 1.51 µM and 0.15 µM, respectively, following administration of 70 mg/m^2 to the mother (Egan *et al.* 1985). The American Academy of Pediatrics Committee on Drugs considers doxorubicin one of the drugs "that may interfere with cellular metabolism of the nursing infant" (American Academy of Pediatrics 2001).

5.16.3 Laboratory animal developmental toxicity

Doxorubicin induced embryolethal and teratogenic effects in laboratory animals with malformations induced as low as 0.8 mg/kg/day in the rat (estimated as 1/14 the human dose **[of 60-75 mg/m^2]** based upon surface area) (Pharmacia & UpJohn Company 2010). The period of organogenesis was most vulnerable to doxorubicin exposure. For example, intraperitoneal injection of 1-2 mg doxorubicin/kg to pregnant Sprague Dawley rats on days 6-15 or 6-9 of gestation induced significantly more malformations than pregnant rats treated on gestation days 9-12 or 12-15 (Thompson *et al.* 1978). The doxorubicin-

induced malformations in rat fetuses included: esophageal and intestinal atresia, trachea-esophageal fistula, hypoplasia of the urinary bladder and various cardiovascular anomalies (Thompson *et al.* 1978). These effects have since been reported in other rat strains, and similar effects are seen in mice at higher doses (4-6 mg doxorubicin/kg/day (reviewed in Gilick et al. (Gillick *et al.* 2008)). The malformations observed following developmental exposure to doxorubicin in rats and mice bear striking resemblance to the human VATER association (vertebral defects, anal atresia, trachea-esphoageal fistula with esophageal atresia, renal defects and/or radial limb dysplasia) (reviewed in (Gillick *et al.* 2008)).

Doxorubicin induced a high rate of spontaneous abortion in pregnant Dutch Belted rabbits administered doxorubicin via an intraperitoneal injection of 0.6 mg/kg/day on days 6-18 of gestation; however, malformations were not induced at doses 0.6 mg/kg/day (Thompson *et al.* 1978). Embryolethality was also observed in rats, but at higher doses than the teratogenic effects. Specifically, there was a significantly higher rate of post-implantation loss in pregnant CD:Crl rats treated with an intraperitoneal injection of 4 mg doxorubicin/kg/day on gestation days 9.5 and 10.5, relative to control and doses of 1-3 mg/kg/day (Menegola E 2001). Doxorubicin also induced embryolethality and teratogenic effects in White Leghorn chicks (Zirvi *et al.* 1985), although the profile of malformations was not the same as in rodent studies. Malformations in the chick embryos injected with a single dose of 1-10 µg/egg on day 1 or 2 were: everted viscera, hemorrhaging, beak abnormalities, short or curved limbs and eye abnormalities ranging from moderate to very severe microphthalmia and anophthalmia (Zirvi *et al.* 1985).

5.16.4 *Human gestational exposure and effects*

Doxorubicin is classified as FDA Pregnancy Category D. There were 414 patients treated with doxorubicin during pregnancy identified from 58 case reports, 25 case series, 4 retrospective case series, 1 registry survey, 7 retrospective surveys, and 2 retrospective cohort studies (Appendix C Table 15). Among these 414 patients, doxorubicin was used to treat breast cancer (n=244 cases), ovarian cancer (n=4 cases), sarcoma (n=4 cases), Ewing sarcoma (n=4 cases), malignant granular cell myoblastoma (n=1 case), adenoid cystic carcinoma (n=1 case), and vaginal cancer (neuroendocrine carcinoma; n=1 case). In addition, doxorubicin was used in the treatment of lymphoma patients including: Hodgkin lymphoma (n=52 cases), and non-Hodgkin lymphoma (n=43), B-cell lymphoma (n=1 case), Burkitt lymphoma (n=4 cases), diffuse B-cell lymphoma (n=2 cases), T-cell leukemia-lymphoma (n=1 case) and subcutaneous panniculitis-like T-cell lymphoma (n=1 case). Doxorubicin was also administered to pregnant patients to treat acute lymphocytic leukemia (n=22), acute myelogeneous leukemia (n=15 cases) and acute promyelogenous leukemia (n=1 case), chronic myelogenous leukemia (n=1), and erythroleukemia (n=1). No cancer type was specified for 4 patients. A total of 417 pregnancies with 420 conceptuses were exposed to doxorubicin, including three twin pregnancies (Cardonick *et al.* 2010, Lycette *et al.* 2006, Nantel *et al.* 1990) and three patients who had two pregnancies each (Aviles and Niz 1988, Dilek *et al.* 2006). Doxorubicin was administered during the 1st trimester in 42 pregnancies (42 conceptuses) and in the 2nd and/or 3rd trimester only in 326 pregnancies (329 conceptuses due to three sets of twins). Timing of exposure for individual patients was not specified in two case series (n=49 cases) (Hahn *et al.* 2006, Jameel and Jamil 2007). However, it was assumed that these cases were likely exposed in the 2nd and/or 3rd trimester with the age of initiation of chemotherapy ranging from 11-34 weeks (median 23 weeks (Hahn *et al.* 2006)) or 12-33 weeks (mean = 24 weeks (Jameel and Jamil 2007)). Thus, the total pregnancies exposed to doxorubicin in the 2nd and/or 3rd trimester only were calculated as 375 pregnancies and 378 conceptuses.

Fetal loss was reported for 12 singleton pregnancies with autopsy data reported for only two fetuses. Spontaneous abortion occurred in two pregnancies following 1st trimester exposure and co-treatment

with vincristine (Peres *et al.* 2001) or vincristine and cytarabine (Awidi *et al.* 1983); no fetal autopsy data were provided. Induced abortion terminated one normal fetus that was exposed to doxorubicin in the 1st trimester and co-exposed to nitrogen mustard, vincristine, procarbazine, bleomycin, vinblastine, and dacarbazine (Peres *et al.* 2001). Although the fetus was not deformed, the authors reported toxic degeneration of the liver and kidneys (Peres *et al.* 2001). A second pregnancy was terminated by induced abortion and no fetal data were available (Zuazu *et al.* 1991). Spontaneous abortion occurred in one pregnancy following 2nd and/or 3rd trimester exposure and co-exposure to cyclophosphamide, vincristine, and dacarbazine (Jameel and Jamil 2007). A third induced abortion was reported following exposure in the 2nd trimester (d'Incalci *et al.* 1983); no fetal data were reported. Normal fetuses were observed in two intrauterine fetal deaths: one death occurred at 30 weeks of gestation following exposure during the 2nd trimester and co-exposure to vincristine, cyclophosphamide, rituximab (Cardonick *et al.* 2010), and a stillbirth was reported at 31 weeks of gestation following exposure during the 3rd trimester and co-exposure to vincristine (Karp *et al.* 1983). Intrauterine fetal demise was reported for three additional pregnancies, which did not provide fetal autopsy data: one intrauterine fetal death occurred at gestation week 26 following 2nd trimester exposure and co-treatment with cytarabine and 6-thioguanine (Zemlickis *et al.* 1992); a stillbirth occurred in the 8th month of pregnancy after 2nd and 3rd trimester exposure and co-exposure to bleomycin, vinblastine, and dacarbazine (Dilek *et al.* 2006); and another pregnancy experienced oligohydramnios and intrauterine growth restriction ending in stillbirth following 2nd trimester exposure and co-treatment with cyclophosphamide, ifosfamide, etoposide, cytarabine, vincristine and rituximab (Peterson *et al.* 2010). In addition, a maternal death resulted in the death of the fetus following exposure in the 2nd trimester (Roboz *et al.* 1979).

There were 408 live born infants exposed in utero to doxorubicin and 18 of these infants had malformations. Major malformations were observed in nine infants. One infant exposed in the 1st trimester had a floating thumb malformation (e.g. partial agenesis of a metacarpal bone and hypoplasia of two phalanges) (Dilek *et al.* 2006). Two additional infants had skeletal malformations following 1st trimester exposure: bilateral loss of radius and 5th digit as well as an atrial septum defect were observed in an infant who was also exposed to cytarabine and vincristine (Ebert *et al.* 1997), and multiple skeletal deformities of the hand, flat nasal bridge, high arched palate, ventriculomegaly, colopocephaly, and a bicuspid aortic valve were reported for an infant co-exposed to cyclophosphamide and 5-fluorouracil (Paskulin *et al.* 2005). An imperforate anus and rectovaginal fistula was reported in one newborn exposed in the 1st and 2nd trimester and co-treated with cyclophosphamide and cobalt radiation therapy (Murray *et al.* 1984). Syndactyly of the 4th and 5th fingers occurred in one infant exposed in the 2nd and 3rd trimesters (Cardonick *et al.* 2010); this infant was co-exposed to bleomycin, vinblastine and dacarbazine. Bilateral partial syndactyly of digits II and III occurred in one infant following 2nd and 3rd trimester exposure and co-exposure to nitrogen mustard, vincristine, procarbazine, bleomycin and vinblastine as well as 2nd trimester exposure to radiation therapy (Van Calsteren *et al.* 2010). Clubfoot (n=1 infant) and Down syndrome (n=1 infant) were observed after 2nd and 3rd trimester exposure and co-exposure to cyclophosphamide and 5-fluorouracil (Hahn *et al.* 2006). Pyloric stenosis occurred in one infant exposed in the 2nd and 3rd trimester and co-exposed to cyclophophamide, docetaxel and paclitaxel (Cardonick *et al.* 2010).

Minor malformations occurred in 9 infants of patients treated with doxorubicin during pregnancy, including three anomalies that resolved. One infant had plagiocephaly following 2nd and 3rd trimester exposure and was co-exposed to bleomycin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Bilateral ureteral reflex occurred in an infant exposed in the 2nd and/or 3rd trimester and co-exposed to cyclophosphamide and 5-fluorouracil (Hahn *et al.* 2006). One infant had a hemangioma on its abdomen

following exposure in the 2nd and 3rd trimesters and co-treatment with cyclophosphamide (Ring *et al.* 2005); the authors deemed this anomaly was not caused by chemotherapy (Ring *et al.* 2005). **[It is possible that the infant with the hemangioma was, instead, treated with cyclophosphamide and either epirubicin or 5-fluorouracil and methotrexate; the authors did not report the treatments of individual patients {Ring, 2005 #373}.]** Double cartilage rings were reported in an infant with 2nd and 3rd trimester exposure and co-exposure to 5-fluorouracil and cyclophosphamide in the 2nd and 3rd trimester as well as radiation therapy in the 1st and 2nd trimesters (Van Calsteren *et al.* 2010). Hip subluxation was reported in another infant exposed in 2nd and 3rd trimesters and co-exposed to cyclophosphamide (Van Calsteren *et al.* 2010). Pectus excavatum occurred in one infant following 2nd and 3rd trimester exposure and co-exposure to nitrogen mustard, vincristine, procarbazine, bleomycin and vinblastine (Van Calsteren *et al.* 2010). Three infants had minor malformations that were resolved without intervention. Suspected holoprosencephaly was reported for a newborn exposed in the 2nd and 3rd trimesters and co-treated with cyclophosphamide and docetaxel (Cardonick *et al.* 2010); however, this infant was normal at age 2.6 years with prominent lateral ventricles. A minor ventricular septal defect occurred in a newborn exposed in the 3rd trimester (Peretz and Peretz 2003); the defect resolved without intervention within 2 years and two of the child's siblings also had ventricular septal defects. Finally, mild hydrocephalus observed in a newborn resolved over several months (Potluri *et al.* 2006); the pregnancy was exposed in the 2nd trimester and co-exposed to cyclophosphamide in the 2nd trimester and docetaxel in the 2nd and 3rd trimesters.

A variety of pregnancy complications and infant health issues were observed with exposure to doxorubicin during pregnancy. Intrauterine growth restriction was reported in 8 singleton pregnancies (D'Emilio *et al.* 1989, Fadilah *et al.* 2006, Lambert *et al.* 1991, Merimsky *et al.* 1999, Ring *et al.* 2005, Ustaalioglu *et al.* 2010), including one with oligohydramnios {Nakajima, 2004 #316} and two with a reduction in amniotic fluid {Cordoba, 2010 #832;Peterson, 2008 #1099}. Oligohydramnios was reported for 3 additional pregnancies {Mir, 2012 #1221}{Meyer-Wittkopf, 2001 #293}{Shieh, 2011 #1065}. Preeclampsia was observed in 8 pregnancies {Anselmo, 1999 #44}{Bartsch, 1988 #615}{Berry, 1999 #484}{Kuerer, 2002 #495}{Gonzalez-Angulo, 2004 #90}{Lambert, 1991 #248}{Potluri, 2006 #361}{Chakravarty, 2011 #860}. Spontaneous preterm labor was reported in 16 pregnancies {Berry, 1999 #484}{Decker, 2006 #403}{Fassas, 1984 #231}{Karp, 1983 #129}{Meador, 1987 #283}{Mir, 2012 #1221}{Moore, 1991 #718}{Nantel, 1990 #317}{Tobias, 1980 #546}{Webb, 1980 #906;Willemse, 1990 #573}, including two pregnancies with transient preterm labor {Lycette, 2006 #265}{Meyer-Wittkopf, 2001 #293}. Maternal hypotension occurred in one case {Turchi, 1988 #433}. Of the 156 infants with individual data on gestational age at delivery, early preterm delivery (<34 weeks) was reported for 31 pregnancies (19.9%), late preterm delivery (34-36 weeks) was reported for 57 pregnancies (36.5%), and 68 pregnancies were delivered at term (43.6%). Twelve newborns were reported to be small for gestational age per the authors (Berry *et al.* 1999)(Dilek *et al.* 2006){Nakajima, 2004 #316}{Magloire, 2006 #268}{Cardonick, 2010 #7}. Respiratory distress and transient breathing difficulties occurred in 31 infants. Hypocapnia with extreme hypotonia occurred in one newborn (Cardonick *et al.* 2010) and another newborn experienced asystole immediately after birth (Willemse *et al.* 1990). Transient myelosuppression was reported in 10 newborns, including: 4 infants with anemia {Aviles, 1988 #772}(Cardonick *et al.* 2010, Nakajima *et al.* 2004), one infant with decreased B-cells (Decker *et al.* 2006), 3 infants with leucopenia (Berry *et al.* 1999, Khurshid and Saleem 1978), 3 infants with neutropenia and/or thrombocytopenia (Cardonick *et al.* 2010, Hahn *et al.* 2006). One of the infants with leukopenia was had necroptizing enterocolitis, which was treated and resolved {Garcia, 1999 #69}. One infant had polycythemia (Dara *et al.* 1981). Two newborns experienced substantial hair loss (Berry *et al.* 1999). Other health effects observed in the live born infants included: jaundice (n=14 infants), hypoglycemia (n=1 infant), and calcium-deficiency requiring intravenous calcium (n=1 infant). One

newborn had gastroesophageal reflux (Cardonick *et al.* 2010) and two additional infants required temporary feeding tubes (Cardonick *et al.* 2010, Nakajima *et al.* 2004). Two infants had cerebral hemorrhage (Hahn *et al.* 2006, Veneri *et al.* 1996). Infections were reported for three neonates, including sepsis (Cardonick *et al.* 2010, Peres *et al.* 2001, Willemse *et al.* 1990) and bronchopneumonia (Peres *et al.* 2001).

Of the 312 infants with follow-up evaluations at 10 weeks to 19 years, normal growth and development were reported for all but 7 children. One infant died at 13 months from a severe autoimmune disorder (Cardonick *et al.* 2010). Delayed growth and development were reported for a 3-year old child, who was born with bilateral ventriculomegaly and colpocephaly as well as a heart defect and skeletal defects of the skull and hands (Paskulin *et al.* 2005). Other developmental delays included: Down syndrome (Hahn *et al.* 2006) and two children with speech delays (Cardonick *et al.* 2010). One child was treated for gastroesophageal reflux, eczema and sinusitis (Cardonick *et al.* 2010). Finally, attention deficit-hyperactivity disorder was reported for one child of school age (Hahn *et al.* 2006). At age 5.8 years, one child was progressing normally after a diagnosis of developmental delay and periventricular leukomalacia at age 2 months followed by early intervention with occupational and physical therapy (Cardonick *et al.* 2010). By 6.5 years, this child had not had a seizure in 1 year. Other notable health effects observed in follow-up evaluations were several children with infections or allergic conditions including: recurrent otitis media, including one with a speech delay (n=5 children); reactive airway disease (n=2 children); asthma (n=1 child); selective IgA deficiency not requiring treatment (n=1 child); and chronic broncholitis (n=1 child) (Cardonick *et al.* 2010).

5.16.5 *Summary of pregnancy outcomes for doxorubicin*

In utero exposure to doxorubicin was documented for 417 pregnancies with a total of 420 conceptuses, including three sets of twins. Of the 42 singleton pregnancies (42 conceptuses) exposed during the 1st trimester, there were four newborns with major malformations. Three infants had skeletal malformations: a floating thumb malformation (e.g. partial agenesis of a metacarpal bone and hypoplasia of two phalanges) (Dilek *et al.* 2006); bilateral loss of radius and 5th digit as well as an atrial septum defect (Ebert *et al.* 1997); and multiple skeletal deformities of the hand, cranium as well as ventriculomegaly, colpocephaly, and a bicuspid aortic valve (Paskulin *et al.* 2005). A fourth infant had an imperforate anus and rectovaginal fistula (Murray *et al.* 1984). In addition, spontaneous abortion occurred in two pregnancies following 1st trimester exposure (Awidi *et al.* 1983, Peres *et al.* 2001); no fetal autopsy data were provided. Induced abortion terminated two pregnancies exposed to doxorubicin in the 1st trimester: one case reported a normal fetus at autopsy (Peres *et al.* 2001) and the second case did not report fetal data (Zuazu *et al.* 1991). The total occurrence of major malformations following 1st trimester exposure is 9.5% (4/42 conceptuses).

There were 375 pregnancies exposed in the 2nd and/or 3rd trimester only for a total of 378 conceptuses due to three sets of twins. The total number of pregnancies exposed in the 2nd and/or 3rd trimester only included two case series of a total of 49 pregnancies in which chemotherapy was initiated between the gestational weeks 11th to 34th (median=23 weeks of gestation) (Hahn *et al.* 2006) and 12th to 33rd (median=22 weeks of gestation) (Jameel and Jamil 2007). Five infants were born with major malformations following exposure to doxorubicin in the 2nd and/or 3rd trimester only. Skeletal malformations were reported for three infants, including: syndactyly of the 4th and 5th fingers (n=1 infant) (Cardonick *et al.* 2010), bilateral partial syndactyly of digits II and III (n=1 infant) (Van Calsteren *et al.* 2010), and clubfoot (n=1 infant) (Hahn *et al.* 2006). The remaining major malformations reported were pyloric stenosis (n=1 infant) (Cardonick *et al.* 2010) and Down syndrome (n=1 infant) (Hahn *et al.* 2006). Minor malformations were observed in 9 infants, including: plagiocephaly (n=1 infant) (Cardonick

et al. 2010); bilateral ureteral reflux (n=1 infant) (Hahn *et al.* 2006); hemangioma (Ring *et al.* 2005), pectus excavatum (n=1 infant), doubled cartilage rings in both ears (n=1 infant) and hip subluxation (congenital hip dysplasia; n=1 infant) (Van Calsteren *et al.* 2010), and suspected holoprosencephaly diagnosed prenatally (n=1 infant) (Cardonick *et al.* 2010). Three of the minor malformations occurring following 2nd and/or 3rd trimester only were resolved without treatment: suspected holoprosencephaly (Cardonick *et al.* 2010), minor ventricular septal defect (Peretz and Peretz 2003), and mild hydrocephalus (Potluri *et al.* 2006). In addition, fetal loss occurred during 8 pregnancies due to spontaneous abortion (n=1 case) (Jameel and Jamil 2007), induced abortion (n=1 case) (d'Incalci *et al.* 1983), maternal death (n=1 case) (Roboz *et al.* 1979), and intrauterine fetal demise/stillbirth (n=5) (Dilek *et al.* 2006, Peterson *et al.* 2010, Zemlickis *et al.* 1992). Autopsy reported normal fetuses for one intrauterine fetal demise (Cardonick *et al.* 2010) and one stillbirth (Karp *et al.* 1983), and the remainder of the pregnancies with fetal loss did not report fetal autopsy data. The total occurrence of major malformations following exposure in the 2nd and 3rd trimester only was 1.3% (5/378 conceptuses).

Pregnancy complications and infant health effects were observed in several pregnancies. Pregnancy complications included intrauterine growth restriction (n=8 singleton pregnancies) {D'Emilio, 1989 #211;Fadilah, 2006 #227;Lambert, 1991 #248}{Merimsky, 1999 #784;Nakajima, 2004 #316;Ustaalioglu, 2010 #830}{Ring, 2005 #373}, including one with oligohydramnios {Nakajima, 2004 #316} and two with a reduction in amniotic fluid {Cordoba, 2010 #832;Peterson, 2008 #1099}. Oligohydramnios was reported for 3 additional pregnancies {Mir, 2012 #1221}{Meyer-Wittkopf, 2001 #293}{Shieh, 2011 #1065}. Of the 156 pregnancies reporting individual gestational age at delivery, preterm delivery was reported for 88 pregnancies. Twelve newborns were reported to be small for gestational age per the authors (Berry *et al.* 1999)(Dilek *et al.* 2006){Nakajima, 2004 #316}{Magloire, 2006 #268}{Cardonick, 2010 #7}. Other frequently occurring health effects in infants with in utero exposure to doxorubicin included respiratory distress and transient breathing difficulties (n=31 infants), transient myelosuppression (n=10 infants), jaundice (n=14 infants), difficulties in feeding (n=3 infants), and infections (n=3 infants). One infant died at 13 months from a severe autoimmune disorder (Cardonick *et al.* 2010). Follow-up evaluations of 308 offspring ranging in age from 10 weeks to 19 years reported normal growth and development for all but 7 children. One infant died at 13 months from a severe autoimmune disorder (Cardonick *et al.* 2010). Delayed growth and development were reported for a 3-year old child, who was born with bilateral ventriculomegaly and colpocephaly as well as cardiac and skeletal defects (Paskulin *et al.* 2005). Two children with speech delays (Cardonick *et al.* 2010), one child had Down syndrome (Hahn *et al.* 2006), and attention deficit-hyperactivity disorder was reported for one child of school age (Hahn *et al.* 2006). Finally, one child was treated for gastroesophageal reflux, eczema and sinusitis (Cardonick *et al.* 2010). One child was progressing well at 5.8 to 6.5 years, after being diagnosed with developmental delay and periventricular leukomalacia at age 2 months and receiving early intervention with occupational and physical therapy (Cardonick *et al.* 2010).

In conclusion, the total occurrence of major malformations in doxorubicin-exposed pregnancies was 2.1% (9/420 conceptuses). The occurrence of major malformations following 1st trimester exposure (4/42 conceptuses) is higher than the prevalence of birth defects in the general population (9.5 ± 8.9% versus 3.0%). The occurrence of major malformations following 2nd and/or 3rd trimester only (5/378 conceptuses) is similar to or lower than the prevalence of birth defects in the general population (1.3% ± 1.2%). Of these five malformations, the two cases of syndactyly and one case of Down syndrome were unlikely to have resulted from chemotherapy exposure in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations in the 2nd and/or 3rd trimester only was 0.5 ± 0.7% (2/378 conceptuses).

5.17 EPIRUBICIN

5.17.1 *Mechanism of action, route of administration, and indications*

Epirubicin (epirubicin hydrochloride) is an anthracycline cytotoxic agent, which is a semi-synthetic derivative of daunorubicin and the 4-epimer of doxorubicin (Mayne 2006). Epirubicin intercalates between nucleic acid base pairs resulting in the inhibition of synthesis of nucleic acids (DNA and RNA) and proteins. The intercalation of epirubicin inhibits the enzyme topoisomerase II, which cleaves DNA. Epirubicin also inhibits DNA synthesis by interfering with the DNA helicase enzyme, the enzyme responsible for separating strands of DNA for replication. Epirubicin may also cause the generation of free radicals. Epirubicin is administered intravenously and is indicated for the treatment of breast cancer.

5.17.2 *Evidence of placental and breast milk transport*

Placental and breast milk transport of epirubicin in humans is currently unknown. However, epirubicin has a low molecular weight (534-580, depending on formulation), which could facilitate its transport across the placenta or into breast milk in humans. In the baboon, the fetal plasma levels of epirubicin were 4.0±1.6% (n=8) of maternal plasma levels when tested at multiple time-points within three hours of intravenous dose administration to the mother (Van Calsteren *et al.* 2010); three of the fetal blood samples were below the lower limit of quantification. Levels of epirubicin reached up to nine times higher in amniotic fluid than in fetal plasma, and fetal tissue levels averaged 8.7±8.1% of maternal tissue concentrations (Van Calsteren *et al.* 2010). A similar rate of transplacental transfer (4.8±3.8%) was observed following intravenous injection of epirubicin to pregnant mice (Van Calsteren *et al.* 2010). It is not known if epirubicin is transfered into breast milk. The manufacturers product label reports that epirubicin was excreted into the milk of rats administered intravenous epirubicin (0.50 mg/kg/day) during peri- and postnatal periods (Mayne 2006).

5.17.3 *Laboratory animal developmental toxicity*

Epirubicin has been shown to induce embryolethal and teratogenic effects in laboratory animals (Mayne 2006). In rats, embryotoxicity (increased resorptions and postimplantation loss) and fetal growth retardation were observed following intravenous epirubicin doses of 0.8 mg/kg/day (~0.04 times the maximum recommended single human dose on a body surface area basis) to pregnant dams on gestation Days 5 to 15; however, no teratogenic effects were observed up to this dose (Mayne 2006). In contrast, embryotoxicity (including dead fetuses), decreases in fetal body weight and placenta weight, and malformations were observed in the fetuses of pregnant rats administered the drug at 2 mg/kg/day intravenously (~0.1 times the maximum recommended single human dose on a body surface area basis) on gestation Day 9 and 10.   Malformations included: anal atresia, misshapen tail, abnormal genital tubercle, visceral malformations (primarily gastrointestinal, urinary, and cardiovascular systems), and skeletal defects, including: deformed long bones and girdles, rib abnormalities, and irregular spinal ossification(Mayne 2006). In the rabbit, dose-dependent effects of epirubicin were observed. Intravenous doses of 0.2 mg/kg/day (~0.02 times the maximum recommended single human dose on a body surface area basis) to pregnant rabbits on gestation days 6 to 18 was not embryotoxic or teratogenic, but doses of 0.32 mg/kg/day were maternally toxic, increased abortions and delayed ossification(Mayne 2006). An increase in spontaneous abortion, but no other toxicity, was reported following administration of a maternally toxic dose of 1 mg epirubicin/kg/day (~0.1 times the maximum recommended single human dose on a body surface area basis) to pregnant rabbits on days 10 to 12 of gestation. In the rat , no permanent changes were observed in the development, functional activity, behavior, or reproductive performance of offspring exposed during lactation to epirubicin via

administration of ≤0.5 mg/kg/day (~0.025 times the maximum recommended single human dose on a body surface area basis)to the rat dam on days 17-21 after delivery were administered to rat dams on day 17 to day 21 after delivery(Mayne 2006).

5.17.4 Human gestational exposure and effects

Epirubicin is classified as FDA Pregnancy Category D. There were 69 patients treated with epirubicin during pregnancy identified from 9 case reports, 5 case series, 2 retrospective case series, 1 retrospective cohort study, 5 retrospective surveys, and 1 registry survey (Appendix C Table 16). Among these patients, epirubicin was used to treat breast cancer (n=60 cases), Hodgkin lymphoma (n=4 cases), non-Hodgkin lymphoma (n=6 cases) and acute lymphocytic leukemia (n=1 case); cancer type was not specified for 2 patients. A total of 69 singleton pregnancies (69 conceptuses) were exposed to epirubicin. There were 7 pregnancies exposed to epirubicin in the 1st trimester, and 61 pregnancies exposed in the 2nd and/or 3rd trimester only; timing of exposure was not specified in 1 cases.

Fetal loss occurred in 5 pregnancies exposed to epirubicin. Two spontaneous abortions occurred following exposure during the 1st trimester and co-exposure to 5-fluorouracil and cyclophosphamide or vincristine and methotrexate (Giacalone *et al.* 1999); no autopsy data were provided. A malformed fetus was terminated by induced abortion following 1st trimester exposure and co-treatment with cyclophosphamide and 5-fluorouracil (1st and 2nd trimesters), methotrexate (2nd trimester), and radiation therapy (1st trimester) (Leyder *et al.* 2010). The malformations included micrognathia, skin syndactyly of 1st and 2nd fingers of both hands, shortened 2nd and 3rd fingers on both hands, and osseous syndactyly of 4th and 5th metatarsal bones on both feet. Intrauterine fetal demise occurred in two pregnancies following 2nd trimester exposure and co-exposure to cyclophosphamide (Giacalone *et al.* 1999) or vincristine (Peres *et al.* 2001); no fetal autopsy data were reported.

Of the 64 live-born infants exposed to epirubicin in utero, malformations were observed in 6 infants. Major malformations occurred in 4 infants. Polycystic kidney was reported in an infant with 2nd trimester exposure (Azim *et al.* 2008); co-treatments were not specified. Clubfoot, a major malformation, and a left eye hemangioma, a minor malformation, were reported in an infant exposed in the 2nd and 3rd trimesters and co-exposed to cyclophosphamide (Cardonick *et al.* 2010). Rectal atresia was observed in two infants with 2nd and 3rd trimester exposure and no co-treatments (Van Calsteren *et al.* 2010) or with co-exposure to paclitaxel (Halaska *et al.* 2009).   Two infants had minor malformations: small bilateral protuberance on phalanx 5 following 2nd and 3rd trimester exposure and co-treatment with 5-fluorouracil and cyclophosphamide (Van Calsteren *et al.* 2010), and a hemangioma located on the abdomen following 2nd and 3rd trimester exposure and co-exposure to cyclophosphamide (Ring *et al.* 2005). **[It is possible that the infant with the hemangioma was, instead, treated with cyclophosphamide and either doxorubicin or 5-fluorouracil and methotrexate; the authors did not report the treatments of individual patients {Ring, 2005 #373}.]** One newborn died 8 days after birth with no obvious malformations (Giacalone *et al.* 1999); no cause of death was determined. This infant was exposed in the 3rd trimester and co-exposed to 5-fluorouracil and cyclophosphamide (Giacalone *et al.* 1999).

Pregnancy complications and other health effects were observed in a few cases following in utero exposure to epirubicin. Premature rupture of fetal membranes {Ginopoulos, 2004 #668} and eclamptic seizures {Muller, 1996 #1332} were reported for one pregnancy each. Spontaneous preterm labor preceded preterm delivery in two cases (Andreadis *et al.* 2004){Sharma, 2009 #391}. Intrauterine growth restriction due to placental insufficiency occurred in one fetus (Ring *et al.* 2005). Of the 29 pregnancies reporting individual delivery date, early preterm delivery (>34 weeks gestation) was

reported for 2 pregnancies (6.8%), late preterm delivery (34-36 weeks gestation) was reported for 19 pregnancies (65.5%) and 8 pregnancies were delivered at term (27.6%). No newborns were reported to be small for gestational age. Breathing difficulties were observed in three infants, including respiratory distress (n=2 infants) (Ring *et al.* 2005) and mild transient tachypnea requiring oxygen treatment (n=1 infant) (Ginopoulos *et al.* 2004). One newborn had leucopenia (Giacalone *et al.* 1999) and another infant had anemia at 21 days (Cuvier *et al.* 1997). Hypoglycemia and feeding difficulties at birth were observed in one infant (Eedarapalli *et al.* 2007). Follow-up evaluations were available for 48 offspring ranging in age from 6 weeks to 29 years and all children had normal growth and development. At age 3, the child with left eye hemangioma at birth had left eye squinting (Cardonick *et al.* 2010).

5.17.5 *Summary of pregnancy outcomes for epirubicin*

In utero exposure to epirubicin was documented for 69 singleton pregnancies (69 conceptuses). Of the 7 pregnancies exposed in the 1st trimester, major malformations were observed in one fetus terminated by induced abortion (Leyder *et al.* 2010); malformations included skin syndactyly and shortened digits affecting two fingers each on both hands, and osseous syndactlyly of 4th and 5th metatarsal bones on both feet. In addition, two spontaneous abortions occurred after 1st trimester exposure and no fetal autopsy data were reported. A total occurrence of major malformations following 1st trimester exposure to epirubicin was 14.3% (1/7 conceptuses). Of the 61 pregnancies with exposure in the 2nd and/or 3rd trimester only, four infants had major malformations. The malformations included polycystic kidney (n=1 infant) (Azim *et al.* 2008), rectal atresia (n=2 infants) (Halaska *et al.* 2009, Van Calsteren *et al.* 2010), and clubfoot as well as left eye hemangioma, a minor malformation (Cardonick *et al.* 2010). Minor malformations were reported for two other infants with exposure in the 2nd and 3rd trimester: a small bilateral protuberance on phalanx 5 (Van Calsteren *et al.* 2010) and hemangioma on the abdomen (Ring *et al.* 2005). Intrauterine fetal demise occurred in two pregnancies exposed in the 2nd and/or 3rd trimester and no fetal autopsy data were reported. The timing of exposure was not specified for 5 singleton pregnancies yielding 5 normal infants. A total occurrence of major malformations following 2nd and/or 3rd trimester was 6.6% (4/61 conceptuses). Pregnancy complications included: premature rupture of fetal membranes (n=1 pregnancy), spontaneous preterm labor (n=1 pregnancy), and signs of premature labor (n=1 pregnancy). Intrauterine growth restriction due to placental insufficiency occurred in one fetus (Ring *et al.* 2005). Of the 29 pregnancies reporting individual gestational age at delivery, preterm delivery was reported for 21 pregnancies. None of the newborns were reported to be small for gestational age. Health effects observed in the infants included respiratory difficulties (n=3 infants), myelosuppression (n=2 infants), and eating difficulties (n=1 infants). Follow up examinations reported normal growth and development for 48 offspring ranging in age from 6 weeks to 29 years.

In conclusion, the total occurrence of major malformation in epirubicin-exposed pregnancies was 7.2% (5/69 conceptuses). The occurrence of major malformations following exposure to epirubicin in the 1st trimester (1/7 conceptuses) was higher than the prevalence of birth defects in the general population (14.3 ± 25.9 versus 3%); however, this estimate may not be accurate because it is based on a small number of reported cases. The occurrence of major malformations following 2nd and/or 3rd trimester exposure only (4/61 conceptuses) is higher than the prevalence of birth defects in the general population (6.6 ± 6.2% versus 3%). Of these four malformations, the two cases of rectal atresia are unlikely to have resulted from chemotherapy exposure in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations following exposure to epirubicin in the 2nd and/or 3rd trimester only was 3.3 ± 4.5% (2/61 conceptuses).

5.18 ETOPOSIDE

5.18.1 Mechanism of action, route of administration, and indications

Etoposide is a semisynthetic antineoplastic agent derived from podophyllotoxin extracted from the roots and rhizomes of Podophyllum species. Etoposide inhibits cell proliferation most dramatically at the G2 stage and metaphase (Bristol-Myers Squibb 2011). Etoposide induces DNA strand breaks by the formation of free radicals and via its interaction with the DNA-topoisomerase II enzyme, and inhibits DNA synthesis. Etoposide is administered via intravenous injection. It is used to treat Hodgkin lymphoma and ovarian, testicular, and small cell lung cancers.

5.18.2 Evidence of placental and breast milk transfer

Placental transport of etoposide in humans is unknown, while breast milk transfer of etoposide has been documented in one lactating patient. Azuno et al. (Azuno *et al.* 1995) measured etoposide in breast milk collected every 3-4 hours for one week beginning with the 3rd of 5 daily doses of etoposide (80 mg/m^2) of a 3rd consolidation therapy. Etoposide was detected in the breast milk samples (580 to 800 ng/mL) collected immediately after administration and was no longer detectable in samples collected 24 hours post-treatment.

5.18.3 Laboratory animal developmental toxicity

Embryolethal and teratogenic effects were observed in rats and mice exposed to etoposide during the period of organogenesis (Bristol-Myers Squibb 2011). Embryotoxicity, skeletal defects, exencephaly, encephalocele, and anopthalamia were observed in rat fetuses of dams administered an intravenous dose of 0.4 mg etoposide/kg/day (~1/20 of the human dose on a mg/m^2 basis) during organogenesis (Bristol-Myers Squibb 2011); this same dose also caused maternal toxicity. Higher doses of 1.2 and 3.6 mg/kg/day etoposide (~1/7 and 1/2 of the human dose on a mg/m^2 basis) resulted in 90% and 100% embryonic resorptions. Embryotoxicity, cranial defects and major skeletal malformations were observed in fetal mice following a single dose of etoposide at 1.0 mg/kg (1/16 of the human dose on a mg/m^2 basis) administered intraperitoneally on days 6, 7, or 8 of gestation. When administered at 1.5 mg/kg intraperitoneally to pregnancy mice on day 7 of gestation, etoposide caused an increase in the incidence of intrauterine death, a decrease in fetal body weight and an increase in fetal malformations, including: exencephaly, encephalocele, hydrocephalus, gastroschisis (including abnormal stomach or liver), microphthalmia or anophthalmia, dextrocardia and axial skeletal defects (Sieber *et al.* 1978). Etoposide administered intravenouslsy at dose levels of 0.25 to 2 mg/kg/day to pregnant Japanese White rabbits (Kb1:JW) on gestation days 7-9 resulted in an increased incidence of fusion, bifurcation, malposition and misshapen ribs and vertebrae; extra ribs were only observed at the 2mg/kg/day dose (Nagao *et al.* 1999). Whole-embryo rat cultures treated with 2 µM etoposide resulted in growth retardation, brain anomalies, and microphthalmia (Mirkes and Zwelling 1990).

5.18.4 Human gestational exposure and effects

Etoposide is classified as FDA Pregnancy Category D. There were 42 published cases of patients treated with etoposide during pregnancy identified from 18 case reports, 7 case series, 2 retrospective case series, 1 retrospective survey, 1 retrospective cohort study, and 1 registry survey (Appendix C Table 17). Among these patients, etoposide was primarily used to treat ovarian cancer (n=19 cases), non-Hodgkin lymphoma (n=10 cases), Burkitt lymphoma (n=2 cases), and Hodgkin lymphoma (n=2 cases). It was also used to treat acute myelogenous leukemia (n=4 cases), acute lymphocytic leukemia (n=1 case), adenocarcinoma (of unknown primary cancer) (n=1 case), choriocarcinoma of the uterus (n=1 case),

lung cancer (n=1 case) and neuroblastoma (n=1 case). A total of 42 singleton pregnancies (42 conceptuses) were exposed to etoposide. Etoposide was administered in the 1st trimester in 3 cases and in the 2nd and/or 3rd trimester only in 39 cases. Although the exact timing of exposure was not specified in one case report (Brudie *et al.* 2011), the administration of chemotherapy occurred after 20 weeks of gestation and, thus, it was included as a pregnancy with 2nd and/or 3rd trimester only exposure

Fetal loss was reported for three pregnancies. One induced abortion followed exposure in the 2nd trimester and co-treatment with daunorubicin and cytarabine (Chelghoum *et al.* 2005); no fetal autopsy data were provided. One intrauterine fetal demise at gestational week 26 of a normal fetus occurred following exposure in the 2nd trimester and co-exposure to cisplatin (Peres *et al.* 2001). Another intrauterine fetal demise (a stillbirth) at gestation week 26 followed oligohydramnios at gestation week 18 and intrauterine growth restriction at gestation week 22, and no fetal autopsy data were reported (Peterson *et al.* 2010). This pregnancy was exposed in the 2nd trimester and co-exposed to cyclophosphamide, doxorubicin, ifosfamide, cytarabine, vincristine, and rituximab (Peterson *et al.* 2010).

Of the 39 live-born infants exposed in utero to etoposide, three infants had malformations. Two of these infants had major malformations. One newborn had ventriculomegaly, which was diagnosed prenatally, and cerebral atrophy (Elit *et al.* 1999); this infant was exposed in the 2nd trimester and co-exposed to bleomycin and cisplatin. Genetic hearing loss (the infant's parents were carriers) and a spontaneous mutation for neurofibromatosis were identified in an infant exposed in the 2nd and 3rd trimesters and co-treated with bleomycin and cisplatin (Cardonick *et al.* 2010). One infant had a minor malformation: mild glandular hypospadias (considered a first degree hypospadias) (Ghaemmaghami *et al.* 2009); the infant was exposed during the 2nd trimester and co-exposed to bleomycin and cisplatin.

A variety of other fetal and infant health outcomes were observed following etoposide exposure during pregnancy. Preeclampsia occurred in two pregnancies {Benjapibal, 2010 #841;Horbelt, 1994 #537;Siu, 2002 #410}, premature rupture of membranes was reported in one pregnancy {Ghaemmaghami, 2006 #77}, and spontaneous preterm labor was reported in three pregnancies {Moore, 1991 #718;Raffles, 1989 #535}{Brudie, 2011 #1094}. Oligohydramnios was observed in two pregnancies {Buller, 1992 #909;Ghaemmaghami, 2009 #76} and a reduction in amniotic fluid was reported for two pregnancies (Scherf and Price 1996){Peterson, 2008 #1099}. An inhibition of fetal growth was observed in 9 pregnancies, including intrauterine growth restriction (Arango *et al.* 1994, Benjapibal *et al.* 2010, Buller *et al.* 1992, Hsu *et al.* 1995, Peterson *et al.* 2010), estimated fetal weight <5th percentile (Ghaemmaghami *et al.* 2009), small for gestational age fetus (Han *et al.* 2005), and a cessation of fetal growth (Murray *et al.* 1994, Scherf and Price 1996). **[Murray et al. (Murray *et al.* 1994) and Scherf et al. (Scherf and Price 1996) appear to be the same case, but are considered as two separate case reports in this evaluation.]** Of the 32 pregnancies reporting age at delivery, early preterm delivery (<34 weeks) was reported for 7 pregnancies (21.9%), late preterm delivery (34-36 weeks) was reported for 11 pregnancies (34.4%), and 14 pregnancies were carried to term (43.8%). Small for gestational age was reported for one newborn (Cardonick *et al.* 2010). Breathing difficulties were reported for six infants (Elit *et al.* 1999, Lam 2006, Malhotra and Sood 2000, Murray *et al.* 1994, Raffles *et al.* 1989, Scherf and Price 1996). Transient myelosuppression was reported in six infants (Horbelt *et al.* 1994, Hsu *et al.* 1995, Murray *et al.* 1994, Peres *et al.* 2001, Raffles *et al.* 1989, Scherf and Price 1996) and one infant had jaundice (Peres *et al.* 2001). One infant, who experienced both respiratory distress and leucopenia with neutropenia in the first 2 weeks of life, also had alopecia at age 10 days (Raffles *et al.* 1989). Follow-up evaluations were available for 25 infants ranging in age from 2 months to 15 years. Normal growth and development were reported in all but four children. One child had genetic hearing loss and a spontaneous mutation for neurofibromatosis and another child with motor/language delay at age one

year (Cardonick *et al.* 2010). One 14-month old infant had delayed motor skills, which the authors suspected were due to premature birth (Lam 2006). Moderate sensorineural hearing loss, but normal neurodevelopmental progress, was reported for a one-year old child (Raffles *et al.* 1989).

5.18.5 *Summary of pregnancy outcomes for etoposide*

In utero exposure to etoposide was documented for 42 singleton pregnancies (42 conceptuses). No major malformations occurred in the three infants born following in utero exposure during the 1st trimester. Thus, the total occurrence of major malformations following exposure to etoposide in the 1st trimester is 0% (0/3 conceptuses); however, the number of reported cases is too small to make an accurate estimate. Of the 39 pregnancies exposed to etoposide in the 2nd and/or 3rd trimester, major malformations were reported in two newborns. One infant had ventriculomegaly, which was diagnosed prenatally, and cerebral atrophy (Elit *et al.* 1999). Another infant had a spontaneous mutation for neurofibromatosis and genetic hearing loss (both of his parents were carriers) (Cardonick *et al.* 2010). One infant had a minor malformation following exposure after gestational week 21: mild glandular hypospadias (Ghaemmaghami *et al.* 2009). In addition, there were two intrauterine fetal deaths (Peres *et al.* 2001, Peterson *et al.* 2010) and one induced abortion (Chelghoum *et al.* 2005) in pregnancies exposed in the 2nd trimester. No fetal autopsy data were provided in the cases with fetal loss, although one pregnancy was complicated by oligohydramnios and fetal growth restriction prior to a stillbirth (Peterson *et al.* 2010). The total occurrence of major malformations following exposure to etoposide in the 2nd and/or 3rd trimester only was 5.1% (2/39 conceptuses).

A variety of pregnancy complications and infant health issues occurred in pregnancies exposed to etoposide. Pregnancy complications included inhibited fetal growth (n= 9 pregnancies) (Arango *et al.* 1994, Benjapibal *et al.* 2010, Buller *et al.* 1992, Ghaemmaghami *et al.* 2009, Han *et al.* 2005, Hsu *et al.* 1995, Murray *et al.* 1994, Peterson *et al.* 2010, Scherf and Price 1996) and reduced amniotic fluid or oligohydramnios (n=4 pregnancies) (Buller *et al.* 1992, Ghaemmaghami *et al.* 2009, Peterson *et al.* 2010, Scherf and Price 1996). Of the 27 pregnancies reporting age at delivery, preterm delivery was reported for 18 pregnancies. Small for gestational age was reported for one newborn (Cardonick *et al.* 2010). Health issues observed in infants exposed in utero to etoposide were: respiratory difficulties (n=6 infants), myelosuppression (n=6 infants), jaundice (n= 1 infant), and alopecia (n=1 infant). Follow-up examinations of 25 infants found normal growth and development of 21 children at ages ranging from 2 months to 16 years. Two infants had delayed language and/or motor skills by 12 to 14 months of age (Cardonick *et al.* 2010, Lam 2006). Moderate sensorineural hearing loss was observed in an infant with normal neurodevelopmental progress by age one year (Raffles *et al.* 1989). A fourth child had genetic hearing loss (parents were carriers) and a spontaneous mutation for neurofibromatosis (Cardonick *et al.* 2010).

In conclusion, the total occurrence of major malformations in etoposide-exposed pregnancies was 4.8% (2/42 conceptuses). The occurrence of major malformations following exposure to etoposide during the 1st trimester (0/3 conceptuses) was less than the prevalence of birth defects in the general population (0% versus 3%); however, there were too few reported pregnancies to calculate an accurate estimate. The total occurrence of major malformations following exposure to etoposide in the 2nd and/or 3rd trimester only (2/39 conceptuses) was similar to the prevalence of birth defects in the general population (5.1 ± 6.9% versus 3%). The case of neurofibromatosis was unlikely to have resulted from exposure to chemotherapy in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations following exposure to etoposide in the 2nd and/or 3rd trimester only was 2.6 ± 5.0% (1/39 conceptuses).

5.19 HYDROXYUREA

5.19.1 Mechanism of action, route of administration, and indications

Hydroxyurea is an anti-neoplastic agent that inhibits the enzyme ribonucleotide reductase, thus blocking the conversion of ribonucleotides to deoxyribonucleotides, which are essential precursors in DNA synthesis (Yarbro 1992). Specifically, hydroxyurea is metabolized to a free radical nitroxide in vivo, which in turn scavenges the tyrosyl free radical of ribonucleotide reductase rendering it inactive. By contrast, hydroxyurea does not affect the synthesis of RNA or protein. Inhibition of the ribonucleotide reductase by hydroxyurea also decreases the abundance of cells in the DNA synthetic phase of the cell cycle (Yarbro 1992). Hydroxyurea also synchronizes other cells at the G1 phase, which may result in greater sensitivity of the cells to radiation therapy (Bristol-Myers-Squibb 2010) or co-treatment with other chemotherapeutic agents (Yarbro 1992), although treatment with radiation is generally not recommended for pregnant women. Hydroxyurea is administered orally one to three times per day. Hydroxyurea is indicated for treatment of chronic myeloid leukemia (also called chronic myelocytic or granulocytic leukemia), melanoma, and ovarian cancer. It is also used as a co-treatment with radiation therapy for primary cell carcinomas of the head and neck, excluding the lip, and is also administered to sickle cell patients to reduce the frequency of blast crises and the need for blood transfusions (Bristol-Myers-Squibb 2010).

5.19.2 Evidence of placental and breast milk transport

Hydroxyurea is known to cross the placenta in rats, monkeys, and rabbits (DeSesso and Goeringer 1990, Wilson *et al.* 1975); however, human placental transport is not known. Hydroxyurea was detected in the breast milk of one lactating patient (Sylvester *et al.* 1987). Milk samples were collected two hours following the last dose of the day in a hydroxyurea dosing regimen that included a 500 mg dose, three times per day; samples were collected for 7 days. The mean concentration of hydroxyurea was 6.1 ± 2.3 mg/L on days 1, 3 and 4; the remaining milk samples did not clear the extraction process, and thus were not measured (Sylvester *et al.* 1987).

5.19.3 Laboratory animal developmental toxicity

It has been observed that hydroxyurea is tetratogenic in many laboratory animal models, including: mice, hamsters, rabbits, cats, dogs, miniature swine and monkeys (Bristol-Myers-Squibb 2010). Hydroxyurea induced fetal malformations of the skeletal system (i.e. partially ossified cranial bones, missing eye sockets, hydrocephaly, dipartite sternebrae, and absent lumbar vertebrae) in rats at 180 mg/kg bw/day and rabbits at 30 mg/kg bw/day, doses which are approximately 0.8 and 0.3 times, respectively, the maximum recommended daily dose in humans per mg/m2 (Bristol-Myers-Squibb 2010). The recommended maximum dose of hydroxyurea is 80 mg/kg bw every 3rd day or 30 mg/kg bw/day (Perry 2008). At higher doses, hydroxyurea exposure was associated with increased cell death of limb buds and the neural tube, and decreased postnatal locomotor activity in rats (Fritz and Hess 1980); impaired cardiac development and neural tube defects in hamsters (Ferm 1966); and impaired cardiac development in rabbits (Millicovsky *et al.* 1981). In addition, exposure to hydroxyurea-induced embryotoxicity manifested as decreased fetal viability and reduced live litter sizes (Millicovsky *et al.* 1981, Wilson *et al.* 1975). It has been hypothesized that the developmental toxicity of hydroxyurea is principally due to decreased DNA synthesis in the embryo leading to delayed cell death, cardiovascular alterations in the mother leading to decrease maternal blood flow to the placenta, and, to a lesser extent, the induction of free radical formation in the embryo leading to rapid cell death (DeSesso and Goeringer 1990).

5.19.4 Human gestational exposure and effects

Hydroxyurea is classified as FDA Pregnancy Category D. There were 65 published cases of patients treated with hydroxyurea during pregnancy identified from 14 case reports, 6 case series, 2 retrospective cohort studies and 2 retrospective surveys (Appendix C Table 18). Among these patients, hydroxyurea was used to treat chronic myeloid leukemia (n=37 cases), acute myeloid leukemia (n=2 cases) and adult T-cell leukemia (n=1 case) as well as non-cancerous diseases, including: essential thrombocythemia (n=22 cases), chronic myeloid splenomegaly (n=2 cases) and sickle cell disease (n= 1 case). The non-cancerous diseases were included in this tally because individual pregnancy outcomes were not available for the 31 patients in one retrospective survey, which included 6 patients with chronic myeloid leukemia (Thauvin-Robinet *et al.* 2001). A total of 68 conceptuses were exposed to hydroxyurea, including 3 twin pregnancies {De Carolis, 2006 #209;Pye, 2008 #364;Thauvin-Robinet, 2001 #430}. Hydroxyurea was administered during the 1st trimester in 41 cases (43 conceptuses due to two set of twins) and in the 2nd and/or 3rd trimester only in 22 cases (n=23 conceptuses due to one set of twins), including 4 cases that began hydroxyurea treatment between gestation weeks 12-33 (Jameel and Jamil 2007). Timing of exposure was not specified to 2 cases.

Fetal loss occurred in 13 pregnancies exposed to hydroxyurea, including one spontaneous abortion, 7 induced abortions, and 5 intrauterine fetal deaths. One spontaneous abortion following 1st trimester exposure. Six pregnancies were terminated by induced abortion following 1st trimester exposure {Thauvin-Robinet, 2001 #430}{Zemlickis, 1992 #576}; no fetal data were provided. Normal fetuses were observed in three stillbirths following exposure during the period of conception through the 3rd trimester (n=1 fetus) (Delmer *et al.* 1992), or 1st trimester alone (n=2 fetuses) (Thauvin-Robinet *et al.* 2001). Meningocele was observed in 2 stillborn fetuses exposed in the 2nd and 3rd trimesters, following co-exposure to imatinib in the 1st and 2nd trimesters (Choudhary *et al.* 2006){Pye, 2008 #364}; **[it is possible that the same case is reported in both studies]**. A normal fetus was also reported from an induced abortion following exposure during the 3rd trimester and co-exposure to daunorubicin, cytarabine, vincristine, and 6-thioguanine (Doney *et al.* 1979).

Of the 55 live-born infants (including 3 sets of twins) with in utero exposure to hydroxyurea, major malformations were observed in 4 infants.   Hip dysplasia occurred in one newborn that was likely exposed in the 1st trimester {Thauvin-Robinet, 2001 #430} and premature closure of the skull sutures (craniosynostosis) was reported for another newborn that was co-exposed to imatinib for the entire pregnancy {Pye, 2008 #364}. Hypospadias occurred in an infant with exposure in the 2nd or 3rd trimester and co-exposure to imatinib during the period of conception and 1st trimester {Pye, 2008 #364}(Ault *et al.* 2006). Pyloric stenosis was diagnosed in two infants with exposure in the 3rd trimester and co-treatment with imatinib during the period of conception and 1st trimester (Heartin *et al.* 2004){Pye, 2008 #364}; **[these two studies may be reporting the same infant]**. Two infants had minor malformations: unilateral renal dilatation and pilonidal sinus, respectively (Thauvin-Robinet *et al.* 2001); individual timing of exposure was not provided, but these infants were likely exposed in the 1st trimester. One infant died 10 days after birth from intracranial bleeding (Dilek *et al.* 2006); this infant was born at 28 weeks of gestation with no malformations.

A few pregnancy complications and infant health issues are reported in pregnancies exposed to hydroxyurea. Intrauterine growth retardation was reported in two pregnancies (Thauvin-Robinet *et al.* 2001). Other pregnancy complications included: eclampsia at gestation week 26 preceding the birth of a stillborn fetus (Delmer *et al.* 1992), placental ischemia was observed in two other stillbirths (Thauvin-Robinet *et al.* 2001), premature placental detachment in one pregnancy (Dilek *et al.* 2006), and spontaneous preterm labor occurred in two pregnancies (Doney *et al.* 1979, Patel *et al.* 1991). Of the 23

pregnancies with age at delivery, early preterm delivery (<34 weeks) was reported for 3 pregnancies (13.0%), late preterm delivery (34-36 weeks) was reported for 6 pregnancies (26.1%), and 1 pregnancy was delivered at term (60.9%). Nine additional infants were reported to be premature(Thauvin-Robinet *et al.* 2001); **[however, authors did not provide gestational age at birth so they are not included in the tally]**. None of the infants were reported by the authors as small for gestation age. Jaundice was observed in two newborns (Peres *et al.* 2001) and five infants had respiratory distress (Thauvin-Robinet *et al.* 2001). One infant suffered from hyponatremia, hyperkalemia, hypocalcemia and hypoglycemia (Doney *et al.* 1979). Follow-up evaluations were available for 21 infants at ages ranging from 1 month to 53 months; age at follow-up was not specified for one infant {Fitzgerald, 1993 #239}. Normal growth and development were reported for all 18 children with follow-up evaluations with the exception of one child {Doney, 1979 #215}. The remaining child had normal neurodevelopment at ages 4 and 13.5 months, but had growth parameters in <3rd percentile at age 13.5 months (Doney *et al.* 1979).

5.19.5   *Summary of pregnancy outcomes for hydroxyurea*

In utero exposure to hydroxyurea occurred in 60 pregnancies for a total of 68 conceptuses, including three sets of twins {De Carolis, 2006 #209;Pye, 2008 #364;Thauvin-Robinet, 2001 #430}. Of the 41 pregnancies (44 conceptuses) exposed to hydroxyurea in the 1st trimester, one infant had a major malformation (hip dysplasia) and two infants had minor malformations (pilonidal sinus and unilateral renal dilation) (Thauvin-Robinet *et al.* 2001). Thavin-Robinet et al. (Thauvin-Robinet *et al.* 2001) did not report timing of exposure for these malformed newborns, but the majority of the patients were treated during the 1st trimester (28/31 cases). In addition, there were 5 induced abortions without fetal autopsy data {Thauvin-Robinet, 2001 #430;Zemlickis, 1992 #576} and three stillbirths of normal fetuses following exposure during the 1st trimester {Delmer, 1992 #676;Thauvin-Robinet, 2001 #430}. The total occurrence of major malformations following 1st trimester exposure to hydroxyurea was 2.3% (1/44 conceptuses).

Of the 22 pregnancies exposed in the 2nd and/or 3rd trimester only, major malformations were observed in two liveborn infants and one stillborn fetus. Hypospadias occurred in an infant with 2nd or 3rd trimester exposure {Pye, 2008 #364}Ault *et al.* 2006). Pyloric stenosis was reported in another infant with 3rd trimester exposure (Heartin *et al.* 2004). Meningocele was reported in one stillbirth following exposure in the 2nd and 3rd trimesters (Choudhary *et al.* 2006). In addition, there was one induced abortion of a normal fetus following 2nd trimester exposure {Doney, 1979 #215}. The total occurrence of major malformations following exposure to hydroxyurea in the 2nd and/or 3rd trimester was 13.6% (3/22 conceptuses). Timing of exposure was not specified for one spontaneous abortion and one live-born infant.

Pregnancy complications occurring with exposure to hydroxyurea include, intrauterine growth retardation (n=2 cases) (Thauvin-Robinet *et al.* 2001), eclampsia (n=1 case), placental ischemia (n=1 case), premature placental detachment in one pregnancy (n=1 case), and spontaneous preterm labor (n=2 cases). Of the 23 pregnancies with age at delivery, preterm delivery was reported for 9 pregnancies. None of the children were small for gestation age. Infant health issues included: jaundice (n=2 newborns), respiratory distress (n=5 newborns), and low nutrient levels (n=1 newborn). One infant died at 10 days from intracranial bleeding (Dilek *et al.* 2006). Normal growth and development were observed for 19 of 20 infants with follow-up evaluations. The remaining child had growth parameters in the <3rd percentile, but normal neurodevelopment, at age 13.5 months (Doney *et al.* 1979).

In conclusion, the total occurrence of major malformations in hydroxyurea-exposed pregnancies was 5.9% (4/68 conceptuses). The occurrence of major malformations following exposure to hydroxyurea in

the 1st trimester (1/44 conceptuses) is equivalent to the prevalence of birth defects in the general population (2.3 ± 4.4% versus 3%). The occurrence of major malformations following 2nd and/or 3rd trimesters (3/22 conceptuses) is higher than the prevalence of birth defects in the general population (13.6 ± 14.3 versus 3%). Two of these malformations, hypospadias and meningocele, are unlikely to have resulted from chemotherapy exposure in the 2nd and/or 3rd trimesters only. It is noteworthy that the three newborns with malformations following hydroxyurea exposure during the 2nd and/or 3rd trimester were all exposed to imatinib around the time of conception and in the 1st trimester. Therefore, the revised occurrence of major malformations following exposure to hydroxyurea during the 2nd and/or 3rd trimester only was 4.5 ± 8.7% (1/22 conceptuses).

5.20 IDARUBICIN

5.20.1 Mechanism of action, route of administration, and indications

Idarubicin (4-demethoxydaunorubicin) is an anthracycline DNA-intercalating analog of daunorubicin. Idarubicin has a high lipophilicity, which allows a higher rate of cellular uptake than other anthracyclines. It inhibits nucleic acid (DNA and RNA) synthesis and interacts with the enzyme topoisomerase II to cause DNA cleavage (Teva 2009). Idarubicin is administered by intravenous injection. It is indicated for the treatment of acute myeloid leukemia.

5.20.2 Evidence of placental and breast milk transport

The transport of idarubicin across the placenta or into breast milk in humans is not known. Achtari et al. (Achtari and Hohlfeld 2000) suggested that the high liposolubility and a long half life of idarubicin may facilitate placental transport. One study measured the levels of idarubicin at delivery and found they were less than the level of detection (<0.932 ng/mL) in both maternal serum and umbilical cord blood (Matsuo *et al.* 2004); the last administration of idarubicin was approximately 2 weeks prior to delivery. There are no published studies of lactational transfer of idarubicin.

5.20.3 Laboratory animal developmental toxicity

Preclinical studies reported in the product label reported that idarubicin is embryotoxic and teratogenic in rats, when administered orally to pregnant rats at a dose of 1.2 mg/m^2/day (one tenth the human dose), which was nontoxic to dams. Embryotoxicity, but not teratogenicity, was observed following administration of a maternally toxic dose of 2.4 mg idarubicin/m^2/day in rabbits; this compares to two tenths the human dose) (Teva 2009). Teratogenic effects of idarubicin are also described in the peer-reviewed literature. As reviewed in Shepard et al. (Shepard and Lemire 2004), adult female rats treated with idarubicin (0.2 mg/kg intravenously) prior to conception and during early pregnancy had increased early fetal loss and fetuses with decreased ossification. Pregnant rats exposed to the same dose during organogenesis had small fetuses and an increase in skeletal anomalies in their fetuses. Idarubicin was more potent (on a molar basis) in producing abnormalities in rat whole embryo culture than daunorubicin, doxorubicin, and epirubicin (Menegola *et al.* 1997). Exposure to 0.05 uM idarubicin resulted in 100% dead embryos, while exposure to 0.025 uM induced abnormalities in70% of embryos (with abnormalities of the development of the nervous system, bracnchial bars and at the caudal level) and a reduction in somite number and embryonic DNA content; while exposure to 0.0125 uM idarubicin had no effect (Menegola *et al.* 1997).

5.20.4 Human gestational exposure and effects

Idarubicin is classified as FDA Pregnancy Category D. There were 22 published cases of patients treated with idarubicin during pregnancy identified from 12 case reports, 1 case series, 1 retrospective case series, 1 retrospective cohort study and 1 retrospective survey (Appendix C Table 19). Among these patients, idarubicin was used to treat acute leukemia: acute leukemia (type not specified; n=4 cases), acute lymphocytic (n=2 cases), and acute myelogenous (n=12 cases) and subtype acute promyelogenous (n=4 cases). A total of 22 singleton pregnancies (22 conceptuses) were exposed to idarubicin. Idarubicin was administered in the 1st trimester only in one pregnancy and during the 2nd and/or 3rd trimester only in 16 pregnancies; timing of exposure was not specified in 5 cases.

Fetal loss occurred in 6 pregnancies exposed to idarubicin. Three pregnancies were ended by induced abortion following exposure to idarubicin and cytarabine in either the 1st (n=1 case) or 2nd trimester (n=2

cases) (Chelghoum *et al.* 2005); no fetal autopsy data were provided. One intrauterine fetal death in the 8th month of gestation followed 2nd and 3rd trimester exposure and co-treatment with cytarabine; no fetal autopsy data were provided (Paşa *et al.* 2009). One stillbirth of a normal fetus occurred following exposure during the 2nd and 3rd trimesters and co-treatmentwith daunorubicin in the 2nd trimester, and cytarabine and mitoxantrone in the 2nd and 3rd trimesters (Reynoso and Huerta 1994). In addition, a normal fetus at autopsy was reported for a second intrauterine fetal death following in utero exposure and co-exposure to cytarabine (timing of exposure not specified) (Peres *et al.* 2001); this pregnancy also experienced oligohydramnios and intrauterine growth restriction.

Of the 16 live born infants exposed to idarubicin in utero, major malformations occurred in one infant. One infant was born with a ventricular septal defect, a major malformation that required surgery at 5 months, as well as a shallow sacral dimple, short digits and limbs, dysplastic fingernails, and a pronounced frontal skull with mild macrognathia (Niedermeier *et al.* 2005). This infant was exposed during the 2nd trimester and co-treated with cytarabine in the 2nd and 3rd trimesters (Niedermeier *et al.* 2005). Two infants had minor malformations. One infant had two small secundum atrial septal defects, moderate dilation of the right atrium and right ventricle, and a small patent ductus arteriousus following exposure in the 2nd and 3rd trimester and co-exposure to all-trans retinoic acid (Siu *et al.* 2002). Another infant born at 28 weeks of gestation had a patent ductus arteriosus as well as pulmonary hypoplasia, bilateral pneumothoraces following exposure during the 2nd trimester and co-exposure to all-trans retinoic acid (Carradice *et al.* 2002). The patent ductus arteriosus observed in this infant closed after treatment with indomethacin.

There were a variety of other pregnancy complications and health effects in infants exposed to idarubicin in utero. The following pregnancy complications preceded preterm birth in three cases: spontaneous preterm rupture of membranes and fetal ascites (n=1 pregnancy) {Carradice, 2002 #187}, spontaneous preterm labor and fetal distress (n=1 pregnancy) {Yucebilgin, 2004 #459}, and early signs of preeclampsia (n=1 pregnancy) {Siu, 2002 #410}. One additional pregnancy had fetal distress {Claahsen, 1998 #197}. Oligohydramnios occurred in three pregnancies (Carradice *et al.* 2002, Matsuo *et al.* 2004, Peres *et al.* 2001). Fetal intrauterine growth retardation was observed in four pregnancies {Baumgartner, 2009 #151;Claahsen, 1998 #197;Peres, 2001 #354}, including one case where it was secondary to placental insufficiency (Carradice *et al.* 2002). One infant with fetal growth retardation also had cardiomyopathy (Baumgartner *et al.* 2009). Of the 12 cases reporting gestational age at delivery, early preterm delivery (<34 weeks) was reported for 5 pregnancies (41.7%), late preterm delivery (34-36 weeks) was reported for 6 pregnancies (50%) and one pregnancy was delivered at term (8.3%). One infant was reported to be small for gestational age {Niedermeier, 2005 #323}. Acute cardiac failure, which occurred on day 1 and resolved on day 3 with treatment, occurred in a newborn (Achtari and Hohlfeld 2000); the authors attributed the cardiac failure to 2nd trimester exposure to idarubicin. This infant, who was born at 28 weeks of gestation, had many complications linked to prematurity including: respiratory distress, necrotizing enterocolitis, and ventricular hemorrhage (Achtari and Hohlfeld 2000). Breathing difficulties were reported for five newborns (Achtari and Hohlfeld 2000, Baumgartner *et al.* 2009, Carradice *et al.* 2002, Ganzitti *et al.* 2010, Siu *et al.* 2002), and cyanosis of the extremities at birth was observed in one infant (Niedermeier *et al.* 2005). Myelosuppression occurred in two infants (Baumgartner *et al.* 2009, Matsuo *et al.* 2004). One of the infants with myelosuppression also had hepatopathy and elevated creatinine kinase levels, which normalized within a week. Jaundice occurred in two infants (Claahsen *et al.* 1998, Ganzitti *et al.* 2010). Finally, meconium-stained amniotic fluid was reported for two newborns (Claahsen *et al.* 1998, Yucebilgin *et al.* 2004). Of the 11 infants with follow-up evaluations, 10 infants had normal development and growth at ages ranging from 1.5 months to 6 years. At age 6 months, the infant born

with pulmonary hypoplasia continued on nasal oxygen and diuretics with significant respiratory effort, and had poor overall growth (Carradice *et al.* 2002). In contrast, the infant with a ventricular septal defect recovered quickly following corrective surgery at age 5 months, and other health effects seen at birth in this infant had resolved by 3 months of age (Niedermeier *et al.* 2005). Similarly, another infant, who was born with two small atrial secundum defects as well as a patent ductus arteriosus, had normal growth at age 1.5 months with no clinical signs of congestive heart failure (Siu *et al.* 2002). Another infant with normal neurological development showed a slight delay in language acquisition (Achtari and Hohlfeld 2000).

5.20.5 *Summary of pregnancy outcomes for idarubicin*

In utero exposure to idarubicin is documented for 22 singleton pregnancies (22 conceptuses). The only pregnancy exposed in the 1st trimester was terminated by induced abortion and fetal autopsy data were not reported (Chelghoum *et al.* 2005). Thus, there was insufficient data to estimate the occurrence of major malformations in conceptuses exposed to idarubicin in the 1st trimester. Of the 16 pregnancies exposed to idarubicin in the 2nd and/or 3rd trimester only, a major malformation was reported for one infant. This infant had a ventricular septal defect, which required surgery at 5 month of age, skeletal malformations (e.g. short limbs and digits) as well as shallow sacral pit and macrognathia (Niedermeier *et al.* 2005). Minor malformations were observed in two newborns: one infant had two small atrial secundum septal defects and a patent ductus arteriosus at birth (Siu *et al.* 2002) and another infant had pulmonary hypoplasia and a patent ductus arteriosus, which closed with treatment (Carradice *et al.* 2002). In addition, fetal loss occurred in 3 pregnancies with 2nd and/or 3rd trimester only exposure, including: two induced abortions and one intrauterine fetal death without fetal data, as well as a stillborn infant without malformations. A total occurrence of major malformations following exposure to idarubicin in the 2nd and/or 3rd trimester only was 6.3% (1/16 conceptuses). The timing of exposure was not reported for 5 pregnancies, including 4 normal newborns (Aviles and Neri 2001) and one intrauterine fetal death of a normal fetus (Peres *et al.* 2001).

Pregnancy complications included: oligohydramnios (n=3 pregnancies) (Carradice *et al.* 2002, Matsuo *et al.* 2004, Peres *et al.* 2001); intrauterine growth retardation (n=4 pregnancies) {Baumgartner, 2009 #151;Claahsen, 1998 #197;Peres, 2001 #354}. One pregnancy with intrauterine growth retardation also was complicated by fetal cardiomyopathy (Baumgartner *et al.* 2009). Fetal distress was reported for 2 pregnancies {Claahsen, 1998 #197;Yucebilgin, 2004 #459}. Preterm birth was reported for 11 of the 12 infants with age at delivery dataSmall for gestational age was reported for one newborn {Niedermeier, 2005 #323}. Common infant health effects were: breathing difficulties (n=5 infants), myelosuppression (n=2 infants), and jaundice (n=2 infants). One infant had acute cardiac failure that resolved following treatment (Achtari and Hohlfeld 2000). Of the 11 children with follow-up examinations, normal growth and development was reported for 10 children at ages 1.5 months to 6 years. One infant, who was born with pulmonary hypoplasia, continued to need nasal oxygen and diuretics, and exhibited poor growth at 6 months of age (Carradice *et al.* 2002).

In conclusion, total occurrence of major malformations in idarubicin-exposed pregnancies was 4.5% (1/22 conceptuses). The occurrence of major malformations following 1st trimester exposure was 0% (0/1 conceptuses), but could not be accurately estimated due to a lack of data. The occurrence of major malformations following exposure in the 2nd and/or 3rd trimester only (1/16 conceptuses) was double the prevalence of birth defects in the general population (6.3 ± 11.9% versus 3%). The ventricular septal defect was not likely caused by exposure to chemotherapy in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations following exposure to idarubicin in the 2nd and/or 3rd trimester was 0% (0/16 conceptuses).

5.21 IFOSFAMIDE

5.21.1 *Mechanism of action, route of administration, and indications*

Ifosfamide is a DNA alkylating agent that is a synthetic structural analogue of cyclophosphamide, another cytotoxic agent. It is thought to act by inhibiting cell proliferation by cross-linking with DNA, and it is cell-cycle non-specific. Ifosfamide is administered by intravenous injection. Ifosfamide is indicated for treatment of germ cell testicular cancer (Baxter Healthcare Corporation 2007). Other uses of ifosfamide not included in the prescribing information include the treatment of bone and soft tissue sarcomas, lung, cervix and ovarian cancers (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695023.html).

5.21.2 Evidence of placental and breast milk transport

Evidence of placental transfer of ifosfamide in humans is not clear, while breast milk transfer has been observed. One study reported that maternal blood levels of ifosfamide were highest (~ 20 µg/mL) at 24 hours after initiation of a 5 g/m^3 injection administered over 48 hours to a pregnant sarcoma patient {Mir, 2012 #1221}. The authors stated that ifosfamide could not be detected in amniotic fluid or cord blood (<5 µg/mL) {Mir, 2012 #1221}. The manufacturer's product information reported that ifosfamide is excreted in breast milk (Baxter Healthcare Corporation 2007).

5.21.3 Laboratory animal developmental toxicity

Ifosfamide is reported to induce teratogenic effects in rats, mice and rabbits (Baxter Healthcare Corporation 2007). In rats, administration of doses of 54 mg isofamide/m^2 on gestation days 6 to 15 caused embryolethal effects, and embryotoxic effects were observed following doses of 18 mg/m^2 over the same dosing period. In mice, administration of 30 mg ifosfamide/m^2 on gestation day 11 resulted in increased resorptions and fetal anomalies. In rabbits, ifosfamide was embryotoxic and increased the number of fetal anomalies following doses of 88 mg/m^2/day on gestation days 6 to 18 (Baxter Healthcare Corporation 2007).

Teratogenic effects of ifosfamide are also described in the peer-reviewed literature. As reviewed in Shepard and Lemire (Shepard and Lemire 2004), administration of ifosfamide (2.5 or 5.0 mg/kg bw) during mating and the first 7 days of gestation in rats resulted in decreased viability of fetuses at term and an increase in stillbirths and hydrocephalus were observed with doses up to 10 mg/kg **[bw]**. An increase in central nervous system defects were observed in rat fetuses exposed to 5 mg/kg **[bw]** during the period of organogensis. In rabbits, administration of ifosfamide during organogenesis at a dose of 20 mg/kg **[bw]** resulted in ectrodactylia (the congenital absence of part or all of one or more fingers or toes) (Shepard and Lemire 2004). Skeletal defects were observed in fetal Swiss Webster mice following exposure of the pregnant dam to ifosfamide at doses of 10 and 20 mg/kg via intraperitoneal injection on gestation day 11 {Bus, 1973 #1344}. Ifosfamide at doses of 20 mg/kg on gestation day 11 significantly increased resorption rate compared to control, induced a wide variety of externally visible anomalies apparent in Day 19 fetuses, and increased the incidence of hydrocephalus {Bus, 1973 #1344}. Ifosfamide administered subcutaneously at 45 mg/kg to PND 1 mice resulted in altered growth and development, including a significant reduction in body weight.

5.21.4 *Human gestational exposure and effects*

Ifosfamide is classified as FDA Pregnancy Category D. There were 11 patients treated with ifosfamide during pregnancy identified from 5 case reports and 2 case series (Appendix C Table 20). Ifosfamide was

used to treat 2 cases of Burkitt lymphoma (Non-Hodgkin lymphoma) and 9 cases of sarcoma, including 2 cases of Ewing sarcoma, 2 cases of high-grade sarcoma, one case of osteosarcoma, and one case of rhabdomyosarcoma. A total of 11 pregnancies (11 conceptuses) were exposed to ifosfamide. The agent was administered in the 1st trimester in 1 pregnancy and in the 2nd and/3rd trimester only in 10 pregnancies. Of these 11 pregnancies, there was one intrauterine fetal death at 26 weeks gestation and 10 live born infants without congenital malformations. The stillbirth occurred following initiation of chemotherapy in the 2nd trimester at 16 weeks of gestation {Peterson, 2010 #670} following observations of oligohydramnios and intrauterine growth restriction at 18 and 22 gestation weeks. No fetal autopsy data were reported; cotreatments included cyclophosphamide, doxorubicin, etoposide, cytarabine, vincristine and rituximab.

A few pregnancy complications and infant health effects were observed following in utero exposure to ifosfamide. Reductions in amniotic fluid and intrauterine growth restriction were observed in three pregnancies {Fernandez, 1989 #235;Nakajima, 2004 #316}, including one pregnancy ending in a stillbirth {Peterson, 2010 #670}. Oligohydramnios was reported in one additional pregnancy {Mir, 2012 #1221}, and mild intrauterine growth restriction was reported in another pregnancy {Merimsky, 1999 #784}. Gestational age at delivery was reported for all 10 live born infants. All 10 cases reported age at delivery; early preterm delivery (<34 weeks) was reported for 4 pregnancies (40%), late preterm delivery (34-36 weeks) was reported for 5 pregnancies (50%) and term delivery (≥37 weeks) was reported for 1 pregnancy (10%). None of the newborns were reported to be small for gestational age. Respiratory difficulties were observed in 2 newborns {Lam, 2006 #247}, including one infant who was treated for hyperbilirubinemia and low hemoglobin {Nakajima, 2004 #316}. Following anhydramnios and intrauterine growth restriction during gestaion, one newborn had bilateral intraventricular hemorrhages and a left occipital meningeal hematoma {Fernandez, 1989 #235}. This newborn also experienced anuria and died at age 7 days; autopsy revealed extensive cerebral lesions (Fernandez *et al.* 1989). Follow-up evaluations were reported for 8 infants at ages ranging from 8 months to 5 years. All infants had normal growth and development, except one healthy infant with mildly delayed motor skills thought to be due to his premature birth at 32 weeks of gestation {Lam, 2006 #247}.

5.21.5 Summary of pregnancy outcomes for ifosfamide

Exposure to ifosfamide is documented for 11 pregnancies (11 conceptuses) and no congenital malformations (major or minor) were observed in any conceptus. Only one pregnancy was exposed in the 1st trimester and it yielded a normal infant. Of the 10 pregnancies exposed in the 2nd and/or 3rd trimester only, there were nine live born infants and one intrauterine fetal death without congenital malformations. Reductions in amniotic fluid and intrauterine growth restriction were observed in three pregnancies {Fernandez, 1989 #235;Nakajima, 2004 #316}, including one pregnancy ending in a stillbirth {Peterson, 2010 #670}. Oligohydramnios was reported in one additional pregnancy {Mir, 2012 #1221}, and mild intrauterine growth restriction was reported in another pregnancy {Merimsky, 1999 #784}. Preterm delivery was reported for 9 of 10 of the pregnancies. Respiratory difficulties were reported for two infants, including one who also suffered from hyperbilirubinemia and low hemoglobin. None of the newborns were reported to be small for gestational age. One neonate died at age 7 days following anuria {Fernandez, 1989 #235}; this pregnancy had suffered from anhydramnios and intrauterine growth restriction. The infant had cerebral hemorrhages and a meningeal hematoma diagnosed at birth, and autopsy confirmed extensive cerebral lesions. Of the 8 children with follow-up evaluations at ages ranging from 8 months to 5 years, all children had normal growth and development, except one healthy child with mildly delayed motor skills {Lam, 2006 #247}.

In conclusion, the total occurrence of major malformations in ifosfamide-exposed pregnancies was 0% (0/11 conceptuses). While the occurrence of major malformations was not greater than the general

population (3%), there were very few cases reporting exposure to ifosfamide during pregnancy. It appears that exposure to ifosfamide may increase the risk of reductions in amniotic fluid and/or intrauterine growth restriction (5 of 11 pregnancies; 45%); however, more data is needed to establish an association.

5.22 IMATINIB

5.22.1 Mechanism of action, route of administration, and indications

Imatinib mesylate (also called imatinib, STI 571, Glivec or Gleevec) is a protein-tyrosine kinase inhibitor. Tyrosine kinases regulate several cellular activities, including proliferation, differentiation and survival, and the deregulation of tyrosine kinases can lead to cancer. Imatinib acts by binding to the kinase and blocks the binding of adenosine triphosphate (ATP), thus inhibiting activation of the tyrosine kinase by blocking the transfer of phosphate from ATP to the tyrosine residues, and inhibiting cell proliferation and inducing cell death (Novartis 2009, Waller 2010). Imatinib is administered orally and targets the bcr-abl tyrosine kinase, a mutant constitutive tyrosine kinase that is created by a reciprocal translocation between chromosomes 9 and 22. The resulting chromosome 22, commonly called the Philadelphia chromosome, is found in chronic myeloid leukemia (CML) patients. Imatinib also inhibits other tyrosine kinases necessary for the growth of chronic myeloid leukemia cells and possibly other rapidly dividing cells in the body, including: non-mutated abl; ARG, an abl-related gene; c-kit, the stem cell factor receptor; c-FMS, the colony-stimulating factor 1 receptor; platelet-derived growth factor receptors (PDGFR)α and β and others (Deininger *et al.* 2005, Nishimura *et al.* 2003). Imatinib is also used to treat gastrointestinal stromal tumors, which are caused by a mutated c-kit tyrosine kinase (Deshaies *et al.* 2010, Novartis 2009). In addition, imatinib is indicated for chronic eosinophilic leukemia and acute lymphoblastic leukemia (Novartis 2009).

5.22.2 Evidence of placental and breast milk transport

Imatinib has been detected in human placenta, umbilical cord blood, and newborn peripheral blood at 12 to 32 hours following maternal administration. Russell et al. (Russell *et al.* 2007) suggested that placental transfer of imatinib to the fetus appeared to be poor, based on the observation of imatinib levels of 157 ng/mL in umbilical cord blood versus 2452 ng/mL in placental tissue at 12 hours after a maternal dose. Further evidence of fetal exposure was detectable levels of imatinib in umbilical cord blood (338.0 ng/mL) and neonatal peripheral blood (478.0 ng/mL) at 16 hours post maternal dose; maternal blood levels of imatinib were 1562 ng/mL at 16 hours post dose (Ali *et al.* 2009). Imatinib is detected in human breast milk collected 10 to 16 hours following last maternal dose (Ali *et al.* 2009, Russell *et al.* 2007). Gambacorti-Passerini et al. (Gambacorti-Passerini *et al.* 2007) measured levels of imatinib at 1, 2, 3, 4 and 9 hours after a 400 mg oral dose of imatinib in the fourth week of lactation. Imatinib levels in breast milk ranged from 1.1 to 1.4 µg/mL breast milk with similar results measured in the second month of lactation. Based on average milk intake of 728 to 777 mL/day, the authors estimated that an infant breastfed by a mother taking imatinib would be exposed to 10% of the maternal dose when adjusted for body weight of the infant (no more than 3 mg/day).

5.22.3 Laboratory animal developmental toxicity

Developmental exposure to imatinib induced embryotoxicity and teratogenicity in laboratory animal studies Imatinib induced teratogenesis when administered at doses ≥ 100 mg/kg bw/day during organogenesis in rats (Novartis 2009). Teratogenic effects included reduced or absent skull bones (i.e., reduced or absent frontal bones and reduced parietal bones), and exencephaly (i.e., a skeletal defect leading to formation of brain outside of skull) or encephalocele (i.e., protrusion of brain through cranial fissure). Total fetal loss was noted in pregnant rats administered doses greater than 100 mg imatinib/kg bw/day (approximately equal to the human dose of 800 mg/day based on AUC). In addition, imatinib caused significant post-implantation loss in female rats at doses ≥45 mg/kg bw/day (approximately equal to the human dose of 400 mg/day based on body surface area) marked by early fetal resorptions, stillbirths, nonviable pups and/or neonatal pup death in the first five days of life. No fetal loss was

reported for rats at doses of ≤30 mg imatinib/kg bw/day and there was no lasting impact of imatinib on fertility in the first generation rats (Novartis 2009).   Imatinib is anti-angiogenic in animal models through inhibitory effects on PDGFR, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). It has been hypothesized that the incidence of exomphalos and/or skeletal system defects in infants exposed to imatinib during pregnancy may be due to effects mediated via the PDFGRα {Apperley, 2009 #46}. PDGFRs play an important role in mammalian organogenesis (Hoch and Soriano 2003). Of note, mice engineered with mutated, nonfunctional PDGFRα receptors displayed similar birth defects as congenital malformations seen in human infants exposed to imatinib in utero, including: omphalocele (i.e., exomphalos), vertebral and rib fusion abnormalities, kidney and urogenital abnormalities, cardiac defects, and facial clefts (comparable to cleft palate) (Soriano 1997). Furthermore, there is evidence from clinical trials as well as laboratory studies that imatinib may disrupt bone remodeling by suppressing osteoclasts, stimulating proliferation, but not maturation of osteoblasts (Vandyke *et al.* 2010), which could have an effect on skeletal development.

5.22.4   *Human gestational exposure and effects*

Imatinib is assigned the FDA Pregnancy Category D. There were 152 published cases of chronic myeloid leukemia patients treated with imatinib during pregnancy identified from 13 case reports, 8 case series, and 1 retrospective survey (Appendix C Table 21).   There were 155 pregnancies exposed to imatinib due to 3 patients having 2 pregnancies each for a total of 157 conceptuses exposed to imatinib, including two sets of twins {Meera, 2008 #285}{Pye, 2008 #364}. Imatinb was administered during the 1st trimester in 134 pregnancies (136 conceptuses due to two sets of twins) and in the 2nd and/or 3rd trimester exposure in 5 pregnancies. The timing of exposure was not specified in 16 cases; however, it was assumed to have been during the 1st trimester until pregnancy was detected because the drug is generally not prescribed to women who are known to be pregnant (Pye *et al.* 2008). Thus, it was assumed that 150 pregnancies (152 conceptuses) were exposed to imatinib during the 1st trimester.

Fetal demise was reported for 57 pregnancies and all cases included 1st trimester exposure. Spontaneous abortion occurred in 19 pregnancies and no fetal malformations were reported (AlKindi *et al.* 2005, Pye *et al.* 2008). Spontaneous abortion occurred in 16 pregnancies following 1st trimester exposure and timing of exposure was not specified for 3 spontaneous abortions **[assumed to be 1st trimester]** {AlKindi, 2005 #243;Pye, 2008 #364}; co-treatments were not administered (n=1 pregnancy) (AlKindi *et al.* 2005) or not specified (n=18 pregnancies) (Pye *et al.* 2008). Thirty-six pregnancies were terminated by induced abortion {Berveiller, 2012 #1327;Pye, 2008 #364}; 29 pregnancies were exposed during the 1st trimester and timing was not specified for 7 pregnancies **[which were assumed to be 1st trimester]**. Of the induced abortions, 34 fetuses were without malformations at autopsy and major malformations were observed in 2 fetuses from 2 singleton pregnancies. Fetal autopsy of one induced abortus revealed a fetus with cleft palate and polydactyly following exposure to imatinib only (Pye *et al.* 2008). A second fetus terminated by induced abortion appeared to have warfarin embryopathy with a depressed nasal bridge, choanal stenosis, Dandy Walker cyst, a ventricular septal defect, coarctation of the aorta, and gastroschisis (Pye *et al.* 2008); this pregnancy was co-exposed to warfarin among other non-cancer chemotherapeutic agents (Pye *et al.* 2008). One fetus of an induced abortion had no malformations, but had hydrops with subcutaneous edema, plural effusion, and ascites {Berveiller, 2012 #1327}; this pregnancy was exposed during the period of conception and the 1st trimester and co-exposed to dasatinib. Induced abortion terminated another singleton pregnancy exposed to imatinib only because of unspecified abnormal findings detected on the prenatal ultrasound along with elevated alpha fetoprotein (Pye *et al.* 2008); elevated levels of alpha fetoprotein suggest a high probability of fetal neural tube defects. Meningocele, a major malformation, was reported in two stillborn fetuses co-exposed to hydroxyurea after the 1st trimester (Choudhary *et al.* 2006, Pye *et al.* 2008). **[It is possible**

that the two stillbirths with meningocele are the same pregnancy as Pye et al. (Pye *et al.* 2008) indicated that they included spontaneous reports, but they did not say which published studies they included.]

Of the 99 live born infants, 10 infants were born with malformations. Major malformations were observed in 9 following 1st trimester exposure to imatinib (Pye *et al.* 2008). Three infants had skeletal malformations accompanied by exomphalos (umbilical hernia): scoliosis was reported in an infant who had no co-treatments; hemivertebrae and right renal agenesis occurred in another infant who was co-exposed to interferon; and hemivertebrae, right shoulder anomaly as well as right kidney agenesis, left duplex kidney and hypoplastic lungs was reported in an infant who had no co-treatments. Hypospadias was reported in two infants, and one of these infants was co-exposed to hydroxyurea after the 1st trimester. Premature closure of the skull sutures (craniosynostosis) was reported for a newborn that was co-exposed to hydroxyurea for the entire pregnancy. An infant born at gestation week 30 had communicating hydrocephalus, cerebral hypoplasia, an atrial septal defect, overriding aorta, ascites, and pericardial effusion; this infant died 45 minutes after delivery, and no co-treatments during pregnancy were specified. Pyloric stenosis was observed in two infants and both infants were co-exposed to hydroxyurea after the 1st trimester (Heartin *et al.* 2004, Pye *et al.* 2008). **[It is possible that the two reports of infants with hypospadias are the same pregnancy as Pye et al. (Pye *et al.* 2008) indicated that they included spontaneous reports, but they did not say which published studies they included.]** One infant had a minor malformation, a non-patent mid-line perineal pit, and was exposed to imatinib during the entire pregnancy with no co-treatments (Russell *et al.* 2007).

There were very few pregnancy complications or infant health effects following in utero exposure to imatinib. Pregnancy complications included: spontaneous preterm labor (n=1 pregnancy) {Meera, 2008 #285}, and signs of placental insufficiency (n=1 pregnancy) {Skoumalova, 2008 #412}. Of the 25 infants with age at delivery data, early preterm delivery (<34 weeks) was reported for 3 infants (12%) and 22 infants were born at term (88%). None of the newborns were reported to be small for gestational age. One infant from a set of twins died at 5 days; the infant had a normal karyotype and no apparent malformation (Meera *et al.* 2008). Of the 15 children with follow-up evaluations, all were healthy with normal development at ages ranging from one to 53 months; age at follow-up was not noted for two children {AlKindi, 2005 #243}{Skoumalova, 2008 #412}.

5.22.5 Summary of pregnancy outcomes for imatinib

In utero exposure to imatinib is documented for 155 pregnancies, including two sets of twins, for a total of 157 conceptuses. Of the 152 conceptuses exposed to imatinib during the 1st trimester, major malformations were observed in 13 conceptuses. Nine of 99 live-born infants had major malformations. One infant had hydrocephalus, cerebellar hypoplasia as well as congenital heart defects, ascites and pericardial effusion; the infant died 45 minutes after birth (Pye *et al.* 2008). Skeletal malformations were seen in four infants, including: premature closure of the skull sutures (n=1 infant); scoliosis and exomphalos (n=1 infant); hemivertebrae, right renal agenesis and exomphalos (n=1 infant); and hemivertebrae, right shoulder anomaly, kidney agenesis, left duplex kidney, hypoplastic lungs and exomphalos (n=1 infant). Hypospadias was reported in two infants, and one of these infants was also exposed to hydroxyurea (Pye *et al.* 2008) and pyloric stenosis was observed in two infants (Heartin *et al.* 2004, Pye *et al.* 2008). A non-patent midline perineal pit, considered a minor malformation, was observed in an otherwise healthy newborn (Russell *et al.* 2007). In addition, fetal loss occurred in 57 singleton pregnancies with major malformations noted in 2 pregnancies terminated by induced abortion and 2 stillborn infants. In particular, one fetus terminated by induced abortion had warfarin embryopathy, a depressed nasal bridge, choanal stenosis, Dandy Walker cyst, a ventricular septal defect,

coarctation of the aorta, and gastroschisis (Pye *et al.* 2008). Cleft palate and polydactyly were observed in another fetus terminated by induced abortion (Pye *et al.* 2008). Meningocele was observed in two stillborn infants (Choudhary *et al.* 2006, Pye *et al.* 2008). One fetus of an induced abortion had no malformations, but had hydrops with subcutaneous edema, plural effusion, and ascites {Berveiller, 2012 #1327}. No fetal autopsy data were reported for the remaining 19 spontaneous abortions and 33 induced abortions. The total occurrence of major malformations following exposure to imatinib during the 1st trimester was 8.5% (13 of 152 conceptuses). No malformations (major or minor) were observed in the 5 pregnancies exposed only during the 2nd and/or 3rd trimester. The total occurrence of major malformations following exposure to imatinib in the 2nd and/or 3rd trimester was 0% (0/5 conceptuses).

There were relatively few pregnancy complications or infant health effects following in utero exposure to imatinib. Pregnancy complications included: spontaneous preterm labor (n=1 pregnancy) {Meera, 2008 #285}, and signs of placental insufficiency (n=1 pregnancy) {Skoumalova, 2008 #412}. Of the 25 pregnancies with age at delivery data, preterm delivery was reported for 3 infants. None of the infants were reported to be small for gestational age. There were two infants deaths: an infant with hydrocephalus died 45 minutes after birth (mentioned above) (Pye *et al.* 2008) and a normal infant from a twin pregnancy died at 5 days of age (Meera *et al.* 2008). Normal growth and development were reported for all 15 children with follow-up evaluations at ages ranging from 1 to 53 months. Finally, it is likely that the total number of pregnancies exposed to imatinib compiled in this review may include some redundancies due to the retrospective nature of the manufacturer's survey reports of clinical trial and spontaneous report data. For example, pyloric stenosis in a live born infant (Hensley and Ford 2003) and a stillborn with meningocele (Choudhary *et al.* 2006) likely occurred in only one pregnancy each, but may have also been reported in the retrospective survey report by the manufacturer (Pye *et al.* 2008).

In conclusion, the total occurrence of major malformations in imatinib-exposed pregnancies was 8.3% (13/157 conceptuses). The occurrence of major malformations following exposure to imatinib in the 1st trimester (13/152 conceptuses) is approximately 3-times the prevalence of birth defects in the general population (8.6 ± 4.4% versus 3%). The occurrence of birth defects following exposure to imatinib in the 2nd and/or 3rd trimester (0/5 conceptuses) was less than the prevalence in the general population. The fetus with Warfarin embryopathy was likely not caused by 1st trimester exposure to imatinib. Therefore, the revised occurrence of major malformations potentially caused by imatinib exposure in the 1st trimester was 7.9 ± 4.4% (12/152 conceptuses).

5.23 INTERFERON ALPHA

5.23.1 Mechanism of action, route of administration and indications

Alpha interferons are a family of naturally occurring proteins that inhibit viral replication, influence cellular protein production, elicit immunomodulatory effects and cause anti-proliferative effects (Chard 1989, Ferrantini *et al.* 2007). The exact mechanisms by which alpha interferons exert anti-tumor activity is poorly understood (Ferrantini *et al.* 2007), however they initiate their cellular activities by binding to specific membrane receptors on the cell surface which initiates a signal transduction cascade of intracellular events (Bekisz *et al.* 2004). Alpha interferons are administered as a subcutaneous or intramuscular injection. Recombinant alpha interferons are indicated for hairy cell leukemia, malignant melanoma, follicular lymphoma, and Philadelphia chromosome positive (Ph-positive) chronic myelogenous leukemia (CML) (Bekisz *et al.* 2004, Roth and Foon 1986). Alpha interferons include many subtypes and will be referred to as interferon alpha throughout the remainder of this chemotherapy agent section.

5.23.2 Evidence of placental and breast milk transport

Interferon alpha does not cross the placental barrier in significant amounts. Pons et al. (Pons *et al.* 1995) reported that fetal blood and amniotic levels of interferon alpha were below the level of detection (<2 international units (IU)) at one and four hours after administration of the drug at 19 and 24 weeks of gestation in two human immunodeficiency virus (HIV) patients terminating their pregnancies. Similarly, maternal serum levels of interferon alpha were 20.8 and 58 IU/ml while newborn levels were only <0.6 and <1 IU/ml, respectively, at birth in a case series of two leukemia patients (Haggstrom *et al.* 1996). Interferon alpha is transferred into breast milk in humans, although at low levels. For example, Haggstrom et al. (Haggstrom *et al.* 1996) reported levels of interferon in breast milk at birth as 1.4 and 6 IU interferon alpha/ml breast milk in the two patients referenced above. Furthermore, the peak levels of interferon alpha in breast milk were detected 4 hours following an intravenous dose of 30 million IU, and were only slightly higher than breast milk levels 5 hours prior to dose administration (1551 versus 1249 IU/ml, respectively (Kumar *et al.* 2000). These data suggest that even following large doses, the high molecular weight of interferon alpha prevents it from being transferred to human milk in relevant amounts (Kumar *et al.* 2000).

5.23.3 Laboratory animal developmental toxicity

Developmental exposure to interferon alpha is associated with embryotoxicity, but not teratogenicity, in laboratory animal studies. Interferon alpha did not induce teratogenic effects in laboratory animals, including rats, rabbits, and monkeys (reviewed in (Shepard and Lemire 2004)). In rabbits, exposure to interferon during organogenesis did not induce teratogenic effects, although it resulted in lower fetal weights and delays in ossification. Interferon alpha has been associated with significant, dose-dependent increases in abortions in laboratory animals at doses well above the recommended human dose. For example, pregnant rhesus monkeys administered interferon alpha 1a at 1, 5, or 25 million IU/kg/d (20 to 500 times the human weekly dose based on body surface area) experienced abortions when treated during the period of organogenesis or during late gestation (Roche Pharmaceuticals 2004). Interferon alpha 2b also induced abortions in pregnant rhesus monkeys administered at doses ranging from 15 to 30 million IU/kg/d (3 to 5 times the human weekly dose based on body surface area) (Schering Corporation 2007).

5.23.4 Human gestational exposure and effects

Interferon alpha is classified as FDA Pregnancy Category C. There were 41 published cases of patients treated with interferon alpha during pregnancy identified from 15 case reports, 10 case series and 2 retrospective survey (Appendix C Table 22). Among these patients, interferon alpha was used to treat chronic myeloid leukemia (n=33 cases), hairy cell leukemia (n=2 cases), melanoma (n=4 cases), and one patient each with Hodgkin lymphoma and multiple myeloma. There were 41 pregnancies (43 conceptuses) born to these patients, including two sets of twins (De Carolis *et al.* 2006, Egberts *et al.* 2006). Interferon alpha was administered during the 1st trimester to 20 patients (21 conceptuses due to one set of twins) and in the 2nd and 3rd trimester only to 19 patients (20 conceptuses due to one set of twins); timing of exposure was not specified in 2 cases {Pye, 2008 #364}. One of the 43 infants exposed in utero to interferon alpha had major malformations. One live born infant had exomphalos, right renal agenesis, and hemivertebrae {Pye, 2008 #364}; this pregnancy was co-treated with imatinib likely in the 1st trimester, which may be responsible for the malformation.

Pregnancy complications were reported for two pregnancies. Intrauterine fetal growth restriction occurred at gestation week 28 following 1st trimester exposure and co-treatments with dacarbazine in the 1st trimester and cisplatin in the 2nd trimester (Gottschalk *et al.* 2009). Another pregnancy experienced fetal growth retardation and severe oligohydramnios following exposure from 1st trimester throughout pregnancy (Mubarak *et al.* 2002). Of the 40 pregnancies with age at delivery data, early preterm birth (<34 weeks) was reported for 3 pregnancies (7.5%), late preterm delivery (34-36 weeks) was reported for 8 pregnancies (20%), and 29 pregnancies were born at term (72.5%). None of the newborns were reported to be small for gestation age. There were no newborn health issues with the exception of one infant with transient thrombocytopenia (Mubarak *et al.* 2002). Follow-up evaluations were available for 25 infants ranging in age from 4 to 96 months; age at follow-up was not specified for 3 children. Normal growth and development were reported for all offspring. In addition, there was also one case report of a melanoma patient treated during 2nd and 3rd trimester of pregnancy with interferon beta (Ishida *et al.* 2009), which is a Type I interferon similar to interferon alpha (Markowitz 2007). This infant was healthy at birth and at age 32 months (Ishida *et al.* 2009).

5.23.5 Summary of pregnancy outcomes for interferon alpha

In utero exposure to interferon alpha was documented for 41 pregnancies, including two sets of twins (43 conceptuses). No major or minor malformations were observed among the 21 infants exposed during the 1st trimester (including one set of twins) or the 19 infants exposed in the 2nd and/or 3rd trimester only (including one set of twins). Major malformations were observed in one infant without timing of exposure, who had exomphalos, right renal agenesis, and hemivertebrae {Pye, 2008 #364}; this pregnancy was co-treated with imatinib likely in the first trimester, which may be responsible for the malformation.   Thus, a total occurrence of major malformations was 2.3% (1/43 conceptuses) following exposure to interferon alpha at any time during pregnancy. Intrauterine growth restriction was observed in 2 pregnancies (Gottschalk *et al.* 2009), including one pregnancy with severe oligohydramnios (Mubarak *et al.* 2002). Of the 40 infants with age at delivery data, preterm birth was reported for 11 pregnancies. None of the newborns were reported to be small for gestation age. Transient myelosuppression (n=1 infant) was the only infant health effect reported following in utero exposure to interferon alpha. Follow-up evaluations of 25 infants at ages 4 to 96 months revealed normal growth and development for all children.

In conclusion, exposure to interferon alpha at any time during pregnancy does not appear to increase the rate of major malformations 2.4% (0/21 conceptuses in the 1st trimester and 0/20 conceptuses in

the 2nd and/or 3rd trimester only; 1/2 conceptuses timing not specified) relative to the prevalence of birth defects in the general population (2.3% versus 3%). The one infant with major malformations was likely exposed in the first semester and was co-treated with imatinib; thus, it is possible that the occurrence of exomphalos, right renal agenesis, and hemivertebrae may be due to exposure to imatinib.

5.24 METHOTREXATE

5.24.1 Mechanism of action, route of administration, and indications

Methotrexate is in the group of antineoplastic agents known as antimetabolites. It inhibits the enzyme dihydrofolic acid reductase, which is essential in the synthesis of purine nucleotides and thymidylate. Inhibition of the synthesis of these compounds interferes with DNA replication and repair and cellular replication. It may be administered by intramuscular, intravenous, intra-arterial, or intrathecal injection. Indications for methotrexate include gestational choriocarcinoma, chorioadenoma destruens, hydatidiform mole, meningeal leukemia (prophylaxis and treatment), breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungiodes, lung cancer, non-Hodgkin lymphoma, and osteosarcoma (Hospira 2008).

5.24.2 Evidence of placental and breast milk transport

Placental and breast milk transport of methotrexate in humans have been documented in a few cases. Schleuning and Clemm (Schleuning and Clemm 1987) reported, with few details, that methotrexate was detected in cord blood at a concentration of 1.86 x10^{-9} M following delivery by a woman who was on weekly methotrexate therapy (20 mg/m^2). Al-Saleh et al. (Al-Saleh *et al.* 2007) reported placental transfer of methotrexate using perfused placentas collected postpartum. Methotrexate (1 mg/mL) or antipyrine (100 ug/L; the reference substance) was injected as a 100 pL bolus into the maternal circulation. Starting one minute later, samples were collected from the fetal venous outflow every 30 seconds for 5 minutes. Methotrexate concentrations were determined using high performance liquid chromatography and antipyrine concentrations were determined using a colorimetric technique. The transport fraction (fraction of the drug appearing in the fetal vein at the end of sampling) averaged 24% for methotrexate and 69% for antipyrine.

Breast milk transfer of methotrexate was reported in one case. Johns et al. (Johns *et al.* 1972) detected low levels of methotrexate in breast milk of a one-month postpartum woman following administration of 15 mg/m^2 (22.5 mg/day) for choriocarcinoma. They collected urine, blood, and milk samples at 2-hour intervals. The peak plasma concentration (1.8 x 10-7 M) occurred at 6 hours and the milk concentration (5.0 x 10-9 M) peaked at 10 hours. The highest milk/plasma ratio was 0.08:1 at about 10 hours. Cumulative excretion of methotrexate in milk at 12 hours was about one ten-thousandth the amount excreted in urine. The American Academy of Pediatrics Committee on Drugs considers methotrexate one of the drugs "that may interfere with cellular metabolism of the nursing infant" (American Academy of Pediatrics 2001).

5.24.3 Laboratory animal developmental toxicity

Embryotoxic and teratogenic effects of methotrexate are described in the peer-reviewed literature. Methotrexate exposure has been reported to cause developmental abnormalities in chicks, mice, rats, and rabbits, but not in monkeys. In the chick, an injection into White Leghorn eggs after three and one-half days of incubation with 5-40 µg of methotrexate resulted in ratio changes of brain weight and cerebellum cell numbers (Zamenhof 1985). Skalko and Gold (Skalko and Gold 1974) reported that no defects were observed at doses below 10 mg methotrexate/kg in ICR mice administered a dose-range of 0.3 to 50 mg methotrexate per single intraperitoneal injection on gestation day 10. However, higher doses caused an increase in embryolethality and teratogenicity in mice, including ectrodactyly and cleft palate at the highest doses (25 and 50 mg/kg) (Skalko and Gold 1974). In vitro studies of rat embryos treated with methotrexate at concentrations as low as 0.05 µg/mL reported malformations of the rhombencephalic and telencephalic brain regions within 48 hours (Schmid 1984). Other malformations

were observed in the caudal trunk, heart and forelimb regions and in the vascular structures (Schmid 1984). Wilson et al. (Wilson *et al.* 1975) reported that intravenous administration of methotrexate to pregnant Wistar rats induced embryolethality at a dose of 0.3 mg/kg on gestation Day 11. In contrast, methotrexate administered intravenously to pregnant rhesus monkeys at 3.0 mg/kg/d on gestation days 29 to 32 caused embryonic growth retardation, but no teratogenicity (Wilson *et al.* 1975). Methotrextate induced malformations in 94% of New Zealand white rabbit offspring when administered intravenous at 19.2 mg/kg to pregnant dams on gestation Day 12. Malformations observed in the methotrexate-treated rabbit fetuses included hydrocephalus (11%), micrognathia (82%), cleft palate (42%), fore-hemimelia (55%), hind-hemimelia (35%), fore-ectrodactyly (90%), and hind-ectrodactyly (77%) (DeSesso and Goeringer 1992).

5.24.4   Human gestational exposure and effects

Methotrexate is classified as FDA Pregnancy Category X. There were 79 patients administered methotrexate to treat cancer during pregnancy identified from 21 case reports, 11 case series, 4 retrospective case series, 2 retrospective cohort studies, 5 retrospective surveys, and one registry survey (Appendix C Table 22). Among these patients, methotrexate was used to treat acute lymphocytic leukemia (n=32 cases), acute myelogenous leukemia (also, called acute granulocytic leukemia; n=7 cases), acute monomyelogenous leukemia (n=1 case), non-Hodgkin lymphoma (n=8 cases), and Burkitt lymphoma (n=3 cases). Methotrexate was also used to treat breast cancer (n=24 cases), choriocarcinoma of the vagina (n=1 case) and of the uterus (n=1 case), and Ewing sarcoma (n=1 case). The cancer type was not specified for one case (Van Calsteren *et al.* 2010). A total of 80 pregnancies (83 conceptuses) were exposed to methotrexate due to one patient gestating two singleton pregnancies (Aviles and Niz 1988) and three sets of twins (Freedman *et al.* 1962, Nantel *et al.* 1990, Turchi and Villasis 1988). Methotrexate was administered during the 1st trimester in 30 pregnancies (30 conceptuses) and in the 2nd and/3rd trimester only in 50 pregnancies (53 conceptuses due to three sets of twins).

Fetal loss occurred in 9 pregnancies, including 4 spontaneous abortions, 2 induced abortions, 1 hysterotomy, and 2 intrauterine fetal deaths. Spontaneous abortions occurred in 4 pregnancies following 1st trimester exposure and co-treatment with: cyclophosphamide and 5-fluorouracil (Ring *et al.* 2005, Zemlickis *et al.* 1992), 6-mercaptopurine and vincristine (Bergstrom and Altman 1998), or epirubicin and vincristine (Giacalone *et al.* 1999); no fetal autopsy data were provided. One pregnancy ended in induced abortion following 1st trimester exposure with no fetal details provided (Molkenboer *et al.* 2005). A normal fetus was observed at autopsy of an intrauterine fetal death following 1st trimester exposure and co-treatment with cyclophosphamide and 5-fluorouracil (Peres *et al.* 2001). Autopsy of one induced abortion reported a fetus with major malformations following exposure in the 2nd trimester with co-exposure to cyclophosphamide and 5-fluorouracil in the 2nd trimester; however, the pregnancy was also exposed in the 1st trimester to epirubicin, cyclophosphamide, 5-fluorouracil and radiation therapy (Leyder *et al.* 2010). Malformations observed at autopsy included: skin syndactyly of 1st and 2nd fingers of both hands, shortened 2nd and 3rd fingers on both hands, and osseous syndactyly of 4th and 5th metatarsal bones on both feet as well as micrognathia (Leyder *et al.* 2010). A normal fetus at autopsy was reported for a hysterectomy in the 4th month of gestation following exposure in the 2nd trimester and co-treatment with cyclophosphamide (Armitage *et al.* 1977). Finally, an intrauterine fetal death occurred following 2nd trimester exposure and co-exposure to vincristine, asparaginase, daunorubicin, and cytarabine (Molkenboer *et al.* 2005); no fetal autopsy data were provided.

Of the 74 live born infants born following in utero exposure to methotrexate, one infant had major malformations, microencephaly, hypertelorism, low-set ears, micrognathia, and a right palmar simian

crease (Bawle *et al.* 1998); this infant was exposed in the 1st, 2nd and 3rd trimesters and co-exposed to 5-fluorouracil and radiation therapy in the 2nd trimester. Minor malformations were observed in three infants. An inguinal hernia occurred in an infant with 1st and 2nd trimester exposure and co-treatment with cyclophosphamide and 5-fluorouracil (Giannakopoulou *et al.* 2000). Hemangiomas were reported in two infants: one infant was exposed in utero during the 2nd and 3rd trimester and co-exposed to vincristine, daunorubicin, cyclophosphamide, asaparginase and 6-mercaptopurine (Van Calsteren *et al.* 2010), and another infant with an abdominal hemangioma was exposed in the 2nd and/or 3rd trimester to combination therapy with methotrexate, cyclophosphamide and 5-fluorouracil (Ring *et al.* 2005). Ring et al. (Ring *et al.* 2005) stated that they did not believe the hemangioma was due to chemotherapy exposure in utero. **[It is possible that onr infant with a hemangioma was, instead, treated with cyclophosphamide and either doxorubicin or epirubicin; the authors did not report the treatments of individual patients {Ring, 2005 #373}.]**

A variety of pregnancy complications and infant health issues occurred following in utero exposure to methotrexate. Pregnancy complications included: preeclampsia (n=2 pregnancies) {Bergstrom, 1998 #159}{Coopland, 1969 #714}, elevated maternal blood pressure (n=1 pregnancy) {Turchi, 1988 #433}, premature rupture of membranes (n=5 pregnancies) {Doney, 1979 #215}{Karp, 1983 #129;Meador, 1987 #283}{Okun, 1979 #691;Udink ten Cate, 2009 #434}, and spontaneous preterm labor (n=9 pregnancies) {Berrebi, 1983 #697}{Brudie, 2011 #1094}{Giannakopoulou, 2000 #84}{Hansen, 2001 #105}{Moore, 1991 #718;Nantel, 1990 #317}{Willemse, 1990 #573}, including two cases with both premature rupture of membrances and spontaneous preterm labor {Karp, 1983 #129}{Meador, 1987 #283}. Intrauterine growth restriction was observed in two singleton pregnancies (Matsouka *et al.* 2008), including one case of intrauterine growth restrictionthought to be caused by placental insufficiency (Ring *et al.* 2005). Transient oligohydramnios occurred in one pregnancy (Hansen *et al.* 2001). Of the 45 pregnancies with age at delivery, early preterm delivery (<34 weeks) was reported for 12 pregnancies (26.7%), late preterm delivery (34-36 weeks) was reported for 8 pregnancies (17.8%), and 25 pregnancies were delivered at term (55.6%). Small for gestational age was reported for 3 newborns {Bawle, 1998 #903;Gulati, 1986 #96;Zemlickis, 1992 #576}. Breathing difficulties were reported in 4 newborns (Giannakopoulou *et al.* 2000, Hansen *et al.* 2001, Ring *et al.* 2005, Willemse *et al.* 1990). Transient myelosuppression was observed in 5 infants (Aviles *et al.* 1991, Aviles and Niz 1988, Dara *et al.* 1981, Khurshid and Saleem 1978, Okun *et al.* 1979) and 2 of these infants had jaundice (Dara *et al.* 1981, Hansen *et al.* 2001). One infant with transient myelosuppression also was hydropic with abdominal distension and was treated for congenital heart failure {Okun, 1979 #691}. Other health effects in newborns included: asystole which accompanied apnea (Willemse *et al.* 1990), meconium aspiration syndrome (Hansen *et al.* 2001), and cushingoid appearance at birth (Doney *et al.* 1979). Twin newborns suffered from diarrhea, which resolved in two weeks, and the female twin was also hypotonic (Turchi and Villasis 1988). One infant had some chromosome breakage and a ring chromosome at birth (Schleuning and Clemm 1987). There were two infant deaths. One infant died of septicemia at age 21 days and another infant died of gastroenteritis at age 90 days (Aviles and Niz 1988).

There were 52 infants with follow-up evaluations at ages 10 weeks to 19 years. Normal health and development were reported for all but 2 children. At age 8.5 years, one child had verbal expressive difficulties, stuttered and had an intelligence quotient of 90 (Bawle *et al.* 1998); this infant had been diagnosed with microencephaly at birth. The second child was below the 5th percentile for height and weight at 14 months of age {Bawle, 1998 #903;Gulati, 1986 #96}.

5.24.5 Summary of pregnancy outcomes for methotrexate

In utero exposure to methotrextate occurred in 80 pregnancies, including three sets of twins (83 conceptuses). Of the 30 singleton pregnancies exposed in the 1st trimester, one newborn had major malformations: microencephaly, hypertelorism, low-set ears, micrognathia, and a right palmar simian crease (Bawle *et al.* 1998). An inguinal hernia, a minor malformation, was reported in another infant with 1st trimester exposure (Giannakopoulou *et al.* 2000). In addition, there were six pregnancies ending in fetal loss following 1st trimester exposure. A normal fetus was reported for an intrauterine fetal death (Peres *et al.* 2001) and no fetal autopsy data were provided for four spontaneous abortions and one induced abortion. A total occurrence of major malformations following 1st trimester exposure to methotrexate was 3.3% (1/30 conceptuses). Of the 50 pregnancies (53 conceptuses due to 3 sets of twins {Freedman, 1962 #887;Nantel, 1990 #317;Turchi, 1988 #433}) exposed to methotrexate in the 2nd and/or 3rd trimester only, major malformations were observed in one induced abortus: multiple distal limb malformations accompanied by micrognathia (Leyder *et al.* 2010); the infant was exposed to radiation therapy and other chemotherapy agents in the 1st trimester. Autopsy revealed a normal fetus for a hysterectomy following exposure in the 2nd trimester (Armitage *et al.* 1977). Hemangiomas, which are considered minor malformations, were reported in two infants (Ring *et al.* 2005, Van Calsteren *et al.* 2010). Thus, a total occurrence of major malformations following in utero exposure to methotrexate in the 2nd and/or 3rd trimester was 1.9% (1/53 conceptuses).

A variety of pregnancy complications and infant health issues occurred following in utero exposure to methotrexate. Pregnancy complications included: transient oligohydramnios (Hansen *et al.* 2001) (n=1 pregnancy), intrauterine growth restriction (n=2 pregnancies) (Matsouka *et al.* 2008, Ring *et al.* 2005). Of the 45 pregnancies with age at delivery, preterm delivery was reported for 20 pregnancies. Small for gestational age was reported for 3 newborns {Bawle, 1998 #903;Gulati, 1986 #96;Zemlickis, 1992 #576}. Common infant health issues included: respiratory difficulties (n=4 infants), transient myelosuppression (n=5 infants), and jaundice (n=2 infants). One infant with transient myelosuppression also was hydropic with abdominal distension and was treated for congenital heart failure {Okun, 1979 #691}. There were two infant deaths: one infant died of septicemia at age 21 days and another infant died of gastroenteritis at age 90 days (Aviles and Niz 1988). One otherwise normal infant had some chromosome breakage and a ring chromosome at birth (Schleuning and Clemm 1987). Off the 52 infants with follow-up evaluations, normal growth and development were observed in all but 2 children. One child had verbal expressive difficulties, stuttered and an intelligence quotient of 90 (Bawle *et al.* 1998); this infant had been diagnosed with microencephaly at birth. The second child was below the 5th percentile for height and weight at 14 months of age {Bawle, 1998 #903;Gulati, 1986 #96}.

In conclusion, the occurrence of major malformations in methotrexate-exposed pregnancies was 2.4% (2/83 conceptuses). The occurrence of major malformations following exposure to methotrexate during the 1st trimester (1/30 conceptuses) is similar to the prevalence of birth defects in the general population (3.3 ± 6.4% versus 3%). Likewise, the occurrence of major malformations following exposure in the 2nd and 3rd trimester only (1/53 conceptuses) is not higher than the prevalence of birth defects in the general population (1.9 ± 3.7% versus 3%). The single case of a malformation, which included skin and osseous syndactyly and shortened fingers, was not likely a result of exposure to methotrexate in the 2nd and/or 3rd trimester only. It is noteworthy that the conceptus was exposed to epirubicin, cyclophosphamide, 5-fluorouracil, and radiation therapy in the 1st trimester. Therefore, the revised occurrence of major malformations likely caused by methotrexate in the 2nd and/or 3rd trimester only was 0% (0/53 conceptuses).

5.25 MITOXANTRONE

5.25.1 Mechanism of action, route of administration, and indications

Mitoxantrone is an anthracycline intercalating agent that damages DNA by causing cross links and strand breaks after binding (APP Pharmaceuticals 2010). Mitoxantrone also interferes with RNA and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling DNA. Mitoxantrone is administered via intravenous injection and indicated for acute non-lymphocytic leukemia (acute myelogenous, acute promyelocytic, monocytic, and erthyroid acute) (APP Pharmaceuticals 2010). It is also used to treat prostate cancer and multiple sclerosis (a non-cancerous disease).

5.25.2 Evidence of placental and breast milk transport

Placental transport of mitoxantrone has not been documented in humans, and there is limited evidence of breast milk transfer of the drug in humans. Placental transfer of mixtantrone may occur as there are data demonstrating limited placental transport of other anthracyline intercalating drugs (e.g., doxorubicin and epirubicin) in humans (D'Incalci *et al.* 1982) and laboratory animal models (Van Calsteren *et al.* 2010, Van Calsteren *et al.* 2010). Mitoxantrone was detected in human breast milk following maternal administration of the drug. Azuno et al. (Azuno *et al.* 1995) reported that detectable levels of mixtoxantrone were present in breast milk at 21 and 28 days post-administration of 6 mg/m^2 to the mother on 3 consecutive days. The levels of mitoxantrone in breast milk were 120 and 18 mg/mL at 21 and 28 days post-treatment.

5.25.3 Laboratory animal developmental toxicity

The product insert reported mixtoxantrone is designated a human teratogen based on its mechanism of action and the development effects of other anthracycline intercalating agents (i.e., doxorubicin and ametantrone) (APP Pharmaceuticals 2010). Mitoxantrone did not induce teratogenic effects in rats and rabbits at the maximum doses tested, which were 2% and 5% of the maximal human dose on a body surface area basis, respectively. Fetal growth retardation in rat and increased incidence of premature delivery in rabbits administered mitoxantrone during the period of organogenesis at ≥ 0.01 mg/kg/day (1% of the recommended human dose on a body surface basis). A similar compound, ametantrone acetate, causes teratogenic effects in rabbit fetuses exposed during the period of organogenesis via oral administration of ≥ 0.4 mg/kg/day to the dam (Petrere *et al.* 1986). No teratogenic effects were observed in the fetuses of pregnant rats treated to a similar dose range of ametantrone acetate**. [There were no reports of embryotoxicity caused by mitoxantrone in developmental toxicity studies in laboratory animals.]**

5.25.4 Human gestational exposure and effects

Mitoxantrone is classified as FDA Pregnancy Category D. There were 17 published cases of patients treated with mitoxantrone during pregnancies identified from 7 case reports, 2 case series, 1 retrospective case series, 1 retrospective cohort study and 1 retrospective survey (Appendix C Table 23). Among these patients, mitoxantrone was administered to treat acute myelogenous leukemia (n=9 cases), acute promyelocytic leukemia (n=2 cases), acute leukemia (type not specified; n=3 cases), non-Hodgkin lymphoma (n=1 case) and breast cancer (n=2 cases). A total of 17 singleton pregnancies (17 conceptuses) were exposed to mitoxantrone. Mitoxantrone was administered during the 1st trimester in two cases, and in the 2nd and/or 3rd trimester only in 12 cases; timing of exposure was not specified for 3 cases. Fetal loss occurred in 3 pregnancies. One spontaneous abortion occurred following 1st trimester exposure and co-treatment with cytarabine (Chelghoum *et al.* 2005); no fetal autopsy data were

reported. One induced abortion ended a pregnancy following 2nd trimester exposure and co-exposure to cytarabine (Chelghoum *et al.* 2005); no fetal autopsy data were provided. A grossly normal fetus was observed following an intrauterine fetal death (Reynoso and Huerta 1994); the pregnancy was exposed during the 2nd and 3rd trimester to mitoxantrone and cytarabine with co-exposure to daunorubicin in the 2nd trimester and co-exposure to idarubicin in the 3rd trimester. Of the 14 live born infants gestationally-exposed to mitoxantrone, there was one infant with a major malformation: bilateral hydronephrosis with dilation of the left proximal ureter (Garcia *et al.* 1999); this infant was exposed in the 3rd trimester and co-treated with daunorubicin and cytarabine in the 3rd trimester following 2nd trimester exposure to cytarabine.

A variety of pregnancy complications and infant health issues occurred following exposure to mitoxantrone in utero. One patient experienced preterm labor early in the 3rd trimester that was treated and resolved followed by premature rupture of membrane leading to preterm delivery at 35 weeks and 4 days gestation (Gondo *et al.* 1990). Oligohydramnios occurred in one pregnancy (Garcia *et al.* 1999) and three fetuses experienced intrauterine growth restriction (Baumgartner *et al.* 2009, Garcia *et al.* 1999, Hsu *et al.* 1995). Two singleton pregnancies experienced fetal heart abnormalities, including: cardiomyopathy (Baumgartner *et al.* 2009) and fetal tachycardia (Garcia *et al.* 1999). Fetal distress was observed in two pregnancies as intermittent sinusoidal fetal heart rate patterns {Yucebilgin, 2004 #459} and an abnormal cardiotocogram (Mavrommatis *et al.* 1998). Other fetal health events were transient ventriculomegaly after initiation of chemotherapy treatment (n=1 infant) (Baumgartner *et al.* 2009) and a low biophysical profile score (n=1 infant)(Mavrommatis *et al.* 1998). Of the 11 pregnancies reporting delivery dates, early preterm delivery (<34 weeks) was reported for 5 pregnancies (45.5%) and late preterm delivery (34-36 weeks) was reported for the remaining 6 pregnancies (54.5%); no births occurred at term. One newborn was identified small for gestational age by the (Giacalone *et al.* 1999). Respiratory difficulties occurred in four newborns (Baumgartner *et al.* 2009, Garcia *et al.* 1999, Giacalone *et al.* 1999, Mavrommatis *et al.* 1998, Reynoso and Huerta 1994). Four newborns had transient myelosuppression, including anemia (Baumgartner *et al.* 2009), neutropenia and thrombocytopenia (Garcia *et al.* 1999), thrombocytopenia and leukocytopenia (Gondo *et al.* 1990), or pancytopenia (Hsu *et al.* 1995). In addition, one newborn experienced hyponatremia, hypoglycemia, seizures, and an intracranial hemorrhage (Garcia *et al.* 1999); the intracranial hemorrhage resolved within a month after birth. Follow-up evaluations were available for 13 infants ranging in age from 2 months to 29 years. Normal growth and development were reported for all the children, except one infant who suffered from failure to thrive and did not gain weight until age 3 months (Garcia *et al.* 1999).

5.25.5 *Summary of pregnancy outcome following in utero exposure to mitoxantrone*

In utero exposure to mitoxtantrone was documented for 17 singleton pregnancies (17 conceptuses). The one pregnancy exposed in the 1st trimester ended in spontaneous abortion with no fetal autopsy data provided (Chelghoum *et al.* 2005). Thus, there were no reports of major malformations induced following exposure to mitoxtantrone during the 1st trimester (0/1 conceptuses) or 2nd and/or 3rd trimester only (0/13 conceptuses). Of the thirteen pregnancies exposed in the 2nd and/or 3rd trimester only, one infant had a minor major malformation: bilateral hydronephrosis with dilation of the left proximal ureter (Garcia *et al.* 1999). In addition, there were two cases with fetal loss following exposure 2nd and/or 3rd trimester only: one intrauterine fetal death of an apparently normal fetus (no fetal autopsy was conducted) (Reynoso and Huerta 1994), and one induced abortion with no fetal autopsy data provided (Chelghoum *et al.* 2005). Thus, a total occurrence of major malformations following exposure to mitoxantrone in the 2nd and/or 3rd trimester was 7.7% (1/13 conceptuses).

Pregnancy complications were reported in a total of 5 pregnancies exposed to mitoxantrone. Intrauterine growth restriction occurred in three pregnancies {Baumgartner, 2009 #151;Garcia, 1999 #69;Hsu, 1995 #111}, including one pregnancy which also experienced oligohydramnios {Garcia, 1999 #69}. Fetal distress occurred in 2 pregnancies {Mavrommatis, 1998 #604;Yucebilgin, 2004 #459}. Fetal cardiotoxicity was reported for 2 pregnancies {Garcia, 1999 #69}{Baumgartner, 2009 #151}. Of the 11 cases with age at delivery data, all pregnancies were delivered preterm either by induced vaginal delivery or C-section. Small for gestational age was reported for one newborn (Giacalone *et al.* 1999). Common infant health issues were respiratory difficulties (n=5 infants) and transient myelosuppression (n=4 infants). One newborn also experienced hyponatremia, hypoglycemia, seizures, and an intracranial hemorrhage (Garcia *et al.* 1999). Normal growth and development were reported for 12 of the 13 infants with follow-up evaluations at ages ranging from 2 months to 29 years. One infant suffered from failure to thrive and did not gain weight until age 3 months (Garcia *et al.* 1999).

In conclusion, the occurrence of major malformations in mitoxantrone-expose d pregnancies was 5.9% (1/17 conceptuses). The occurrence of major malformations following exposure to mitoxantrone during the 1st trimester could not be accurately assessed because there were too few cases (0/1 conceptuses). The occurrence of major malformations following exposure during the 2nd and/or 3rd trimester (0/13 conceptuses) was similar to the prevalence of major malformations in the general population (0% versus 3%); however, there were very few published cases of pregnancy outcomes of cancer patients being treated with this drug during pregnancy.

5.26 NITROGEN MUSTARD (Mechlorethamine)

5.26.1 Mechanism of action, route of administration, and indications

Nitrogen mustard (mechlorethamine) is an anti-neoplastic alkylating agent that inhibits rapidly proliferating cells (Merck 2004). Nitrogen mustard acts via the crosslinking of its active metabolites to DNA, which results in inhibition of DNA synthesis and function (Perry 2008). Nitrogen mustard is administered via intravenous injection. Nitrogen mustard is indicated in the treatment of several types of cancer, such as Hodgkin lymphoma, lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, lung cancer (e.g. non-small cell lung cancer) and mycosis fungoides (cutaneous T-cell lymphoma) (Merck 2004). Nitrogen mustard is also used to treat non-cancerous blood disorders, such as polycythemia vera, and may be injected into body spaces, such as the chest, abdomen or the sack containing the heart, to stop the accumulation of fluids (effusion) caused by cancer (Merck 2004).

5.26.2 Evidence of placental and breast milk transport

Placental and breast milk transport of nitrogen mustard in humans is not known. It is not known whether this drug is excreted in human milk. The low molecular weight of about 156 suggests that the drug may be found in breast milk.

5.26.3 Laboratory animal developmental toxicity

Teratogenic effects have been reported following the administration of nitrogen mustard to rats and ferrets. A single subcutaneous injection of 1 mg/kg mechlorethamine (2-3 times the maximum recommended human dose) produced congenital malformations in rats and ferrets (Merck 2004). Teratogenic effects of nitrogen mustard are also described in the peer-reviewed literature. Nitrogen mustard administered to pregnant Wister rats by a single intraperitoneal injection on the 11th or 12th day of gestation at doses of 0.5- 0.7 mg/kg induced malformations (Chaube et al. 1968). Malformations within the teratogenic dose range included: encephalocele or exencephaly, cleft palate, retarded or clubbed for or rear leg, etrodactylous, polydactylous, syndactylous, brachydactylous and short, kinky or absent tail (Chaube et al. 1968). In addition, Charles River CD rat embryos exposed to 1 to 5 µg nitrogen mustard in vitro on gestation day 11 resulted in severe growth retardation (Sanyal et al. 1981).

5.26.4 Human gestational exposure and effects

Nitrogen mustard is classified as FDA Pregnancy Category D. There were 30 cases of women treated with nitrogen mustard during pregnancy identified from 7 case reports, 4 case series, 3 retrospective case series, 4 retrospective cohort studies, and 1 retrospective survey (Appendix C Table 24). Nitrogen mustard was used to treat Hodgkin lymphoma (n=27 cases), acute lymphocytic leukemia (n=1 case), and cancer type was not specified in two cases. A total of 30 singleton pregnancies (30 conceptuses) were exposed to nitrogen mustard. Nitrogen mustard was administered during the 1st trimester in 17 cases (17 conceptuses), and in the 2nd and/or 3rd trimester only in 13 cases (13 conceptuses). Fetal loss occurred in 6 pregnancies exposed to nitrogen mustard. Autopsy following a hysterotomy at gestation week 13 revealed a normal fetus with very small, malpositioned kidneys (Mennuti et al. 1975); the pregnancy was exposed during the 1st trimester and co-exposed to vincristine and procarbazine. A fetus from a spontaneous abortion was grossly normal following exposure during the period of conception and 1st trimester and co-exposure to 6-mercaptopurine in the 1st trimester (Hoover and Schumacher 1966); histological analysis of the fetus was not conducted. A second spontaneous abortion occurred following exposure during the 1st trimester (Zemlickis et al. 1992); fetal data were not reported. Autopsy following an induced abortion revealed a normal fetus with toxic degeneration of the liver and

kidneys (Peres *et al.* 2001); the pregnancy was exposed during the 1st trimester and co-treated with vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarbazine. Fetal autopsy data were not reported in the remaining two induced abortions (Blatt *et al.* 1980, Zemlickis *et al.* 1992).

Of the 24 live born infants, major malformations were reported in 3 infants. One newborn had four digits per foot, webbing between the 3rd and 4th digits, and an abnormal pinna and a bowed tibia on the right leg (Garrett 1974); this infant had been exposed during the period of conception and 1st trimester and co-treated with vincristine and procarbazine. One infant with hydrocephaly died 4 hours after birth (Zemlickis *et al.* 1992); this pregnancy was exposed during the 1st trimester and co-exposed to procarbazine and vincristine. Bilateral syndactyly of digits II and III was observed in an infant following 2nd and 3rd trimester exposure and co-exposure to vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarbazine (Van Calsteren *et al.* 2010). Pectus excavatum, a minor malformation, was observed in an infant also exposed to during the 2nd and 3rd trimester and co-treated with vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarbazine (Van Calsteren *et al.* 2010). There were three infant deaths following in utero exposure to nitrogen mustard. One infant weighed 1 pound and 6 ounces **[1076 gm]** at birth in approximately gestation month 5, and died 2 days later (Boland 1951); the pregnancy was exposed during the 1st trimester. As described above, one infant with hydrocephalus died 4 hours after birth (Zemlickis *et al.* 1992). A third infant died of severe gastroenteritis at age 3 months (Dilek *et al.* 2006); this infant was exposed during the period of conception and the 1st trimester and co-exposed to vincristine and procarbazine.

One pregnancy complication and a variety of infant health issues were reported in infants with in utero exposure to nitrogen mustard. Spontaneous preterm labor was reported in one pregnancy (Johnson and Filshie 1977). Of the 17 pregnancies with age at delivery data, early preterm delivery (<34 weeks) was reported for 4 pregnancies (23.5%), late preterm delivery (34-36 weeks) was reported to one pregnancy (5.9%), and 12 pregnancies were delivered at term (70.6%). None of the infants were reported to be small for gestational age. One newborn had jaundice, anemia and hepatomegaly at birth, but progressively improved (Deuschle and Wiggins 1953). Mild anemia occurred in another infant (Johnson and Filshie 1977). Cerebral hemorrhage was reported in an early preterm infant (Garrett 1974). Another infant was bronchoscoped for excess mucus shortly after birth and was sluggish for a few hours, but then progressed well (Zoet 1950). Follow-up examinations were available for 15 infants at ages ranging from 2 months to 2 years. All 15 children had normal growth and development.

5.26.5 *Summary of pregnancy outcomes for nitrogen mustard*

In utero exposure to nitrogen mustard was reported for 30 singleton pregnancies (30 conceptuses). Of the 17 pregnancies exposed during the 1st trimester, major malformations occurred in two infants. One newborn had four digits per foot, webbing between the 3rd and 4th digits, and an abnormal pinna and a bowed tibia on the right leg (Garrett 1974). Hydrocephaly occurred in another infant, who died 4 hours after birth (Zemlickis *et al.* 1992). In addition, fetal loss occurred in 6 pregnancies exposed in the 1st trimester, including: two spontaneous abortions, three induced abortions and one hysterotomy. Normal fetuses at autopsy were observed for the hysterotomy (Mennuti *et al.* 1975), one spontaneous abortion (Hoover and Schumacher 1966) and one induced abortion (Peres *et al.* 2001). No fetal data were available for the remaining one spontaneous and two induced abortions. Two additional infants died following exposure to nitrogen mustard during the 1st trimester. One premature infant died 2 days after birth (Boland 1951), and another infant died at 3 months from severe gastroenteritis (Dilek *et al.* 2006). Thus, a total occurrence of major malformations following exposure during the 1st trimester to nitrogen mustard was 11.8% (2/17 conceptuses). Of the 13 pregnancies with exposure during the 2nd and/or 3rd trimester only, a major malformation was reported for one infant: bilateral syndactyly of

digits II and III (Van Calsteren *et al.* 2010). Pectus excavatum, a minor malformation, occurred in another infant with 2nd and 3rd trimester exposure (Van Calsteren *et al.* 2010). The total occurrence of major malformations following exposure to nitrogen mustard in the 2nd and/or 3rd trimester only was 7.7% (1/13 conceptuses).

Relatively few infant pregnancy complications or health issues were associated with exposure to nitrogen mustard during pregnancy. Spontaneous preterm labor was reported in one pregnancy (Johnson and Filshie 1977). Of the 14 pregnancies with age at delivery data, preterm birth was reported for 5 pregnancies. None of the infants were reported to be small for gestational age. Health issues in infants exposed during pregnancy to nitrogen mustard included: jaundice, anemia and hepatomegaly (n=1 infant), mild anemia (n=1 infant), cerebral hemorrhage (n=1 infant) and excess mucus treated with bronchoscopy (n=1 infant).

In conclusion, the occurrence of major malformations in nitrogen mustard-exposed pregnancies was 10.0% (3/30 conceptuses). The occurrence of major malformation following 1st trimester exposure to nitrogen mustard (2/17) was almost four times the prevalence of birth defects in the general population (11.8 ± 15.3% versus 3%). The occurrence of major malformations in the 2nd and/or 3rd trimester only (1/13 conceptuses) was approximately double the occurrence in the 1st trimester (7.7 ± 14.5% versus 3%). This single major malformation, bilateral syndactyly, was not likely the result of exposure to nitrogen mustard during the 2nd and/or 3rd trimester only. The revised occurrence of major malformations following exposure to nitrogen mustard in the 2nd and/or 3rd trimester only was 0% (0/13 conceptuses).

5.27 PACLITAXEL

5.27.1 Mechanism of action, route of administration, and indications

Paclitaxel (Taxol) is an antineoplastic agent isolated from the Pacific yew tree, *Taxus brevifolia*. Paclitaxel is an antimicrotubule agent that inhibits the normal reorganization of the microtubule network that is essential for interphase and mitotic cellular functions (Bristol-Myers Squibb 2010). Paclitaxel binds to microtubules, enhances polymerization and prevents depolymerization, which inhibits mitosis in the M-phase of the cell cycle and promotes apoptosis (Leslie *et al.* 2005). Paclitaxel is administered intravenously. Paclitaxel is indicated for the treatment of advanced ovarian cancer, breast cancer, non-small cell lung cancer and AIDS-related Kaposi sarcoma (Bristol-Myers Squibb 2010).

5.27.2 Evidence of placental transfer and presence in breast milk

Placental transfer in humans is not known, however the high molecular weight and extensive protein binding (>95%) of paclitaxel suggest transplacental transfer may be limited (Van Calsteren *et al.* 2010). Van Calsteren et al. (Van Calsteren *et al.* 2010), report that transplacental transfer of paclitaxel did not occur in the C57/Bl6J mouse model. Paclitaxel is a substrate for the transporter protein P-glycoprotein located in the placenta at the blood exchange border of the fetal and maternal compartments. This P-glycoprotein appears to block the paclitaxel from passing into the fetus, thus sparing the developing fetus toxic effects of paclitaxel (Smit *et al.* 1999). Specifically, when pregnant mice were administered paclitaxel and co-treated with a compound that blocked availability of the P-glycoprotein, 16-fold more paclitaxel passed into the fetus compared to pregnant mice that were only exposed to paclitaxel (Smit *et al.* 1999). In humans, maternal transfer of paclitaxel to the infant via breast milk is not known (Bristol-Myers Squibb 2010). Intravenous administration of carbon 14-labeled Taxol to rats on days 9 to 10 postpartum resulted in concentrations of radioactivity in milk that were higher than plasma and declined in parallel with the plasma concentrations (Bristol-Myers Squibb 2010).

5.27.3 Laboratory animal developmental toxicity

Paclitaxel is embroylethal in rabbits, mice, rats and chicks (Bristol-Myers Squibb 2010, Shepard and Lemire 2004) and is teratogenic in rats and chicks (Scialli *et al.* 1995, Scialli *et al.* 1997). Paclitaxel induced resorptions and fetal death in rabbits when administered during organogenesis at a dose of 3.0 mg/kg/day (0.2 times the daily maximum recommended human dose on a mg/m^2 basis) (Bristol-Myers Squibb 2010). In a review by Shepard et al. {Shepard, 2004 #871}, paxclitaxel caused a reduction in the number of implantations and live fetuses of mice intravenously exposed to 1.0 mg paclitaxel/kg before pregnancy and during the first week of gestation. No teratogenic effects were observed in mice treated with up to 0.6 mg per day of paclitaxel during organogenesis (Shepard and Lemire 2004). Free (non-encapsulated) paclitaxel induced 100% fetal death and maternal toxicity when administered as a single intravenous dose of 10.0 mg/kg on gestation day 8 in Wistar rats (Scialli *et al.* 1997). At lower doses (2.0 and 0.67 mg/kg on gestation day 8), free paclitaxel reduced fetal body weight, implantation number, and it induced malformations at 2.0 mg/kg, including: exencephaly/anencephaly, ventral wall defects, facial clefts, anophthalmia, diaphragmatic hernia and defect of the kidney, cardiovascular system and tail (Scialli *et al.* 1997). It has been speculated that the embryotoxicity observed with paclitaxel treatment in laboratory animal studies is associated with the vehicle in which paclitaxel is administered, Cremaphor EL (ethanol/polyethoxylated castor oil) (Scialli *et al.* 1997). Liposome encapsulation of paclitaxel attenuated the toxic effects, such that 10 mg/kg of the encapsulated drug produced effects similar to 2 mg/kg free (non-encapsulated) drug.

5.27.4   Human gestational exposure and effects

Paclitaxel is classified as FDA Pregnancy Category D. There were 30 published cases of patients treated with paclitaxel during pregnancy identified from 16 case reports, 3 case series, and 1 registry survey (Appendix C Table 25). Among these 30 patients, paclitaxel was used to treat cancers of the breast (n=14 cases), ovary (n=8 cases), cervix (n=6 cases), and lung (n=2 cases). A total of 30 pregnancies and 31 conceptuses (due to one set of twins; (Lycette *et al.* 2006)) were exposed to paclitaxel. No patients were exposed to paclitaxel during the 1st trimester. All 30 patients (31 conceptuses) were administered paclitaxel in the 2nd and/or 3rd trimester only. Of the 31 liveborn infants, only one infant had a major malformation. Pyloric stenosis was reported in an infant exposed during the 2nd and 3rd trimesters and co-exposed to doxorubicin, cytarabine and docetaxel (Cardonick *et al.* 2010).

A variety of pregnancy complications and newborn health issues occurred in pregnancies exposed to paclitaxel. Pregnancy complications included oligohydramnios (n=2 pregnancies) (Bader *et al.* 2007, Shieh and Mehta 2011). One of the pregnancies with oligohydramnios also had cessation of fetal abdominal growth and fetal renal failure (Bader *et al.* 2007). One pregnancy each had preeclampsia {Gonzalez-Angulo, 2004 #90} and pregnancy-induced hypertension {Raghunath, 2006 #662}. Spontaneous preterm labor occurred in three pregnancies {Azim, 2009 #63}, including two pregnancies of transient preterm labor that was treated and subsided {Li, 2011 #962}{Lycette, 2006 #265}. One pregnancy was terminated by C-section at gestation week 30 due to maternal tonic-clonic seizures induced by brain metastases (Garcia-Gonzalez *et al.* 2008). Of the 22 pregnancies with age at delivery data, early preterm delivery (<34 weeks) was reported for 4 pregnancies (13.6%), late preterm delivery (34-36 weeks) was reported for 13 pregnancies (59%), and 5 pregnancies were delivered at term (22.7%). Small for gestational age was reported for one newborn (Cardonick *et al.* 2010). Three infants experienced respiratory distress (Bader *et al.* 2007, Garcia-Gonzalez *et al.* 2008, Hubalek *et al.* 2007). One infant each had anemia (Hubalek *et al.* 2007), neutropenia (Cardonick *et al.* 2010), and jaundice (Cardonick *et al.* 2010). Another infant had transient renal failure, hypotension, and was treated for bacterial sepsis (Bader *et al.* 2007). As mentioned above, this infant also experienced renal failure in utero in a pregnancy complicated by oligohydramnios and it is suspected that these effects are most likely due to the co-treatment with trastuzumab during pregnancy, rather than in utero exposure to paclitaxel (Bader *et al.* 2007). Follow-up evaluations were reported for 22 infants ranging in age from 12 weeks to 7.3 years of age. All 22 children had normal growth and development.

5.27.5   Summary of pregnancy outcomes for paclitaxel

In utero exposure to paclitaxel was documented for 30 pregnancies, including one set of twins (31 conceptuses). There were no pregnancies exposed in the 1st trimester, thus all pregnancies were exposed in the 2nd and/or 3rd trimester. A major malformation was reported in only one of 31 infants gestationally exposed to paclitaxel: pyloric stenosis (Cardonick *et al.* 2010). A total occurrence of major malformations following exposure to paciltaxel in the 2nd and/or 3rd trimester was 3.2% (1/31 conceptuses). Pregnancy complications included oligohydramnios in two pregnancies (Bader *et al.* 2007, Shieh and Mehta 2011). In addition to oligohydramnios, one of these pregnancies also experienced cessation of fetal abdominal growth and fetal renal failure, which may be attributable to co-treatment with trastuzumab (Bader *et al.* 2007). Of the 22 pregnancies with age at delivery data, preterm birth was reported for 17 pregnancies. Small for gestational age was reported for one newborn (Cardonick *et al.* 2010). Infant health effects included: respiratory difficulties (n=2 infants), transient myelosuppression (n=2 infants), and jaundice (n=1 infant). One newborn had transient renal failure, hypotension, and sepsis (Bader *et al.* 2007). Of the 28 infants with follow-up evaluations, normal

growth and development were reported for all children at ages ranging from 12 weeks to 7.3 years of age.

In conclusion, the total occurrence of major malformations in paclitaxel-exposed pregnancies was 3.2% (1/31 conceptuses). No published cases of paclitaxel chemotherapy during the 1st trimester of pregnancy were identified. The occurrence of major malformations following exposure to paclitaxel during the 2nd and/or 3rd trimester (1/31 conceptuses) is comparable to the prevalence of birth defects in the normal populations (3.2 ± 6.2% versus 3%).

5.28 PROCARBAZINE

5.28.1 Mechanism of action, route of administration, and indications

Procarbazine, an analog of hydrazine and an alkylating agent, is an antineoplastic agent whose exact mechanism of action is not known. Procarbazine is metabolized into cytotoxic metabolites (Gutterman *et al.* 1969). The cytotoxic metabolites of procarbazine may inhibit the transmethylation of methyl groups of methionine into t-RNA rendering it non-functional, which could inhibit protein synthesis and, consequently, DNA and RNA synthesis. In addition, procarbazine may directly damage DNA by generating free radicals that attack sulfhydryl groups in residual protein, which is bound to DNA (Sigma-tau 2004). Procarbazine is administered as an oral dose. It is indicated for Hodgkin and non-Hodgkin lymphomas as well as in the treatment of malignant gliomas. It is frequently used in combination chemotherapy with nitrogen mustard (methchlorethamine hydrochloride), vincristine (oncovirin), and prednisone (also called MOPP) (Sigma-tau 2004)

5.28.2 Evidence of placental and breast milk transport

Placental and breast milk transport of procarbazine is not documented in either humans or animals. However, the administration of procarbazine during pregnancy results in cytogenetic damage in fetal blood cells in mice (e.g., a dose-dependent increase in micronucleated red blood cells following in utero exposure to 20, 50 or 80 mg/kg procarabaine on gestation day 15 or 16) (King and Wild 1979) and methylation of fetal DNA in rats (Wiestler *et al.* 1984), which suggests that procarbazine crosses the placenta in rodents. In particular, there was a dose-dependent increase in fetal micronucleated red blood cells collected 25-26 hours following administration of procarbazine at 20, 50 or 80 mg/kg to mouse dams on gestation day 15 or 16 (King and Wild 1979). In rats, methylated DNA was observed in fetal liver, brain, lung and intestines collected 4 hours following administration of radiolabelled procarbazine at 125 mg/kg on gestation day 22 (Wiestler *et al.* 1984). There are no published reports dealing with the presence of procarbazine in breast milk in humans or animals.

5.28.3 Laboratory animal developmental toxicity

Procarbazine causes embryo lethal and teratogenic effects in rats exposed in utero. According to the product label (Sigma-tau 2004), procarbazine hydrochloride is teratogenic in rats at doses 4-13 times the maximum recommended human therapeutic dose of 6 mg/kg/day. Chaube and Murphy (Chaube and Murphy 1969) reported malformations in offspring of pregnant rats administered a single intraperitoneal injection of procarbazine on gestation days 5, 6, 7 or 8, 9, 10, 11, 12, 14, or 17. Thirteen different doses were used ranging from 5 to 500 mg/kg. Malformations included: limb, digit, and tail defects; jaw defects; clefts of the palate, lip, and face; malformations of the brain, skull and spine; acephaly and omphalocele. Lower doses caused embryo lethality and malformations when administered during the period of organogenesis. Procarbazine also induced malformations when administered at doses of 5-10 mg/kg orally to pregnant rats on gestation day 8-14 (reviewed in (Shepard and Lemire 2004)). Treatment before gestation day 12 produced almost exclusively eye defects, whereas defects of the limbs were reported following treatment after gestation Day 12. Administration of 200 mg/kg by gavage to pregnant rats on gestation day 14 resulted in cleft palate in 94% of the offspring, as well as other skull abnormalities (Bienengraber *et al.* 1999). Malek et al. (Malek *et al.* 2003) treated pregnant rats with 25 or 50 mg/kg procarbazine by gavage on gestation day 14. They reported that both dose levels resulted in a reduction in live fetuses and an increase in resorptions, that some physical measurements of the fetuses were reduced, but that no teratogenic effects were noted. When pregnant Sprague Dawley rats were treated orally with doses of 2.5, 5.0, 7.5 or 10 mg

procarbazine/kg/day on gestation Day 12-15, the 21-day old pups had reduced weights of the neocortex brain region (Johnson *et al.* 1985).

5.28.4   *Human fetal exposure and developmental effects*

Procarbazine is classified as FDA Pregnancy Category D. There were 31 published cases of patients treated with procarbazine during pregnancy identified from 8 case reports, 2 case series, 2 retrospective case series, 2 retrospective cohort studies, and 3 retrospective surveys (Appendix C Table 26). Among these patients, procarbazine was used to treat Hodgkin lymphoma (n=27 cases), non-Hodgkin lymphoma (n=1 case), diffuse histiocytic lymphoma (n=1 case), and two cases did not specify cancer type. Procarbazine was administered during the 1st trimester in 19 singleton pregnancies (19 conceptuses) and in the 2nd and/or 3rd trimester only in 12 singleton pregnancies (12 conceptuses). Fetal loss occurred in seven pregnancies, all of which were exposed during the 1st trimester. One spontaneous abortion followed exposure in the 1st trimester and co-treatment with nitrogen mustard and vincristine (Zemlickis *et al.* 1992); no fetal autopsy data were provided. A hysterectomy was performed at gestation week 13 of a singleton pregnancy and fetal autopsy revealed small, malpositioned kidneys, but no malformations (Mennuti *et al.* 1975); the pregnancy was exposed during the 1st trimester and co-treated with nitrogen mustard and vincristine. Autopsy of a fetus following an induced abortion revealed toxic degeneration of the liver and kidneys, but no malformations (Peres *et al.* 2001); the pregnancy was exposed during the 1st trimester exposure and co-exposed to: nitrogen mustard, vincristine, doxorubicin, bleomycin, vinblastine and dacarbazine. Fetal autopsy data were not provided for the remaining 4 induced abortions (Blatt *et al.* 1980, Thomas and Peckham 1976, Zemlickis *et al.* 1992, Zuazu *et al.* 1991).

Of the 24 live born infants, major malformations were reported in five infants. Major malformations were observed in four infants following exposure during the 1st trimester. One infant had only four toes on each foot with webbing between the 3rd and 4th toes of the right foot as well an abnormal pinna and bowed tibia on the right leg (Garrett 1974); this infant was exposed in the 1st trimester and co-treated with nitrogen mustard and vincristine. Cleft lip and cleft palate were reported in an infant with 1st trimester to procarbazine, lomustine and vincristine and co-treatment with vinblastine from 1st through 3rd trimesters (Mulvihill *et al.* 1987). A small secundum atrial septal defect was observed post-mortem in an infant who developed respiratory distress and died at age 2 days (Thomas and Peckham 1976); this infant was exposed during the period of conception and 1st trimester and co-exposed to vinblastine and vincristine   Hydrocephalus occurred in another newborn, who died 4 hours after birth (Zemlickis *et al.* 1992); this pregnancy was exposed in the 1st trimester and co-treated with nitrogen mustard and vincristine. One infant had a major malformation and two infants had minor malformation following exposure to procarbazine in the second and/or third trimester. Bilateral syndactyly of digits II and III, a major malformation, was observed in one infant exposed during the 2nd and 3rd trimesters and co-treated with nitrogen mustard, vincristine, doxorubicin, vinblastine and bleomycin as well as radiation therapy in the 1st and 2nd trimesters (Van Calsteren *et al.* 2010). One infant had a minor malformation, pectus excavatum, following exposure in the 2nd and 3rd trimesters and co-treatment with nitrogen mustard, vincristine, doxorubicin, vinblastine and bleomycin (Van Calsteren *et al.* 2010). Health anomalies were reported for two other infants. Another infant had a hemangioma, a minor malformation, following exposure during: the period of conception and 1st trimester (through gestation day 38) (Wells *et al.* 1968).

A few pregnancy complications and infant health effects occurred following in utero exposure to procarbazine. There was one case of spontaneous preterm labor (Johnson and Filshie 1977). Of the 16 pregnancies reporting age at delivery, early preterm delivery (<34 weeks) was reported for two

pregnancies (12.5%), late preterm delivery (34-36 weeks) was reported for two pregnancies (12.5%) and 12 pregnancies were delivered at term (75%). None of the newborns were reported small for gestational age. One infant had a large cerebral hemorrhage (Garrett 1974), and two infants had anemia (Johnson and Filshie 1977, Zuazu *et al.* 1991). As mentioned above, one newborn with respiratory distress and an atrial septal defect died on postnatal day 2 (Thomas and Peckham 1976). Another infant death occurred at age 3 months due to gastroenteritis (Dilek *et al.* 2006). Follow-up evaluations were available for 13 infants at ages ranging from 3 months to 17 years. Normal growth and development were reported for all children. One child, who was developing normally at age 2 years, was diagnosed as human immunodeficiency virus (HIV) positive; her mother was HIV positive at the time of pregnancy (Okechukwu and Ross 1998).

5.28.5   *Summary of pregnancy outcomes for procarbazine*

In utero exposure to procarbazine is documented for 31 singleton pregnancies (31 conceptuses). Of the 19 pregnancies exposed during the 1st trimester, major malformations were observed in four newborns. One infant had only four toes on each foot with webbing between the 3rd and 4th toes on the right foot, an abnormal pinna and a bowed tibia on the right leg (Garrett 1974). Cleft lip and cleft palate were reported in another infant (Mulvihill *et al.* 1987). A small secundum atrial septal defect was observed postmortem in an infant who developed respiratory distress and died on day 2 (Thomas and Peckham 1976). Hydrocephalus was diagnosed in an infant who died at age 4 hours (Zemlickis *et al.* 1992). In addition, hemangioma, considered a minor malformation, was reported in an infant exposed to procarbazine in the 1st trimester (Wells *et al.* 1968). Fetal loss was reported for 7 pregnancies exposed to procarbazine in the 1st trimester, including: one spontaneous abortion, 5 induced abortions and a hysterectomy. At autopsy, normal fetuses (i.e., no malformations) were reported from the hysterectomy (Mennuti *et al.* 1975) and one induced abortion (Peres *et al.* 2001). Fetal autopsy data was not available for the remaining cases of fetal loss. The occurrence of major malformations following 1st trimester was 21.1% (4/19 conceptuses).

Of the 12 pregnancies exposed to procarbazine in the 2nd and/or 3rd trimester only, one major malformations was observed: bilateral syndactyly of digits II and III {Van Calsteren, 2010 #437}. One infant had a minor malformation: pectus excavatum The total occurrence of major malformations following exposure in the 2nd and/or 3rd trimester only was 8.3% (1 of 12 conceptuses). Pregnancy complications and infant health effects observed following exposure to procarbazine during pregnancy included: spontaneous preterm labor (n=1 pregnancy), cerebral hemorrhage (n=1 infant), anemia (n=2 infants), and respiratory distress (n=1 infant). Preterm birth was reported in 4 of 16 infants in cases reporting gestational age at delivery. None of the newborns were reported small for gestational age. Follow-up examinations available on 13 children at ages 3 months to 17 years found normal growth and development in all children.

In conclusion, the total occurrence of major malformations in procarbazine-exposed pregnancies was 16.1% (5/31 conceptuses). The occurrence of major malformations following exposure to procarbazine during the 1st trimester (4/19 conceptuses) was about 7 times that in the general population (21.1 ± 18.3% versus 3%). The occurrence of major malformations in the 2nd and/or 3rd trimester (1/12 conceptuses) was higher than the prevalence of birth defects in the general population (8.3% ± 15.6 versus 3%). This single major malformation, bilateral syndactyly, was not likely the result of exposure to procarbazine during the 2nd and/or 3rd trimester only. Thus, the revised occurrence of major malformations following exposure to procarbazine in the 2nd and/or 3rd trimester only was 0% (0/12 conceptuses).

5.29 RITUXIMAB

5.29.1 Mechanism of action, route of administration, and indications

Rituximab is a genetically engineered chimeric murine/human IgG 1 monoclonal antibody that is directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The CD20 antigen (also called human B-lymphocyte-restricted differentiation antigen, Bp35) is involved in the activation process for cell cycle initiation and differentiation, and may also act as a calcium ion channel (Genentech 2011). Rituximab binds to the CD20 antigen and depletes the CD20-expressing cells by cell death. Rituximab is administered by intravenous injection. Rituximab is indicated for treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia as well as non-cancer diseases, including adult rheumatoid arthritis, Wegner's granulomatosis and microscopic polyangiitis (Genentech 2011).

5.29.2 Evidence of placental and breast milk transport

Placental transfer of rituximab has been documented in humans, while breast milk transport of rituximab in humans is unknown. Friedrichs et al. (Friedrichs *et al.* 2006) detected rituximab in maternal and cord blood serum at delivery **[timing of last dose not provided]**. Of note, the cord blood level of rituximab (32.1 µg/mL) was three-times the level of rituximab in maternal serum (9.8 µg/mL). This infant also experienced a complete depletion of B-cells at birth; however, the B-cell population had recovered by 4 months and the infant had normal immune function. Decler et al. (Decker *et al.* 2006) reported comparable concentrations of rituximab in maternal and infant serum at birth (0.2 versus 0.3 g/L, respectively); the last dose of rituximab was administered two months prior to delivery. The infant also had nearly complete depletion of B-cells at birth, and B-cells recovered to normal levels within 12 weeks of birth (Decker *et al.* 2006). Rituximab was also detected in the serum of a third newborn born at 38 weeks gestation (four weeks after her mother's last dose of rituximab); the mother was treated with rituximab for idiopathic thrombocytopenia purpura (Chakravarty *et al.* 2011). Rituximab has been detected in the milk of lactating cynomolgus monkeys. Vaidyanathan et al. (Vaidyanathan *et al.* 2011) reported that the levels rituximab in breast milk were 0.2-0.3% of maternal serum levels on postnatal day 28, following daily administration of rituximab from gestation day 10 through postpartum day 28 in cynomolgus monkeys. Breast milk transport of rituximab in humans has not been documented. However, endogenous maternal IgG is excreted in human milk suggesting that IgG-type drugs may pass into breast milk (Friedrichs *et al.* 2006, Pentsuk and van der Laan 2009, Telemo and Hanson 1996).

5.29.3 Laboratory animal developmental toxicity

Rituximab did not induce embryolethal or teratogenic effects in cynomolgus monkeys, however administration of the drug during organogenesis caused immunosuppression in the offspring (Genentech 2011, Vaidyanathan *et al.* 2011). Pregnant cynomolgus monkeys were administered rituximab loading doses of 15, 37.5 and 75 mg/kg/day on days 20, 21 and 22 and then weekly on Days 29, 36 43, and 50 at doses of 20, 50 or 100 mg/kg/week via intravenous injection. No mortality, body weight changes in fetuses or teratogenic effects were observed in monkey fetuses at any dose, including the 100 mg/kg/week dose which was comparable to 80% of the exposure (based on AUC) of a 2 gram dose in humans. However, B-cells depletion in fetal lymph tissues was observed using immunohistochemistry. Similarly, prenatal and lactational exposure to rituximab decreased B cell levels in the offspring, but normal B-cell levels were restored within six months postpartum (Vaidyanathan *et al.* 2011). There was no substantial loss of immunologic function of the monkey offspring, following prenatal and lactational exposure to rituximab.

5.29.4 Human developmental exposure and effects

Rituximab is classified as FDA Pregnancy Category C. There were 24 published cases of patients treated with rituximab during pregnancy identified from 8 case reports, 1 registry survey and 2 retrospective cohort studies (Appendix C Table 27). Among these patients, rituximab was used to treat Hodgkin lymphoma (n=1 case), non-Hodgkin lymphoma (n=15), Burkitt lymphoma (n=6 cases), B-cell lymphoma (n=1 case), and diffuse large B-cell lymphoma (n=1 case). Rituximab was administered in the 1st trimester in 6 singleton pregnancies (6 conceptuses) and in the 2nd and/or 3rd trimester only in 18 singleton pregnancies (18 conceptuses). Fetal loss was reported in 3 singleton pregnancies. Spontaneous abortion occurred at gestation week 10 in one pregnancy exposed during the period of conception and the 1st trimester (Chakravarty *et al.* 2011); no fetal data were provided. Intrauterine fetal death of a normal fetus at 30 weeks gestation was reported following 2nd and 3rd trimester exposure and co-treatment with cyclophosphamide, vincristine and doxorubicin (Cardonick *et al.* 2010). The stillbirth of a singleton fetus occurred at gestation week 26 following pregnancy complications of oligohydramnios and intrauterine growth restriction beginning at gestation week 18 (Peterson *et al.* 2010). The pregnancy was exposed during the 2nd trimester and co-exposed to cyclophosphamide, vincristine, doxorubicin, cytarabine, etoposide, and ifosfamide and no fetal autopsy data were provided (Peterson *et al.* 2010). Of the 21 live-born infants exposed to rituximab during pregnancy, only one infant had major malformations. A ventricular septal defect and patent ductus arteriosus were reported in an infant exposed during the period of conception through the first month of pregnancy (1st trimester exposure); no data were provided on co-exposure to other chemotherapy agents (Chakravarty *et al.* 2011). The infant, born at 38 weeks of gestation, also had a patent foramen ovale, considered a minor malformation (Chakravarty *et al.* 2011).

A variety of pregnancy complications and health effects were reported in pregnancies exposed to rituximab. Pregnancy complications included preeclampsia (n=1 case) {Chakravarty, 2011 #860}, spontaneous preterm labor (n=2 cases) {Decker, 2006 #403}, including one case yielding a stillborn infant following decreased amniotic fluid and intrauterine fetal growth restriction (Peterson *et al.* 2010). Of the 17 cases reporting delivery dates, early preterm delivery (<34 weeks) was reported for 5 pregnancies (29.4%), late preterm delivery (34-36 weeks) was reported for 5 pregnancies (29.4%), and 7 pregnancies were delivered at term (41.2%). One newborn was identified as small for gestational age (Magloire *et al.* 2006). A deficiency or absence of B-cells was noted for two newborns (Decker *et al.* 2006, Friedrichs *et al.* 2006). B-cell levels recovered to their normal range by age 12 and 18 weeks, respectively (Decker *et al.* 2006, Friedrichs *et al.* 2006). Transient myelosuppression was reported in two additional infants: one infant had granulocytopenia and lymphopenia (Kimby *et al.* 2004) and another infant leucopenia and anemia (Chakravarty *et al.* 2011). Other health effects included: transient tachypnea and jaundice in one infant (Cardonick *et al.* 2010) and respiratory distress and omphalitis (inflammation of the navel) in another infant (Cordeiro *et al.* 2009). Follow-up evaluations were reported for 7 infants. Normal development was observed in all 7 children ranging from 46 days to 5.3 years. One follow-up evaluation reported a child with speech delay that was improving with intervention (Cardonick *et al.* 2010). Normal immunological function was reported for two infants who experienced myelosuppression as neonates (Decker *et al.* 2006, Kimby *et al.* 2004).

5.29.5 Summary of pregnancy outcomes for rituximab

In utero exposure to rituximab was documented for 24 singleton pregnancies. Of the 6 pregnancies exposed to rituximab in the 1st trimester, one infant had major malformations: ventricular septal defect and patent ductus arteriosus accompanied by patent foramen ovale (Chakravarty *et al.* 2011). One pregnancy ended in spontaneous abortion following 1st trimester exposure to rituximab (Chakravarty *et*

al. 2011); no fetus autopsy data were provided. A total occurrence of major malformations following exposure to rituximab in the 1st trimester was 16.7% (1/6). Of the 18 infants exposed to rituximab only in the 2nd and/or 3rd trimester only, no major or minor malformations were reported. Intrauterine fetal demise occurred in two pregnancies exposed in the 2nd trimester (no fetal autopsy data provided) (Peterson *et al.* 2010) or 2nd and 3rd trimesters (normal fetus at autopsy) (Cardonick *et al.* 2010). A total occurrence of major malformations following exposure to rituximab in the 2nd and/or 3rd trimester only was 0% (0/18 conceptuses).

Pregnancy complications and infant health effects reported following in utero exposure to rituximab included: preeclampsia (n=1 pregnancy), spontaneous preterm labor (n=2 pregnancies), oligohydramnios (n=1 pregnancy), and intrauterine growth restriction (n=1 pregnancy). Preterm delivery was reported for 10 infants of 17 infants with data on gestational age at birth. One infant was small for gestational age {Magloire, 2006 #268}. Infant health effects included: transient myelosuppression (n=4 infants), respiratory difficulties (n=2 infants), jaundice (n=1 infant) and omphalitis (n=1 infant). Normal growth and development were reported for the 7 infants with follow-up evaluations at ages ranging from 46 days to 5.3 years.

In conclusion, the total occurrence of major malformations in rituximab-exposed pregnancies was 4.2% (1/24 conceptuses). The occurrence of major malformations following 1st trimester exposure to rituximab (1/6 conceptuses) was greater than the prevalence of birth defects in the general population (16.7 ± 29.8% versus 3%). However, the small number of reported cases exposed in the 1st trimester limits the accuracy of this estimate. There were no major malformations reported in pregnancies exposed in the 2nd and/or 3rd trimester only (0/18 conceptuses), which is lower than the prevalence of birth defects in the general population.

5.30 TAMOXIFEN

5.30.1 Mechanism of action, route of administration, and indications

Tamoxifen is a non-steroidal anti-estrogen used in the treatment of certain types of breast cancer. Some breast cancers are classified as estrogen receptor-positive (also known as hormone sensitive), and these breast cancer cells need estrogen to grow. In estrogen-receptor positive breast cancer, tamoxifen works as an anti-estrogen by binding to the estrogen receptor and blocking the stimulatory effects of estrogen on the cancerous cells. Although tamoxifen acts *against* the effects of estrogen in breast tissue, it acts *like* an estrogen in other tissues (i.e., the uterus). Thus, tamoxifen is called a Selective Estrogen Receptor Modulator or SERM (http://www.cancer.gov/cancertopics/factsheet/Therapy/tamoxifen). Tamoxifen is administered orally and is indicated for the treatment of estrogen receptor-positive breast cancer (Savient 2006).

5.30.2 Evidence of placental and breast milk transport

Placental and breast milk transport of tamoxifen in humans is unknown. No published papers were found that directly addressed the issue of placental transport of tamoxifen, in either laboratory animals or humans. It is not known if tamoxifen is excreted in human milk; however, tamoxifen has been reported to inhibit lactation. Two placebo-controlled studies in over 150 women have shown that tamoxifen significantly inhibits early postpartum milk production. In both studies tamoxifen was administered within 24 hours of delivery for between 5 and 18 days (Masala *et al.* 1978, Shaaban 1975). Tamoxifen was very effective in preventing milk secretion and breast engorgement when administered within two hours after delivery (Shaaban 1975).

5.30.3 Laboratory animal developmental toxicity

Tamoxifen exposure during pregnancy induced teratogenicity in rats, but not rabbits or marmosets, when administered during organogenesis (Savient 2006). Pregnant CD (SD) IGS rats treated orally with 0.12, 0.6 or 3 µg/kg/day on gestational day 6 to postnatal day 21, resulted in a delay in timing of puberty in male offspring in all dose groups, and cleft phallus was observed in the female offspring of the 0.6 and 3 µg/kg/day dose groups when evaluated at 10 weeks of age (Yamasaki *et al.* 2005). Pregnant Sprague-Dawley rats treated subcutaneously with 20 µg of tamoxifen on days 15 and 20 of gestation caused abnormalities in the development and function of the reproductive tract, including a delayed onset of puberty and changes in uterine wet weights (Halakivi-Clarke *et al.* 2000). Tamoxifen induced wavy ribs, a reversible effect, but did not cause teratogenic effects in rats when administered on gestation days 7 to 19 in doses up to 2 mg/kg (the maximum dose which did not terminate pregnancy) (Furr and Jordan 1984). Tamoxifen also did not induce teratogenic effects following in utero exposure to 2 mg/kg/day (Furr 1979). No fetal abnormalities were noted among the offspring of pregnant marmosets treated during the period of organogenesis with tamoxifen at 10 mg /kg/day (about 2-fold the daily maximum recommended human dose on a mg/m^2 basis) during organogenesis (Furr and Jordan 1984, Savient 2006) or in the last half of pregnancy (Savient 2006). Although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of malformations (Savient 2006).

Finally, tamoxifen appears to disrupt the process of implantation. Tamoxifen administered orally twice a day for 10 days during proestrus, estrus, or early diestrus at 1 mg/kg body weight was effective in preventing or terminating pregnancy in dogs (Bowen *et al.* 1988). Failure of implantation was found after treatment of female guinea pigs within a few days of conception with 4 times the human dose of tamoxifen (Wisel *et al.* 1994) or after treatment of female bonnet monkeys immediately before and

after conception with tamoxifen at a dose of 6 mg/day (Moudgal *et al.* 1996). Tamoxifen had a dose-dependent effect on pregnancy rate, litter size, embryo resorption and embryonic weight in Wistar rats treated with 0.06 to 0.25 mg/kg on gestation day 2 (prior to implantation) (Kaplan-Kraicer *et al.* 1996). No live embryos were found in the uteri of Day 14 rat dams treated with 0.25 mg/kg tamoxifen by oral gavage on gestation day 2 (Kaplan-Kraicer *et al.* 1996).

5.30.4   Human gestational exposure and effects

Tamoxifen is classified as FDA Pregnancy Category D. There were 13 published cases of cancer patients treated with tamoxifen during pregnancy identified from 12 case reports and 1 retrospective cohort study (Appendix C Table 28). Among these patients, tamoxifen was used to treat breast cancer (n=11 cases) and melanoma (n=2 cases). A total of 13 pregnancies (14 conceptuses) were born following in utero exposure to tamoxifen, including one set twins (Beale *et al.* 2009). Tamoxifen was administered during the 1st trimester of pregnancy in 10 cases (11 conceptuses) and in the 2nd and/or 3rd trimester only in 3 cases (4 conceptuses).

Of the 14 newborns with gestational exposure to tamoxifen, major malformations occurred in three newborns. One infant had a combination of malformations consistent with Goldenhar syndrome: right-sided microtis and hemifacial microsomia (Cullins *et al.* 1994); this infant, who also had preauricular skin tags, was exposed during the period of conception and the 1st and 2nd trimesters. Another infant exposed during the period of conception and the 1st trimester had multiple skeletal malformations including: cleft palate and glossoptosis (diagnostic of Pierre Robin syndrome), hypoplastic mandibles and thin mandibular condyles as well as clubfoot, and acetabular and sacral dysplasia (Berger and Clericuzio 2008); the infant had a family history of small mandibles, but no clefting. Ambiguous genitalia were reported in one female newborn exposed to tamoxifen during the period of conception and the 1st and 2nd trimesters (Tewari *et al.* 1997). Specifically, this infant had only one perineal opening representing both the urethra and the vagina, fused labioscrotal folds, and an enlarged phallic-like clitoris (Tewari *et al.* 1997). Preauricular skin tags, a minor malformation, occurred in an otherwise normal infant following exposure to tamoxifen during the period of conception throughout pregnancy (Isaacs *et al.* 2001). Three infants had health anomalies, and two of these infants died within the first 3 months of life. Microphthalmos and severe hypermetropia were diagnosed in an infant at age 1 year (Li *et al.* 2007); this pregnancy was exposed in the 1st through 3rd trimesters. Atelectasis (partial or complete absence of lung expansion at birth) was diagnosed in an infant born at 37 weeks gestation with pulmonary hypoplasia, and the infant died 40 minutes following extubation on day 1 (Warraich and Smith 2009). The pregnancy, which was complicated by anhydramnios at 28 weeks, was exposed during the 1st and 2nd trimesters and co-exposed to trastuzumab from 1st trimester through 3rd trimester (Warraich and Smith 2009). In a twin pregnancy complicated by oligohydramnios, the male twin had enlarged kidneys and a dilated ureter at birth as well as respiratory distress; however at age 12 weeks, he developed chronic renal failure and died of respiratory arrest at age 13 weeks (Beale *et al.* 2009). The second twin was normal other than requiring oxygen at birth and the pregnancy had been exposed during the period of conception and the 1st and 2nd trimester and co-exposed to trastuzumab (Beale *et al.* 2009).

There were several pregnancy complications and infant health issues. Gestational diabetes, preeclampsia and spontaneous preterm labor affected one pregnancy (Berger and Clericuzio 2008). Spontaneous pre-term labor, chorioamniotis and abnormal lie of the fetus complicated a second pregnancy (Cullins *et al.* 1994), and "signs of premature delivery" **[presumed spontaneous preterm labor]** was reported for another pregnancy (Andreadis *et al.* 2004). Oligohydramnios or anhydramnios complicated two pregnancies that were also co-exposed to trastuzumab (Beale *et al.* 2009, Warraich

and Smith 2009). Of the 11 pregnancies with age at delivery data, early preterm birth (<34 weeks) occurred for 6 pregnancies (46.2%), late preterm pregnancies (34-36 weeks) occurred for two pregnancies (15.4%), and three pregnancies were delivered at term (23.1%). None of the infants were reported to be small for gestational age. Respiratory difficulties were reported for four infants (Beale *et al.* 2009, Isaacs *et al.* 2001, Warraich and Smith 2009). The infant with the glossoptosis required a tracheotomy due to airway obstruction (Berger and Clericuzio 2008). In addition, one infant was treated for enterocolitis (Isaacs *et al.* 2001).

Follow-up evaluations were reported for 8 infants. Normal growth and development was reported for all children at ages ranging from 6 months to 5.5 years of age. The female infant with ambiguous genitalia underwent surgery to reconstruct the low-lying vagina at 6 months of age without complications (Tewari *et al.* 1997). In addition to these 12 case reports, the manufacturer reported (via personal communication on September 1993) on the pregnancy outcomes of 50 pregnancies associated with tamoxifen (Cullins *et al.* 1994). They are not included in the current evaluation because the study was not published, individual data were not available on the patients' disease type or timing of exposure to tamoxifen, and it was not known whether any of the data were published in other case reports.

5.30.5 *Summary of pregnancy outcomes for tamoxifen*

In utero exposure to tamoxifen was documented for 13 pregnancies, including one set of twins (14 conceptuses). Of the 10 pregnancies (11 conceptuses) exposed during the 1st trimester, major malformations were observed in three infants. One infant had a combination of malformations consistent with Goldenhar syndrome: right-sided microtis and hemifacial microsomia as well as preauricular skin tags (Cullins *et al.* 1994). Another infant had multiple skeletal malformations, including: cleft palate and glossoptosis (diagnostic of Pierre Robin syndrome), hypoplastic mandibles and thin mandibular condyles as well as clubfoot, and acetabular and sacral dysplasia (Berger and Clericuzio 2008); the infant had a family history of small mandibles, but no clefting. The third infant had only one perineal opening that was both urethra and vagina, fused labioscrotal folds, and an enlarged phallic-like clitoris (Tewari *et al.* 1997). A total occurrence of major malformations following exposure in the 1st trimester was 27.3% (3/11 conceptuses). Minor malformations were observed in one infant exposed during the 1st trimester: preauricular skin tags (Isaacs *et al.* 2001). Health anomalies were observed in three infants with 1st trimester exposure, and two of these infants died by age 3 months. One infant had microphthalamia was diagnosed at age 1 year (Li *et al.* 2007). One infant died on day 1 due to respiratory distress caused by atelectasis and pulmonary hypoplasia (Warraich and Smith 2009) and a second infant died at age 13 weeks of respiratory distress following chronic renal failure at age 12 weeks (Beale *et al.* 2009); both of these pregnancies were co-exposed to trastuzumab and experienced anhydramnios or oligohydramnois, respectively. No malformations, major or minor, were reported in the two infants exposed to tamoxifen in the 2nd and/or 3rd trimester only. The total occurrence of major malformations in infants with exposure to tamoxifen in the 2nd and/or 3rd trimester was 0% (0/3 conceptuses), although the number of infant in this exposure group was too low to provide an accurate estimate.

There were a variety of pregnancy complications and infant health effects that occurred in pregnancies exposed to tamoxifen. Oligohydramnios (Beale *et al.* 2009) and anhydramnios (Warraich and Smith 2009) occurred in one infant each. Preterm deliveries were reported for 8 of the 12 infants with age at delivery data and none of the infants were small for gestational age. Respiratory difficulties were reported for a total of 4 infants and one infant was treated for enterocolitis. An infant with the glossoptosis required a tracheotomy due to airway obstruction (Berger and Clericuzio 2008). Normal growth and development was reported for all 8 infants with follow-up evaluations at ages ranging from

6 months to 5.5 years of age. The female infant with ambiguous genitalia underwent surgery to reconstruct the low-lying vagina at 6 months of age without complications (Tewari *et al.* 1997).

In conclusion, the total occurrence of major malformations in tamoxifen-exposed pregnancies was 21.4% (3/14 conceptuses). The occurrence of major malformations following exposure during the 1st trimester (3/11 conceptuses) was much higher than the prevalence of birth defects in the general population (27.3 ± 26.3% versus 3%). The occurrence of major malformations in the 2nd and/or 3rd trimester only (0/3 conceptuses) was no higher than the prevalence in the general population; however, there were too few reported cases that were exposed in the 2nd and/or 3rd trimester only to accurately estimate this percentage.

5.31 TRASTUZUMAB

5.31.1 Mechanism of action, route of administration, and indications

Trastuzumab is a recombinant humanized monoclonal antibody (an IgG1 kappa), which selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2; also called Neu and erbB2) protein and blocks activation of its tyrosine kinase. HER2 promotes cell proliferation and inhibits cell death in a tyrosine-kinase dependent manner. There are several possible mechanisms by which trastuzumab blocks tyrosine kinase signaling: inhibition of HER2 dimerization, acceleration of endocytotic degradation of HER2, inhibition of release of the extracellular domain, and immune system activation (reviewed in (Hudis 2007)). Trastuzumab is administered as an intravenous (IV) infusion. Trastuzumab is indicated for HER2 positive breast cancers, which account for 20 to 30% of invasive breast cancers.

5.31.2 Evidence of placental and breast milk transport

The transfer of trastuzumab via the placenta or in breast milk has not been documented in humans. However, transplacental transport of IgG antibodies has been documented for humans, non-human primates, as well as rabbits and guinea pigs (reviewed in (Pentsuk and van der Laan 2009)). In humans, the levels of maternal IgG are first detected in the second trimester of pregnancy and continue to increase to term (Simister 2003). Placental transfer of trastuzumab has been observed in cynomolgus monkeys at doses 25 times the weekly human maintenance dose of 2 mg/kg (Genentech 2010). Furthermore, placental transfer of another anti-cancer monoclonal IgG antibody, rituximab, has been reported in humans (Decker *et al.* 2006, Friedrichs *et al.* 2006). Lactational transfer of trastuzumab was observed in cynomolgus monkeys administered trastuzumab at a dose 12.5 times higher than the human maintenance dose by detection of trastuzumab in the breast milk and the serum of the neonatal monkey (Genentech 2010).   While lactational transfer of trastuzumab in humans is not known, endogenous maternal IgG antibodies are secreted in breast milk and absorbed by the fetal gut in the first 1-2 days of life (Pentsuk and van der Laan 2009, Telemo and Hanson 1996) suggesting that lactational transfer of trastuzumab may also occur.

5.31.3 Laboratory animal developmental toxicity

No embryolethal or fetotoxic effects have been reported in laboratory animal studies of trastuzumab. No fetal toxicity was observed in a reproductive study of cynomolgus monkeys administered trastuzumab at a dose 25 times higher than the recommended weekly human dose of 2 mg/kg bw (Genentech 2010). In contrast, an increased incidence of maternal cardiotoxicity has been observed when trastuzumab is co-administered with an anthracycline (Genentech 2010). In mice, erbB2 protein (mouse equivalent of the human HER2) has been detected in the fetal neural tissues and cardiac myocytes (Lee *et al.* 1995). Mice engineered without the erbB2 gene died during early gestation likely due to the absence of trabeculae in the myocardium, which is responsible for blood flow during early heart development (Lee *et al.* 1995). HER2 has also been detected in adult and fetal kidneys in humans (Goodyer *et al.* 1993, Press *et al.* 1990) and the epidermal growth factor is highly expressed in the rat kidney during late gestation (Cybulsky *et al.* 1994). Vascular epidermal growth factor (VEGF), another epidermal growth factor, is expressed in the placenta in humans and laboratory animals. In animal studies, VEGF affects permeability of the fetal membranes and plays a role in regulating amniotic fluid volume in animal studies (Cheung 2004). Trastuzumab is also known to inhibit VEGF expression in tumor cells injected into nude mice (Petit *et al.* 1997), and it has been hypothesized that trastuzumab may be reducing amniotic fluid volume in humans by inhibiting VEGF (Pant *et al.* 2008). An alternate hypothesis is that trastuzumab may be altering the function of aquaporins, a family of channel-forming

proteins responsible for fluid regulation in various tissues, including fetal membranes (Liu *et al.* 2008, Sekar and Stone 2007).

5.31.4 Human gestational exposure and effects

Trastuzumab is assigned the FDA Pregnancy category D. There were 19 published cases of breast cancer patients treated with trastuzumab during pregnancy identified from 17 case reports and 1 case series (Appendix C Table 29). Trastuzumab was administered during the following trimester period: 1st only (n=4 cases), 2nd only (n=2 cases), 3rd only (n=1 case), 1st and 2nd trimesters (n=6 cases), 2nd and 3rd trimester (n=3 cases) and during the entire pregnancy (n=3 cases). Thus, 13 pregnancies (14 conceptuses due to one set of twins (Beale *et al.* 2009)) were exposed to trastuzumab during the 1st trimester and 6 pregnancies were exposed in the 2nd and/or 3rd trimester only. There were a total of 20 conceptuses yielding 19 live-born infants born, including one set of twins, and one induced abortion in the first trimester for an ectopic pregnancy {Berveiller, 2008 #397}. No malformations, neither major nor minor, were reported in the peer-reviewed literature for any of the conceptuses exposed to trastuzumab during pregnancy.   However, the manufacturer reported that in post-marketing reports, "… use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death" (Genentech 2010).

With the exception of two pregnancies (Goodyer *et al.* 2009, Roberts and Auld 2010), anhydramnios or oligohydramnios (absent or deficient levels of amniotic fluid, respectively) was reported for all pregnancies in which exposure to trastuzumab occurred during the 2nd and/or 3rd trimesters. In particular, anhydramnios was documented in 5 pregnancies {El-Safadi, 2012 #1225;Gottschalk, 2011 #1328}{Sekar, 2007 #389;Warraich, 2009 #444;Watson, 2005 #446} and oligohydramnios was documented in eight pregnancies, including one twin pregnancy (Bader *et al.* 2007, Beale *et al.* 2009, Fanale *et al.* 2005, Mandrawa *et al.* 2011, Pant *et al.* 2008, Shrim *et al.* 2007, Weber-Schoendorfer and Schaefer 2008, Witzel *et al.* 2008). Failure of kidney function occurred in three infants with oligohydramnios. One newborn, who suffered from fetal renal failure prenatally, had transient renal failure and was discharged from the hospital at 6 weeks in healthy condition (Bader *et al.* 2007); this infant was co-exposed to paclitaxel. One of the twin infants had large kidneys and chronic renal failure at birth, and died at 13 weeks from renal failure and respiratory distress (Beale *et al.* 2009). This twin pregnancy was also exposed to tamoxifen, and the other twin had a normal renal ultrasound. The third infant had dysmorphic/hypoplastic left kidney and kidney congestion, and died at 4 months due to decreased kidney function (Weber-Schoendorfer and Schaefer 2008). There were two additional deaths among the pregnancies experiencing an- or oligohydramnios. One newborn with oligohydramnios also had a very strong capillary leak, and developed respiratory distress, infections, and necrotizing enterocolitis, and ultimately died at 21 weeks due to multiple organ failure (Witzel *et al.* 2008). Pulmonary hypoplasia and atelectasis (collapse of lung tissue) was observed in another newborn that died shortly after birth (Warraich and Smith 2009). The pregnancy suffered from anhydramnios and was co-exposed to tamoxifen; however, normal kidneys were observed during fetal ultrasound. Pulmonary hypoplasia is known to be secondary to many health conditions in infants, including oligohydramnios (Nakamura *et al.* 1992). Thus, exposure to trastuzumab appears to be associated with low levels of amniotic fluid when treatment occurs during the 2nd and/or 3rd trimester.

There were a few other pregnancy complications and health effects observed with in utero exposure to trastuzumab. Pregnancy complications included: premature rupture of amniotic membranes (n=1 pregnancy), premature detachment of the placenta (n=1 pregnancy), maternal vaginal bleeding at 26 gestation weeks (n=1 pregnancy), intrauterine growth restriction (n=1 fetus) (Sekar and Stone 2007),

and cessation of abdominal growth (n=1 fetus) (Bader *et al.* 2007). Of the 18 pregnancies with age at delivery, early preterm delivery (<34 weeks) was reported for 8 pregnancies (44.4%), late preterm delivery (34-36 weeks) was reported for 2 pregnancies (11.1%), and 8 pregnancies were delivered at term (44.4%). One newborn was reported to be small for gestational age {Gottschalk, 2011 #1328}. Respiratory difficulties, which ranged from transient tachypnea to respiratory distress, were reported for 10 infants (Bader *et al.* 2007, Beale *et al.* 2009, Goodyer *et al.* 2009, Mandrawa *et al.* 2011, Pant *et al.* 2008, Roberts and Auld 2010, Shrim *et al.* 2007, Witzel *et al.* 2008). Other health effects included: bacterial sepsis and hypotension (Bader *et al.* 2007), elevated creatinine (Beale *et al.* 2009), and transient conductive hearing loss, gastroenteritis, mild hypotonia, hyperreflexia, and tightening of the Achilles tendon (Goodyer *et al.* 2009). Follow-up evaluations were reported for 11 infants at ages ranging from 2 months to 5 years; age at follow-up evaluation not specified for one child {El-Safadi, 2012 #1225}. All infants were healthy and without malformations, including one infant with a persistent minimal tightening of the left Achilles tendon (Goodyer *et al.* 2009).

5.31.5   *Summary of pregnancy outcomes for trastuzumab*

In utero exposure to trastuzumab is documented for 19 pregnancies (20 conceptuses). No malformations (major or minor) were observed in the 13 infants exposed to trastuzumab during the 1st trimester, including one set of twins. In addition, one ectopic pregnancy was terminated by induced abortion on gestation week 6 without histological examination of the embryo (Berveiller *et al.* 2008). Similarly, no malformations (major or minor) occurred in the 6 live-born infants exposed in the 2nd and/or 3rd trimester only. Thus, the total occurrence of major malformations following exposure at any time during pregnancy was 0% (0/20 conceptuses). In contrast, anhydramnios or oligohydramnios occurred in 13 of 15 pregnancies exposed to trastuzumab during the 2nd and/or 3rd trimester. Renal failure or low renal function was reported in three infant who experienced deficient amniotic fluid in the womb (Bader *et al.* 2007, Beale *et al.* 2009, Weber-Schoendorfer and Schaefer 2008). There were 4 infant deaths, all of whom had experienced oligohydramnios during pregnancy. These infants died following: severe pulmonary hypoplasia and atelectasis (collapse of lung tissue) (Warraich and Smith 2009), chronic renal failure and respiratory arrest (Beale *et al.* 2009), multiple organ failure (Witzel *et al.* 2008), and infections as well as decreased kidney function (Weber-Schoendorfer and Schaefer 2008).

There were a few other pregnancy complications and health effects observed with in utero exposure to trastuzumab. Intrauterine growth restriction or a cessation in fetal abdominal growth occurred in 2 pregnancies (Sekar and Stone 2007)(Bader *et al.* 2007). Preterm delivery was reported for 10 of the 18 pregnancies with age at delivery. One newborn was reported to be small for gestational age {Gottschalk, 2011 #1328}. One common infant health outcomes was respiratory difficulties (n=1 infants). Follow-up evaluations reported normal growth and development for 11 infants at ages ranging from 2 months to 5 years of age; age at follow-up was not specified for one child.

In conclusion, the total occurrence of major malformations in trastuzumab-exposed pregnancies from the peer-reviewed literature was 0.0% (0/20 conceptuses). The occurrence of major malformations following exposure to trastuzumab at any time during pregnancy (0/14 conceptuses in 1st trimester; 0/4 conceptuses in 2nd and/or 3rd trimester only) appears to be no higher than the prevalence of birth defects in the general population (0% versus 3%). However, exposure to trastuzumab appears to be associated with absent or deficient amniotic fluid and, possibly, an effect on kidney development, when exposure occurs during the 2nd and/or 3rd trimester. In addition, post-marketing reports indicate that administration of Herceptin during pregnancy can result "…in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death" (Genentech 2010).

5.32 VINBLASTINE

5.32.1 Mechanism of action, route of administration, and indications

Vinblastine is one of the vinca alkaloids, a group of natural or semisynthetic substances extracted from the periwinkle plant. These substances bind to tubulin and inhibit polymerization thereby disrupting microtubule formation during mitosis. This leads to the death of cells arrested in M-phase. Vinblastine is administered via intravenous injection (Ben Venue Laboratories 2001). Vinblastine is indicated for the treatment of Hodgkin lymphoma and non-Hodgkin lymphoma. It is also used in the treatment of Kaposi sarcoma, choriocarcinoma resistant to other chemotherapeutic agents, and advanced testicular cancer as well as the non-cancerous malignancy of Letterer-Siwe disease (histiocytosis X) (Ben Venue Laboratories 2001).

5.32.2 Evidence of placental and breast milk transport

Placental transfer and breast milk transport of vinblastine in humans is not known. However, vinca-alkaloids are highly protein-bound (>99%), which may limit their ability to cross the blood-placental barrier (Wiebe and Sipila 1994). Specifically, this agent is a substrate for P-glycoprotein, an efflux transporter for xenobiotics. P-glycoprotein is highly expressed on the maternal compartment of the placenta suggesting a role in protecting the fetus against the potential toxic effects of these agents (Mir *et al.* 2008). Placental transfer of vinblastine has been demonstrated in mice (Van Calsteren *et al.* 2010) and baboons (Van Calsteren *et al.* 2010). In C56BL/J mice, fetal plasma levels of vinblastine were 13.8± 5.8%) of maternal plasma concentrations at ninety minutes after intravenous injection of 6 mg vinblastine/kg to mouse dams on gestation day 18.5 (plasma concentrations: 8.1 ng/mL, fetal versus 58.8 ng/mL, maternal) (Van Calsteren *et al.* 2010). In the baboon model, the transplacental transfer of vinblastine was 18.5 ± 15.5% at a median age of 139 gestation days (group range: 93 to 169 gestation days) (Van Calsteren *et al.* 2010). Vinblastine was not detected in amniotic fluid or in cerebral spinal fluid of the maternal or fetal baboon (Van Calsteren *et al.* 2010). In vitro, cultures of human placental choriocarcinoma epithelial cells (BeWo cells) demonstrated the uptake of vinblastine (Ushigome *et al.* 2000). There are no published accounts of breast milk transfer of vinblastine in humans or laboratory animals (Ben Venue Laboratories 2001).

5.32.3 Laboratory animal developmental toxicity

Vinblastine is embryotoxic and teratogenic in hamsters, mice, rats and rabbits. The administration of vinblastine (0.25 mg/kg) via intravenous injection to pregnant golden hamsters on gestation day 8 resulted in fetal malformations, including microphthalmia, anophthalmia, spina bifida, and skeletal defects (rib fusions and vertebral arch deformities) (Ferm 1963). Joneja et al. (Joneja and Ungthavorn 1969) reported that vinblastine induced fetal mortality, significant fetal growth retardation and gross morphological defects in three strains of mouse fetuses (DBA/2L, ICR/Ha, and CH3/HeL) following a single intraperitoneal injection (0.25, 0.30 or 0.35 mg/kg, respectively) on gestation day 9 to the mouse dam. The malformations included: bilateral or unilateral anophthalmia, gastroschisis, accessory liver lobe, umbilical hernia and twisted hindlimbs (Joneja and Ungthavorn 1969). Ohzu and Shoji (Ohzu and Shoji 1965) observed harelip and hindfoot polydactyly in gestation day 18 mouse fetuses as well as an increase in frequency of late fetal death following administration of 2.5 mg vinblastine/kg via subcutaneous injection to MT strain mouse dams on days 11-14 of gestation. Intraperitoneal injection of vinblastine (0.25 mg/kg/day) on gestation days 7-12 to pregnant Wistar rats increased congenital malformations by 9% and increased the fetal mortality rate to 40.5% compared to the effect of the 0.12 mg/kg/day dose **[no control data were provided]** (Cohlan and Kitay 1965). Sixty percent of the malformed fetuses displayed a common group of anomalies, including: exencephaly, iniencephaly,

rachischisis, gastroschisis, and bilateral clubbed feet posteriorly retroflexed. There was also a six-fold increase in mitotic figure count in vinblastine treated fetuses compared to controls, which the authors interpreted as the role of mitosis inhibition by vinblastine on consequential embryopathy (Cohlan and Kitay 1965). Vinblastine induced fetal death and face-brain malformations following intramuscular injection of a 0.25 mg dose to pregnant rats on gestation day 8 (Demyer 1964). The malformations observed in rats included anophthalmia, microphthalmia, micrognathia, cephalic or spinal dysrhaphism and eventration (Demyer 1964). In New Zealand White rabbits, vinblastine lowered the number of normal fetuses at term (Morris *et al.* 1967).

5.32.4 *Human gestational exposure and effects*

Vinblastine is classified as FDA Pregnancy category D.   There were 71 published cases treated with vinblastine during pregnancy identified from 15 case reports, 6 case series, 1 retrospective case series, 4 retrospective survey studies, 1 retrospective cohort study, and 1 registry survey (Appendix C Table 30). Among these patients, vinblastine was used to treat Hodgkin lymphoma (n=66 cases), ovarian cancer (n=3 cases), and cancer type was not specified in two cases (Van Calsteren *et al.* 2010). A total of 72 pregnancies (73 conceptuses) were exposed to vinblastine with one patient having two pregnancies (Dilek *et al.* 2006) and another patient having a set of twins (Cardonick *et al.* 2010). Vinblastine was administered during the 1st trimester in 16 pregnancies (16 conceptuses) and in the 2nd and/or 3rd trimester only in 54 pregnancies (55 conceptuses); the timing of exposure was not specified for 2 pregnancies (2 conceptuses). Fetal loss occurred in 5 pregnancies. A spontaneous abortion occurred at gestation week 6 following 1st trimester exposure (Mulvihill *et al.* 1987); no fetal autopsy data were reported. Fetal autopsy following an induced abortion revealed a normal fetus with toxic degeneration in the liver and kidneys (Peres *et al.* 2001); the pregnancy was exposed in the 1st trimester and co-exposed to nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, and dacarbazine. One intrauterine fetal death occurred in the 8th month of gestation following 2nd and 3rd trimester exposure and co-treatment with doxorubicin, bleomycin and dacarbazine (Dilek *et al.* 2006); no fetal autopsy data were reported. Finally, there were two additional induced abortions without fetal autopsy data following 1st trimester exposure (Thomas and Peckham 1976) and 2nd trimester exposure (d'Incalci *et al.* 1983).

Of the 68 live born infants with in utero exposure to vinblastine, major malformations occurred in 7 infants. Partial agenesis of metacarpal and hypoplasia of two phalanges on the left hand occurred in a newborn that was exposed in the 1st trimester and co-treated with doxorubicin, bleomycin and dacarbazine (Dilek *et al.* 2006). Another infant had only 4 toes per foot with webbing on right foot (Garrett 1974); this infant was exposed during the period of conception and the 1st trimester and co-exposed to procarbazine and nitrogen mustard. One infant suffered from cleft lip and cleft palate following exposure in the 1st, 2nd and 3rd trimesters and co-exposure to lomustine, vincristine, and procarbazine (Mulvihill *et al.* 1987). Hydrocephalus occurred in another infant exposed during 1st trimester with no co-treatments (Mulvihill *et al.* 1987). A small secundum atrial septal defect was observed at the autopsy of a newborn that developed respiratory distress and died at age 2 days (Thomas and Peckham 1976); this infant was exposed during the 1st trimester and co-exposed to vincristine and procarbazine.   One infant had syndactyly of the 4th and 5th fingers which required surgery (Cardonick *et al.* 2010); this infant was exposed during the 2nd and 3rd trimesters and co-exposed to doxorubicin, bleomycin and dacarbazine. Bilateral syndactyly of the 2nd and 3rd digits was reported in an infant with 2nd and 3rd trimester exposure and co-treatment with nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin and dacarbazine (Van Calsteren *et al.* 2010); this infant was also exposed to radiation therapy in the 2nd trimester. Minor malformations were reported in 2 newborns. Plagiocephaly was diagnosed in a newborn exposed in utero during the 2nd and 3rd trimesters and co-

treated with doxorubicin, bleomycin and dacarbazine (Cardonick *et al.* 2010). Pectus excavatum occurred in a newborn with in utero exposure during the 2nd and 3rd trimesters and co-treatment with nitrogen mustard, vincristine, procarbazine, doxorubicin, and bleomycin (Van Calsteren *et al.* 2010).

A variety of pregnancy complications and infant health effects occurred in pregnancies exposed to vinblastine. Pregnancy complications included one case each of preeclampsia, spontaneous preterm labor, and septicemia, which was treated and resolved. One patient experienced maternal hypertension, a reduction in amniotic fluid and intrauterine growth restriction (Motegi *et al.* 2007). One additional fetus was identified with intrauterine growth restriction (Fadilah *et al.* 2006). Of the 34 pregnancies reporting age at delivery, early preterm birth (<34 weeks) was reported for 6 pregnancies (17.6%), late preterm birth (34-36 weeks) was reported 10 pregnancies (29.4%), and term birth occurred for 18 pregnancies (52.9%). Small for gestational age was reported for for one newborn (Dilek *et al.* 2006). Two infants suffered from respiratory difficulties (Malone *et al.* 1986) and, as mentioned above, one of the infants died on postnatal day one (Thomas and Peckham 1976). Two infants had anemia (Johnson and Filshie 1977, Zuazu *et al.* 1991). Cerebral hemorrhage occurred in one infant (Garrett 1974) and hypoglycemia occurred in three infants (Cardonick *et al.* 2010). Follow-up evaluations were reported for 40 infants at ages ranging from 2 months to 14 years of age; age at follow-up was not specified for 4 children. All children demonstrated normal growth and development. One child each had: chronic broncolitis, recurrent otis media, and asthma (Cardonick *et al.* 2010). One healthy child tested positive for human immunodeficiency virus (HIV) at age 2; her mother was HIV positive at the time of pregnancy (Okechukwu and Ross 1998).

5.32.5 *Summary of pregnancy outcomes for vinblastine*

In utero exposure to vinblastine was documented for 72 pregnancies (73 conceptuses). Of the 16 pregnancies exposed in the 1st trimester, five newborns had major malformations. Three infants had skeletal malformations: a floating thumb malformation involving the partial agenesis of a metacarpal bone and hypoplasia of two phalanges (Dilek *et al.* 2006); bilateral absence of one toe per foot, webbing between the 3rd and 4th toes, an abnormal right pinna and a bowed tibia (Garrett 1974); and cleft lip and cleft palate (Mulvihill *et al.* 1987). A small secundum atrial defect was reported at the autopsy of a fourth infant, who developed respiratory distress on day 2 and died (Thomas and Peckham 1976). Hydrocephalus was reported in another infant with 1st trimester exposure (Mulvihill *et al.* 1987). In addition, there was one spontaneous abortion and two induced abortions following 1st trimester exposure. Fetal autopsy observed a normal fetus in one induced abortion (Peres *et al.* 2001) and no fetal autopsy data were reported for the remaining two fetal losses. A total occurrence of major malformations following exposure during the 1st trimester was 31.3% (5/16 conceptuses). Of the 54 pregnancies (55 conceptuses) exposed to vinblastine during the 2nd and/or 3rd trimester only, there were 2 infants with major malformations. One infant had syndactyly of the 4th and 5th fingers, which required surgery (Cardonick *et al.* 2010) and a second infant had bilateral syndactyly of the 2nd and 3rd digits (Van Calsteren *et al.* 2010). Minor malformations observed in 2 newborns exposed in utero during the 2nd and/or 3rd trimester including: plagiocephaly (n=1 infant), and pectus excavatum (n=1 infant) (Cardonick *et al.* 2010, Van Calsteren *et al.* 2010). In addition, there was one intrauterine fetal death and one induced abortion following exposure during the 2nd and/or 3rd trimester; no fetal autopsy data were reported. A total occurrence of major malformations following exposure to vinblastine in the 2nd and/or 3rd trimester only was 3.6% (2/55). No malformations were observed in two infants without data on timing of exposure during pregnancy (Jameel and Jamil 2007).

There were a few pregnancy complications and infant health effects observed following in utero exposure to vinblastine. One patient experienced maternal hypertension, a reduction in amniotic fluid

and intrauterine growth restriction (Motegi *et al.* 2007). Intratuterine growth restriction was observed in a second pregnancy (Fadilah *et al.* 2006). Of the 34 pregnancies reporting age at delivery, 16 pregnancies were delivered preterm. Small for gestational age was reported for for one newborn (Dilek *et al.* 2006). Other effects reported were: respiratory difficulties (n=2 infants), anemia (n=2 infants), cerebral hemorrhage (n=1 infant), and hypoglycemia (n=3 infants). Follow-up evaluations were reported for 40 infants at ages ranging from 2 months to 14 years of age. All children demonstrated normal growth and development. One child each had: chronic broncolitis, recurrent otis media, and asthma (Cardonick *et al.* 2010). One healthy child tested positive for HIV at age 2 years; her mother was HIV positive at the time of pregnancy (Okechukwu and Ross 1998).

In conclusion, the total occurrence of major malformations in vinblastine-exposed pregnancies was 9.9% (7/73 conceptuses). Exposure to vinblastine in the 1st trimester resulted in a greater occurrence of major malformations (5/16 conceptuses) than the prevalence of birth defects in the general population (31.3 ± 22.7% versus 3%). The occurrence of major malformations following 2nd and/or 3rd trimester only exposure (2/56 conceptuses) was similar to the prevalence of birth defects in the general population (3.6 ± 4.9% versus 3%). Both these malformations were syndactylies and were unlikely to have been the result of vinblastine exposure in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations possibly attributed to vinblastine in the 2nd and/or 3rd trimester only was 0% (0/56 conceptuses).

5.33   VINCRISTINE

5.33.1   Mechanism of action, route of administration, and indications

Vincristine is a vinca alkaloid, antineoplastic drug isolated from the periwinkle plant (*Catharanthus roseus*) that binds to tubulin and inhibits microtubule formation in the M-phase of the cell cycle, thereby arresting mitosis. Vincristine is administered intravenously. Vincristine is indicated for the treatment of acute leukemia (Hospira 2008). It has also been used in combination with other chemotherapeutic agents for treatment of Hodgkin disease, rhadomyosarcoma, neuroblastoma, Wilm tumor, and non-Hodgkin lymphomas (histocytic, lymphocytic, mixed cell, undifferentiated, nodular and diffuse types).

5.33.2   Evidence of placental and breast milk transport

Placental and breast milk transfer of vincristine in humans is not known. Vinca alkaloids are highly protein-bound (>99%), which may limit their ability to cross the blood-placental barrier (Wiebe and Sipila 1994). The vinca alkaloids are substrates for P-glycoprotein, an efflux transporter for xenobiotics. P-glycoprotein is highly expressed on the maternal compartment of the placenta suggesting a role in protecting the fetus against the potential toxic effects of these agents (Mir *et al.* 2008). In vitro studies of human placental choriocarcinoma epithelial cell line (BeWo cells) demonstrated that the uptake of vincristine was increased by cotreatment with P-glycoprotein inhibitors suggesting a disruption of the efflux of the drug out the cells (Ushigome *et al.* 2000Of note, placental transfer of another vinca alkaloid, vinblastine, was observed in mice {Van Calsteren, 2010 #869) and baboons (Van Calsteren *et al.* 2010). Maternal transfer of vincristine to the infant via breast milk is not known.

5.33.3   Laboratory animal developmental toxicity

Vincristine is reported to cause fetal loss and/or malformations in variety of laboratory animals (Hospira 2008). Ferm et al. (Ferm 1963) report a dose-dependent increase in the rate of fetal mortality of golden hamster dams administered vincristine at 0.1 – 2.6 mg/kg via IV on gestation day 8. In addition, congenital malformations occurred in the surviving fetuses at a rate of ~11 to 15%, including: microphthalmia, anophthalmia, mild exencephaly, and rib defects. Similar results were reported for Wistar rats administered a single intraperitoneal injection of one of three dose levels vincristine on the 8th and 9th days of gestation in the rat (Tamaki *et al.* 1966). Fetal mortality was highest following exposure to gestation day 9 regardless of vincristine dose (48 to 94%). Fetal malformations were the most diverse following administration of 0.2 mg vincristine/kg on gestation day 8. The most frequently occurring malformations were anophthalmos, microphthalmos, exencephaly, microtia, and talipomanus (clubhand) (Tamaki *et al.* 1966). Intraperitoneal administration of vincristine at doses of 0.25 to 0.35 mg/kg bw on gestation day 9 resulted in fetal mortality (45-57%), and congenital anomalies (32-66% of surviving fetuses) as well as growth retardation (12.6 to 32% of surviving fetsuses) in three strains of mice (C3H, DBA/2J and Swiss ICR/Ha strains) (Joneja and Ungthavorn 1969). Finally, five pregnant monkeys (Macaca mulatta) were administered 0.15 to 0.2 mg vincristine/kg IV on individual gestation days 27, 28, 29, 33 or 34 (Courtney and Valerio 1968). Syndactyly and encephalocele were observed in two monkey offspring exposed in utero to 0.175 mg vincristine/kg on gestation day 27 or 29, respectively. The remaining three monkey offspring were normal (Courtney and Valerio 1968).

5.33.4   Human gestational exposure and effects

Vincristine is classified as FDA Pregnancy Category D. There were 220 published cases of patients treated with vincristine during pregnancy identified from 70 case reports, 22 case series, 5 retrospective case series, 8 retrospective surveys, 2 retrospective cohort studies, and 1 registry survey (Appendix C

Table 31). Among these patients, vincristine was predominately used to treat leukemias and lymphomas, including: acute leukemia (n=3 cases), acute lymphocytic leukemia (n=57 cases), acute myelogenous or granulocytic leukemia (n=24 cases), acute myelomonocytic leukemia (n=2 cases), acute promyelogenous leukemia (n=2 cases), chronic myelogenous leukemia (n=1 case), Hodgkin lymphoma (n=24 cases), non-Hodgkin lymphoma (n=57 cases), Burkitt lymphoma (n=8 cases), B-cell lymphoma (n=1 case), diffuse large B-cell lymphoma (n=1 case), T-cell lymphoma (n=2 cases), and adult T-cell leukemia/lymphoma (n=1 case). Vincristine was also used to treat the following non-blood-related cancers: breast (n=5 cases), cervix (n=6 cases), kidney (Wilm tumor, n=1 case), lung (n=1 case), skin (melanoma, n=1 case), ovary (n=6 cases), choriocarcinoma of the uterus (n=1 case, vaginal cancer (neuroendocrine carcinoma; n=1 case) as well as sarcoma (n=3 cases), Ewing sarcoma (n=3 cases), rhabdomyosarcoma (n=3 cases) and soft tissue sarcoma (n=1 case). The cancer type was not specified in three additional cases. A total of 221 pregnancies with 223 conceptuses were exposed to vincristine, one patient who had two pregnancies (Aviles and Niz 1988) and two twin pregnancies (Nantel *et al.* 1990, Turchi and Villasis 1988). The drug was administered during the 1st trimester in 56 pregnancies (58 conceptuses) and in 165 pregnancies (167 conceptuses) during the 2nd and/or 3rd trimester of pregnancy only.

Fetal loss occurred in 30 pregnancies, including 6 spontaneous abortions, 1 hysterotomy, 2 maternal/fetal deaths, 13 induced abortions, and 8 intrauterine fetal deaths . Spontaneous abortion occurred following exposure during the 1st trimester in 6 cases and following 2nd trimester exposure in 1 case; no cases reported fetal autopsy results. Spontaneous abortion occurred in the 1st trimester following exposure to vincristine and the following co-treatments: cyclophosphamide (Zuazu *et al.* 1991), daunorubicin, cytarabine and 6-thioguanine (Zuazu *et al.* 1991), doxorubicin and cytarabine (Awidi *et al.* 1983), epirubicin and methotrexate (Giacalone *et al.* 1999), methotrexate and 6-mercaptopurine (Bergstrom and Altman 1998), and cyclophosphamide, doxorubicin and dacarbazine (Jameel and Jamil 2007). One pregnancy ended in a hysterotomy and fetal autopsy revealed a normal fetus with small, mal-positioned kidneys (Mennuti *et al.* 1975); this pregnancy was exposed in the 1st trimester and co-exposed to procarbazine and nitrogen mustard. Two pregnancies ended in maternal and fetal death. Fetal autopsy revealed a normal fetus from one maternal and fetal death at gestation week 23 following in utero exposure during the 1st and 2nd trimester and co-exposure to 6-mercaptopurine, daunorubicin and cytarabine (Feliu *et al.* 1988). The second maternal and fetal death occurred in the 2nd trimester [in ~gestation week 24] following exposure during the 2nd trimester and co-exposure to daunorubicin and cytarabine (Greenlund *et al.* 2001); no fetal autopsy data were reported.

 Induced abortion was used to terminate the pregnancy in 13 cases and normal fetuses at autopsy were reported for three cases. One normal fetus of an induced abortion had toxic degenerative changes in the liver and kidneys (Peres *et al.* 2001); this pregnancy was exposed during the 1st trimester and co-treated with nitrogen mustard, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarabazine. Another normal fetus from an induced abortion was exposed during the 2nd trimester and co-treated with hydroxyurea, daunorubicin, cytarabine, and 6-thioguanine (Doney *et al.* 1979). The third normal fetus from an induced abortion was exposed in the 2nd trimester and co-exposed to daunorubicin, cytarabine, and 6-thioguanine (Lilleyman *et al.* 1977). No fetal autopsy data were reported for the remaining 10 induced abortions (Blatt *et al.* 1980, Chelghoum *et al.* 2005, Fassas *et al.* 1984, Molkenboer *et al.* 2005, Zemlickis *et al.* 1992, Zuazu *et al.* 1991). Intrauterine fetal death occurred in 8 pregnancies. Fetal autopsies reported normal fetuses in three cases of intrauterine fetal death: one fetus was exposed during the 2nd and 3rd trimester and co-exposed to doxorubicin, cyclophosphamide, and rituximab (Cardonick *et al.* 2010), one fetus was exposed during the 3rd trimester and co-exposed to doxorubicin and radiation therapy (Karp *et al.* 1983), and another fetus was exposed during the 3rd

trimester and co-exposed to daunorubicin, cytarabine and 6-thioguanine (Zuazu *et al.* 1991). The remaining five pregnancies ending in intrauterine fetal death did not report fetal autopsy data. Two pregnancies ending in intrauterine fetal death were exposed during the 1st trimester and co-exposed to the following chemotherapy agents: doxorubicin (Peres *et al.* 2001) and co-exposure to asparaginase, daunorubicin, methotrexate (intrathecal) (Molkenboer *et al.* 2005). The three pregnancies ending in intrauterine fetal death were exposed to vincristine in the: 2nd and 3rd trimester and cotreated with daunorubicin (Jameel and Jamil 2007), 2nd trimester and cotreated with epirubicin (n=1 case) (Peres *et al.* 2001), and 2nd trimester and co-exposed to cyclphosphamide, doxorubicin, ifosfamide, etoposide, cytarabine and rituximab (Peterson *et al.* 2010). Oligohydramnios and intrauterine growth restriction occurred in one of the pregnancies ending in stillbirth (Peterson *et al.* 2010).

Of the 193 live born infants exposed to vincristine in utero (including 2 sets of twins), there were five infants with major malformations. Four infants with major malformations were exposed to vincristine during the 1st trimester. One newborn had bilateral loss of the radius and the 5th digit as well as an atrial septal defect following exposure in the 1st trimester and co-exposure to cytarabine and doxorubicin (Ebert *et al.* 1997). A small secundum atrial septal defect was observed at the autopsy of an infant who developed respiratory distress and died on day 2 (Thomas and Peckham 1976); this pregnancy was exposed during the 1st trimester and co-treated with vinblastine and procarbazine. Cleft lip and cleft palate were observed in an infant following 1st trimester exposure and co-treatment with lomustine, procarbazine, and vinblastine (Mulvihill *et al.* 1987). Hydrocephalus was reported in a newborn that died 4 hours after birth (Zemlickis *et al.* 1992); this infant was exposed during the 1st trimester and co-treated with nitrogen mustard and procarbazine. A major malformation occurred in one infant following exposure to vincristine in the 2nd and 3rd trimesters. Bilateral syndactyly of digits II and III occurred in an infant exposed during the 2nd and 3rd trimester (Van Calsteren *et al.* 2010); this infant was also co-exposed to nitrogen mustard, procarbazine, doxorubicin, bleomycin, vinblastine as well as radiotherapy in the 2nd trimester. Two infants had minor malformations following exposure in the 2nd and 3rd trimester. One infant had pectus excavatumfollowing exposure during the 2nd and 3rd trimester and co-exposure to nitrogen mustard, procarbazine, doxorubicin, bleomycin, and vinblastine (Van Calsteren *et al.* 2010). A hemangioma was reported in another infant following exposure in the 2nd and 3rd trimester and co-treatment with methotrexate, daunorubicin, cyclophosphamide, asparaginase, and 6-mercaptopurine (Van Calsteren *et al.* 2010).

A variety of pregnancy complications and infant health issues were reported following in utero exposure to vincristine. Pregnancy complications included: preeclampsia (n=4 pregnancies) {Barnes, 2007 #146;Bartsch, 1988 #615;Chakravarty, 2011 #860;Coopland, 1969 #714}, and premature rupture of membranes (n=7 pregnancies) {Ali, 2009 #709;Doney, 1979 #215;Karp, 1983 #129;Meador, 1987 #283;Okun, 1979 #691}{Udink ten Cate, 2009 #434;Webb, 1980 #906}. Spontaneous preterm labor occurred in 17 pregnancies {Berrebi, 1983 #697;Decker, 2006 #403;Doney, 1979 #215;Fassas, 1984 #231} {Berrebi, 1983 #697;Decker, 2006 #403;Doney, 1979 #215;Fassas, 1984 #231}{Karp, 1983 #129;Kim, 1989 #134}{Martin, 1997 #277;Moore, 1991 #718;Nantel, 1990 #317}{Reynoso, 1987 #372;Tobias, 1980 #546;Wells, 1968 #449;Willemse, 1990 #573}, including two pregnancies with transient labor {Ortega, 1977 #335}{Hansen, 2001 #105} and 3 pregnancies with premature rupture of membranes {Karp, 1983 #129;Meador, 1987 #283;Webb, 1980 #906}. Three pregnancies experienced a reduction in amniotic fluid: transient oligohydramnios (Hansen *et al.* 2001), a reduction in amniotic fluid (Peterson *et al.* 2010), and anhydramnios {Fernandez, 1989 #235}. The infant with anhydramnios developed after the first course of chemotherapy in the 2nd trimester (Fernandez *et al.* 1989); the female infant did not pass urine from birth through age 7 days, when she died. Fetal distress was reported in three cases (Ali *et al.* 2009, Mavrommatis *et al.* 1998, Veneri *et al.* 1996). Intrauterine growth restriction

was observed in four pregnancies {Matsouka, 2008 #279}{Lambert, 1991 #248}, including two pregnancies with reductions in amniotic fluid {Fernandez, 1989 #235;Peterson, 2010 #670}. Of the 153 pregnancies reporting gestational age at delivery, early preterm delivery (<34 weeks) occurred in 40 pregnancies (26.1%), late preterm delivery (34-36 weeks) were reported for 36 pregnancies (23.5%) and 72 pregnancies (47.1%) were delivered at term. Chelghoum et al. (Chelghoum *et al.* 2005) reported two infants were premature; **[however, age at delivery and the definition of premature were not specified so they are not included in the tally.]** Small for gestational age was reported for 3 newborns {Cardonick, 2010 #7}{Magloire, 2006 #268}{Gulati, 1986 #96}. Respiratory distress and other breathing difficulties were reported for 15 newborns (Achtari and Hohlfeld 2000, Ali *et al.* 2009, Bader *et al.* 2007, Cardonick *et al.* 2010, Corapcioglu *et al.* 2004, Cordeiro *et al.* 2009, Haerr and Pratt 1985, Lam 2006, Matsouka *et al.* 2008, Mavrommatis *et al.* 1998, Papantoniou *et al.* 2008, Thomas and Peckham 1976, Veneri *et al.* 1996, Willemse *et al.* 1990), including one infant requiring oxygen treatment after meconium aspiration (Hansen *et al.* 2001). Transient myelosuppression was observed in 11 neonates, including: anemia (Cardonick *et al.* 2010, Doney *et al.* 1979, Gambino *et al.* 2011) {Aviles, 1988 #772}, absent or low levels of B-cells (n=4 infants) (Chakravarty *et al.* 2011, Decker *et al.* 2006, Friedrichs *et al.* 2006), slight leucopenia (Khurshid and Saleem 1978), , and myelosuppression (Okun *et al.* 1979, Udink ten Cate *et al.* 2009). One infant with myelosuppression was hydropic with abdominal distention, and was treated for congestive heart failure (Okun *et al.* 1979). One infant with anemia was also hyperkalemic, hypoglycemic, and hyponatremic (Doney *et al.* 1979).

Several other health effects were observed in newborns gestationally exposed to vincristine. One newborn required intravenous calcium (Haerr and Pratt 1985). Polycythemia (Dara *et al.* 1981) and low hemoglobin (Gulati *et al.* 1986) were observed in one infant each. Jaundice was observed in 7 infants (Cardonick *et al.* 2010, Dara *et al.* 1981, Hansen *et al.* 2001, Matsouka *et al.* 2008, Papantoniou *et al.* 2008, Peres *et al.* 2001). Cerebral hemorrhages were observed in three early preterm infants (Achtari and Hohlfeld 2000, Fernandez *et al.* 1989, Veneri *et al.* 1996). In particular, one infant with bilateral intraventricular hemorrhages died at age 7 days and autopsy revealed a meningeal hematoma (Fernandez *et al.* 1989); this infant had anuria and experienced anhydramnios during pregnancy. Cardiac effects were observed in two infants, including: acute cardiac failure on day 1, which resolved in three days with treatment (Achtari and Hohlfeld 2000) and asystole (in addition to apnea, then respiratory distress) on day of birth (Willemse *et al.* 1990). Several infants suffered from infections, such as: necrotizing enterocolitis (Achtari and Hohlfeld 2000), omphalitis (Cordeiro *et al.* 2009), septicemia resulting in death at 21 days (Aviles and Niz 1988), and gastroenteritis resulting in the death of two infants at age 90 days (Aviles and Niz 1988, Dilek *et al.* 2006). One infant had Cushingoid appearance at birth, but was normal at 8 weeks of age (Doney *et al.* 1979). One set of twins had diarrhea shortly after birth and were successfully treated (Turchi and Villasis 1988). Some chromosomal breakage and a ring chromosome were observed in an otherwise normal newborn (Schleuning and Clemm 1987).

Follow-up evaluations were reported for 135 children ranging in age from 8 weeks to 19 years; age at follow-up was not specified for 5 children {Bergstrom, 1998 #159}{Khurshid, 1978 #818}{Seamon, 2009 #405}{Willemse, 1990 #573}. Normal growth and development were reported for all but 5 children who had delayed development or depressed growth. One child had a mild delay in motor skills at 14 months (Lam 2006), two children had speech delay at 18 months (Achtari and Hohlfeld 2000) or in 4.3 years old (Cardonick *et al.* 2010). One child had normal Denver Developmental Screening test results, but his growth was in the 3rd percentile at 13.5 months (Doney *et al.* 1979). At 26 months, another child's body weight was <10th percentile and had a constant cold (Gulati *et al.* 1986); however, the infant's immune function test and complete blood count were normal. One child with normal growth and development at age 2 years tested HIV positive; her mother was HIV positive (Okechukwu and Ross 1998).

5.33.5 Summary of pregnancy outcomes for vincristine

Exposure to vincristine is documented for 221 pregnancies and 223 conceptuses, including two twin pregnancies. Of the 56 singleton pregnancies (56 conceptuses) exposed in the 1st trimester, there were four infants with major malformations. One newborn had bilateral loss of the radius and the 5th digit as well as an atrial septal defect (Ebert *et al.* 1997). Cleft lip and cleft palate were observed in another infant (Mulvihill *et al.* 1987). A small secundum atrial septal defect was observed at the autopsy of an infant who developed respiratory distress and died on day 2 (Thomas and Peckham 1976), and hydrocephalus was reported in a newborn who died 4 hours after birth (Zemlickis *et al.* 1992). In addition, there were 18 pregnancies ending in fetal loss following 1st trimester exposure, including 6 spontaneous abortions, 9 induced abortions, 1 intrauterine fetal death and one pregnancy each ending in a hysterotomy or a maternal/fetal death. A normal fetus at autopsy was reported for one induced abortion (Peres *et al.* 2001). Normal fetuses were observed at autopsy of a pregnancy ended due to a hysterotomy (Mennuti *et al.* 1975) and a pregnancy ended by maternal and fetal death (Feliu *et al.* 1988). No fetal autopsy data were provided for the remaining 17 cases of fetal loss. A total occurrence of major malformations following 1st trimester exposure to vincristine was 7.1% (4/56 conceptuses).

Of the 165 pregnancies (167 conceptuses) exposed to vincristine during the 2nd and/or 3rd trimesters only, major malformations were observed in one infant: bilateral syndactyly of digits II and III (Van Calsteren *et al.* 2010). Two infants had minor malformations following exposure in the 2nd and/or 3rd trimester: pectus excavatum (n=1 infant) and hemangioma (n=1 infant) (Van Calsteren *et al.* 2010). In addition, fetal loss occurred in 12 pregnancies exposed to vincristine in the 2nd and/or 3rd trimester, including 4 induced abortions, 7 intrauterine fetal deaths, and one maternal/fetal death. Normal fetuses at autopsy were reported for 2 induced abortions {Doney, 1979 #215;Lilleyman, 1977 #770}, and three intrauterine fetal deaths (Cardonick *et al.* 2010, Karp *et al.* 1983, Zuazu *et al.* 1991). Fetal autopsy data were not provided for the remaining fetal deaths. A total occurrence of major malformations following 2nd and/or 3rd trimester exposure to vincristine was 0.6% (1/165 conceptuses).

 A variety of pregnancy complications and infant health issues were reported following in utero exposure to vincristine. Oligohydramnios occurred in two pregnancies (Hansen *et al.* 2001, Peterson *et al.* 2010), and in another pregnancy, anhydramnios developed in the 2nd trimester, and the infant suffered from anuria for 7 days, and then died (Fernandez *et al.* 1989). Fetal distress was reported in three cases (Ali *et al.* 2009, Mavrommatis *et al.* 1998, Veneri *et al.* 1996). Intrauterine growth restriction was observed in four pregnancies (Fernandez *et al.* 1989, Lambert *et al.* 1991, Matsouka *et al.* 2008, Peterson *et al.* 2010). Preterm deliveries were reported for 76 of 153 pregnancies reporting gestational age at delivery. Small for gestational age was reported for 3 newborns {Cardonick, 2010 #7}{Magloire, 2006 #268}{Gulati, 1986 #96}. The most common infant health effects included respiratory difficulties (n=15 infants), transient myelosuppression (n=11 infants) and jaundice (n=7 infants). One normal appearing infant had abnormal chromosomes (Schleuning and Clemm 1987). There were 5 infant deaths: 1 infant died of septicemia at 21 days (Aviles and Niz 1988), two infants died of gastroenteritis (Aviles and Niz 1988, Dilek *et al.* 2006) and, as previously mentioned, one infant died following respiratory distress on day 2 (Thomas and Peckham 1976), and another infant with hydrocephalus died 4 hours after birth (Zemlickis *et al.* 1992). Of the 135 children with follow-up information, normal growth and development was reported at ages ranging from 8 weeks to 19 years with the exception of 5 children. One child had a mild delay in motor skills at 14 months old (Lam 2006), two children that had speech delay at 18 months (Achtari and Hohlfeld 2000) or in 4.3 years old (Cardonick *et al.* 2010), one child that had delayed growth (Doney *et al.* 1979), and another child that had body weight in the < 10th percentile (Gulati *et al.* 1986).

In conclusion, the total occurrence of major malformations in vincristine-exposed pregnancies was 22.4% (5/223 conceptuses). The occurrence of major malformations following exposure during the 1st trimester (4/56) was approximately twice the prevalence of birth defects in the general population (7.1 ± 6.7% versus 3%). The occurrence of major malformations following exposure in the 2nd and/or 3rd trimester only (1/167) was not higher than that in the general population (0.6 ± 1.2% versus 3%). This single malformation, syndactyly, was unlikely to have resulted from chemotherapy exposure in the 2nd and/or 3rd trimester only. Therefore, the revised occurrence of major malformations following exposure to vincristine in the 2nd and/or 3rd trimester only is 0%.

5.34 VINORELBINE

5.34.1 Mechanims of action, route of administration, and indications

Vinorelbine is a semi-synthetic vinca alkaloid, which interferes with microtubule assembly (GlaxoSmithKline 2002). Vinorelbine is administered intravenously. Vinorelbine is indicated as a single agent or in combination with cisplatin for the treatment of advanced non-small cell lung cancer (GlaxoSmithKline 2002), but is also used for the treatment of breast cancer {Pharmaceutical Partners of Canada Inc, 2009 #1152}.

5.34.2 Evidence of placental and breast milk transport

Placental and breast milk transport of vinorelbine in humans is not known. In rats, placental transport of vinorelbine occurred in low levels (Kobayashi *et al.* 1993). The percent of maternal dose detected in rat fetuses was 0.2%, 0.4% and 0.6% at 0.5, 4 and 24 hours after a single injection of 1.2 mg/kg radiolabelled vinorelbine to pregnant rats on gestation day 19. Maternal transfer of vinorelbine to the infant via breast milk has not been reported (GlaxoSmithKline 2002).

5.34.3 Laboratory animal developmental toxicity

Vinorelbine induced embryo lethal and teratogenic effects in laboratory animal studies. Embryo and/or fetal toxicity **[no details provided]** was observed following doses of 9 mg/m^2 to mice and 5.5 mg/m^2 rabbits (doses that are 1/3rd and 1/6th the human dose, respectively) (GlaxoSmithKline 2002). In addition, decreases in fetal body weight and delays in bone maturation were observed at doses that were not toxic to the dams. As reviewed in Shepard et al. (Shepard and Lemire 2004), vinorelbine increased axial skeletal defects in rat fetuses at the highest dose of 0.50 mg/kg, but not at 0.22 mg/kg, when rats dams were administered the drug orally during organogenesis.

5.34.4 Human gestational exposure and effects

Vinorelbine is classified as FDA Pregnancy Category D. There were 15 published cases of patients treated with vinorelbine during pregnancy identified from 5 case reports, 2 case series, 1 retrospective survey, and 1 registry survey (Appendix C Table 32). Among these patients, vinorelbine was used to treat cancer of the breast (n=11 cases), lung (n=3 cases), as well as one case with rhabdomyosarcoma. Vinorelbine was administered during one pregnancy (1 conceptus) in the 1st trimester and in the 2nd and/or 3rd trimester only during the remaining 14 pregnancies (14 conceptuses). Of these pregnancies, there were 15 live born infants and no fetal losses. One infant had major congenital malformations: cleft palate, tracheoesophageal fistula, and esophageal atresia {Abellar, 2009 #29}; this pregnancy was exposed during the 1st through 3rd trimesters and was co-exposed to oxalplatin and irinotecan (Abellar *et al.* 2009).

Pregnancy complications and infant health issues occurred following in utero exposure to tamoxifen. Oligohydramnios, occasional fetal cardiac decelerations, and decreased fetal movements at gestation week 34 were reported following 2nd trimester exposure(Fanale *et al.* 2005), and an additional pregnancy experienced anhydramnios {El-Safadi, 2012 #1225}; both of these pregnancies were co-treated with trastuzumab in the 2nd and 3rd or 3rd trimesters. Maternal respiratory difficulties due to the progression of lung cancer lead to an emergency C-section (Janne *et al.* 2001). Of the 14 pregnancies with age at delivery data, early preterm delivery occurred in 4 pregnancies (26.7%), late preterm delivery occurred in 5 pregnancies (33.3%), and 5 pregnancies were delivered at term (33.3%). No infants were small for gestational age. Transient myelosuppression was observed in 3 infants (Giacalone *et al.* 1999){Cuvier, 1997 #402}, includingone infant had a decrease in white blood cells and neutrophils at 10 days of age, which resolved 3 weeks later (Janne *et al.* 2001). Of the 12 offspring with follow-up evaluations, normal development was observed in all children ranging from 4 to 80 months.

5.34.5 *Summary of pregnancy outcomes for vinorelbine*

In utero exposure to vinorelbine was documented for 15 singleton pregnancies (15 conceptuses). Major malformations were observed in the only pregnancy exposed during the 1st trimester: one newborn had cleft palate, tracheoesophagheal fistula and esophageal atresia (Abellar *et al.* 2009); this infant was co-exposed to oxaliplatin and irinotecan. The occurrence of major malformations following exposure to vinorelbine during the 1st trimester was 100% (1/1 conceptus); however, there were too few reported pregnancy outcomes to make an accurate estimate. No malformations were observed in the 14 infants exposed in utero during the 2nd and/or 3rd trimester only, so the total occurrence of major malformations following exposure to vinorelbine in the 2nd and/or 3rd trimester only was 0% (0/14 conceptuses). Oligohydramnios, fetal cardiac decelerations and decreased fetal movement preceded one induced birth (Fanale *et al.* 2005) and anhydramnios occurred in another pregnancy {El-Safadi, 2012 #1225}; both pregnancies were co-exposed to trastuzumab. Preterm delivery was reported for 9 of 14 infants with age at delivery data, and no infants were small for gestational age. Transient myelosuppression was observed in 3 infants. Follow-up evaluations on 12 infants at ages ranging from 4 to 80 months revealed normal growth and development.

In conclusion, the total occurrence of major malformations in vinorelbine-exposed pregnancies was 6.7% (1/15 conceptuses). The occurrence of major malformations observed following 1st trimester exposure to vinorelbine (1/1 conceptus) was greater than prevalence of birth defects in the general population (100% versus 3%). The occurrence of major malformations following exposure to vinorelbine in the 2nd and 3rd trimester only (0/14 conceptuses) was less than the prevalence of birth defects in the general population (0% versus 3%). However, these data should be interpreted cautiously as there were too few cases reported on pregnancy outcomes of vinorelbine during pregnancy to accurately assess the occurrence of major malformations in either the 1st trimester or the 2nd and/or 3rd trimester only.

6.0 LONG-TERM EVALUATIONS OF GROWTH AND DEVELOPMENT

The few studies, which have conducted longer-term evaluations of the gestationally exposed offspring at ages ranging from 18 months to 20 years, have observed no effects on general health and growth and no increase in auditory, neurological or cardiac morbidity (Amant *et al.* 2012, Aviles *et al.* 2012); however, the authors observed subtle change in cardiac function and neurological outcome, which merit further follow-up evaluation (Amant *et al.* 2012).

Seven of the larger follow up studies of long-term growth and development following gestational exposure to cancer chemotherapy are summarized here.

- Sokal and Lessman (Sokal and Lessmann 1960) published one of the earliest reviews of pregnancy outcomes and follow up studies on children exposed in utero to various chemotherapy agents. Following a literature search to identify cases of exposure to chemotherapeutics during pregnancy, they corresponded with physicians to obtain information on the fate of the children. Of the 50 cases they identified, they obtained follow up information on 17 children born to mothers who received cancer chemotherapy while pregnant. The children ranged in age at examination from 2 months to 9.5 years. All 17 children were reported to be "normal."

- Reynoso et al. (Reynoso *et al.* 1987) reported follow up information on 6 children born to mothers who were treated with chemotherapy for acute leukemia while pregnant. These children were from 1 year to 16 years of age when the follow up examinations were performed. Five of these 6 were reported to have no late complications. One male child exposed throughout pregnancy to cyclophosphamide and prednisone had low IQ and papillary thyroid cancer at age 11 years, and stage III neuroblastoma at age 14 years. He was diagnosed with metastatic papillary thyroid cancer at age 16 and had suffered two reoccurrences by age 22 years. His twin sister had no health complications (Reynoso *et al.* 1987, Zemlickis *et al.* 1993).

- Avilés and colleagues published a series of follow up studies in the offspring of patients with hematological cancers treated with cancer chemotherapy during pregnancy (Aviles *et al.* 1991, Aviles and Neri 2001, Aviles and Niz 1988). In their 2001 paper, Avilés et al. (Aviles and Neri 2001) reported on 84 offspring that ranged in age from 6 to 29 years at the time of follow up examination. A thorough assessment of each child was conducted and included a physical examination, complete blood count, serum chemistry, hepatic test, test for cardiac function, a test for cytogenetic abnormalities, and assessments of height weight, neurological, and psychological development. In addition, school performance was assessed and records of degrees and diplomas were collected. The authors concluded that all 84 offspring had normal growth, development, educational performance, and behavior. Hematological, renal, hepatic, and cardiac functions were normal, as was the cytogenetic analysis, and no cancers were observed. Among the 84 prenatally exposed offspring, sixteen offspring were married, with 12 second-generation offspring. All second-generation offspring were considered normal, although clinical and laboratory studies of the offspring of the in utero-exposed individuals were not conducted.

- Van Calsteren et al. (Van Calsteren *et al.* 2006) conducted a thorough neurologic and cardiologic assessment of 10 children of women who received cancer chemotherapy while pregnant. A pediatric neurologist conducted a neurological clinical evaluation. A pediatric cardiologist performed a transthoracic echocardiogram to measure ventricular dimensions, mass, wall thickness and fractional shortening and a blood pool Doppler to assess diastolic function; echocardiographic data were compared to a matched control group. The children ranged in age from 2 months to 66 months. Three children born prematurely showed neurologic abnormalities: one born at 32 weeks had a persistent asymmetric tonic neck reflex and delayed visual fixation at 10 weeks, one born at 28 weeks had a minor delay in expressive language development at 21 months, and one born at 33 weeks had an autistic disorder, mental and mild motor retardation related to polymicrogyria. The cardiologic assessments of the patients did not differ significantly from the controls. However, they did report a trend toward reduced ventricular wall thickness and left ventricular index mass in children exposed to anthracycline cancer chemotherapeutic agents (n=7 children). They considered this worrisome because chemotherapy, specifically the anthracycline drugs, may interfere with cardiac development.

- Avilés et al. (Aviles *et al.* 2006) also conducted cardiologic assessments in 81 children of women who received cancer chemotherapy with anthracyclines (doxorubicin, daunorubicin,

mitoxantrone, or idarubicin) while pregnant. Baseline echocardiogram data were collected when the children were 5 years old and were repeated at 5-year intervals until age 20 years or until the last follow up. They evaluated left ventricular internal dimensions, septal wall thickness, and posterior wall thickness, and fractional shortening (FS) of the left ventricle, and selected an FS value of <28% to define the presence of cardiac toxicity. The authors report that echocardiograms provided no evidence of cardiac disease and that FS values were normal in the baseline study and all subsequent determinations. These results appear to be consistent with the findings reported by Van Calsteren et al. (Van Calsteren *et al.* 2006).

- Nulman et al. (Nulman *et al.* 2001) reviewed the literature (1966 to 2001) on neurodevelopment in children born to mothers treated for cancer while pregnant. They identified 6 publications reporting on 111 children exposed in utero to cancer chemotherapy agents. The age at assessment ranged from one month to 22 years and was generally, but not in every case, assessed using the Denver Developmental Screening test, Wechsler and Bender-Gestalt cognitive tests, and/or school reports. In all cases, the results of the in utero-exposed offspring were either normal development or not different from controls.

- Amant et al. (Amant *et al.* 2012) reported the results of a follow-up study involving collaboration among three hospitals in Europe, University Hospitals Leuven in Belgium, Radboud University Nijmegen Medical Centre in the Netherlands, and Faculty Hospiital Motol, Charles University in the Czech Republic. They conducted follow-up health assessments on 70 children exposed prenatally to cancer chemotherapy agents at ages ranging from 18 months to 18 years. None of the children were exposed during the first trimester. Examinations included assessments of general health and development, and cardiological, cognitive, behavioral, and neurological development. Median age at follow-up was 22.3 months (range 16.8 to 211.6 months). The authors concluded that for all the health endpoints assessed, the children exposed prenatally to chemotherapy were not different from the general population. Considering the effects of preterm delivery, they report an increase in average IQ scores of 11.1 points for each month increase in pregnancy duration.

While these reports provide some evidence that in utero exposure to chemotherapy agents does not result in adverse health effects later in life, the evidence is generally based on assessments conducted on a small number of individuals, carried out early in life, and involving a limited number of health endpoints in each individual. There is a need for larger, longer-term studies with more comprehensive health assessments as noted by several of the authors cited above, and in reviews of this topic by authors such as Garber (Garber 1989) and Partridge (Partridge and Garber 2000).

7.0 PREGNANCY OUTCOMES OF MEDICAL PERSONNEL EXPOSED TO CANCER CHEMOTHERAPEUTICS

Exposure to cancer chemotherapy agents may occur in an important group of people who do not have cancer: health care workers involved in preparation and administration of chemotherapy medications, as well as other workers involved with the care of cancer patients. These health care workers include pharmacists, pharmacy technicians, nurses, physicians, veterinarians, veterinarian technicians, and other hospital and clinic personnel. Other workers with potential exposures to chemotherapy agents include those who manufacture, package, and transport the agents. While the effects of occupational exposure on pregnancy outcomes are not evaluated in this monograph, it is important to point out that individuals exposed in this manner include women of reproductive age, including pregnant women. Although the levels of such exposures are thought to be much lower than those administered to cancer

patients, they are usually unrecognized, may occur over a longer period of time, and may involve a greater number of chemotherapy agents.

The topic of health care worker exposures to antineoplastic drugs and their possible health effects was thoroughly reviewed by Conner and McDiarmid (Connor and McDiarmid 2006). The following information is taken from that review. Evidence for exposure of health care workers to chemotherapy agents began appearing in the 1970s with reports of elevated mutagenic activity in the urine of workers who prepared and administered such agents. 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 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, Conner et al. (Connor *et al.* 2010) reported that surface contamination persists in pharmacy and nursing areas of some hospital-based cancer centers.

The possible effects of occupational exposures on pregnancy outcomes among female health care workers are not yet well established. Published studies have reported associations between exposures and increased fetal loss, congenital malformations, low birth weights, and infertility. Dranitsaris et al. (Dranitsaris *et al.* 2005) conducted a meta-analysis of 14 studies that were performed between 1966 and 2004 in the United States and Europe, evaluating occupational exposure to cytotoxic drugs and adverse health effects in health care workers. Reproductive effects examined included spontaneous abortions (n=5 studies), stillbirths (n=2 studies), and congenital malformations (n=4 studies). The only statistically significant association identified by the meta-analysis was between exposure and spontaneous abortion (OR = 1.46; 95% confidence interval: 1.11 to 1.92). Lawson et al. (Lawson *et al.* 2011) reported on data of 7482 female participants in the Nurses' Health Study II, a prospective cohort study of nurses from 14 states in the United States. They reported a statistically significant association between exposure to anti-neoplastic agents and the incidence of spontaneous abortion (OR =1.94; 95% confidence interval: 1.41-2.76) following adjustments made for age, five occupational exposures (i.e., anesthetic gases, antineoplastic agents, antiviral agents, sterilizing agents, and X-ray radiation), parity, shift work, and number of hours worked. Additional references regarding occupational exposure to cancer chemotherapeutics are located in Appendix F of the NTP monograph.

8.0   DISCUSSION

Incidence of major congenital malformations

Major congenital malformations were more frequently observed in conceptuses exposed to cancer chemotherapy during the first trimester than in conceptuses exposed to cancer chemotherapy in the second and/or third trimester only (Table 20). Of the 1271 conceptuses evaluated in this monograph, the apparent rate of major malformations was 9.8% (40/410 conceptuses) following exposure to any cancer chemotherapy during the first trimester compared to the apparent rate of 2.7% (22/823 conceptuses) of major malformations following exposure during the second and/or third trimester only; timing of exposure was not specified for 38 conceptuses (none were malformed). As a point of comparison, the prevalence of major congenital malformations in the general population of the United

States is about 3% (Correa *et al.* 2007). These data are consistent with the current medical paradigm for treatment of the pregnant cancer patient which is to avoid, whenever possible, administration of cancer chemotherapy during the first trimester due to the vulnerability of organogenesis (gestational weeks 3 through 8) to chemical perturbation (Loibl *et al.* 2006, Rizack *et al.* 2009, Azim *et al.* 2010). Exposure during the second and/or third trimester poses less risk of gross major malformations at birth, but may result in more functional deficits (Moore 2003). When the data were examined by individual chemotherapy agent (administered either singly or in combination therapy), there were generally no patterns of increased rates of major malformations when examining the data by classes of agents working via similar mechanisms of action (See Table x for chemical-specific breakdown)(Figure 1; Appendix Table A).

It is worth noting that some of the major congenital malformations observed in this review of the literature were not likely to be associated with cancer chemotherapy use during pregnancy.   For example, cancer chemotherapy exposure were not likely associated with malformations observed prior to birth {Rouzi, 2009 #376;Sham, 1996 #627} or inherited conditions (e.g., familial polydactyly (Volkenandt *et al.* 1987)). In addition, the following major malformations were not likely caused by exposure to cancer chemotherapy in the second and/or third trimester only because they occur in structures or organs that are formed during the first trimester of pregnancy: agenesis (absence) of the right kidney and ureter, Down syndrome, gastroschisis, hypospadias, meningocele, neurofibromatosis (spontaneous mutation), pulmonary artery fistula, rectal atresia, syndactyly of fingers or toes, and ventricular septal defect (Moore 2003). It is possible that the following reported malformations may be influenced or induced by second and/or third trimester only exposure to cancer chemotherapeutic agents: cerebral atrophy, club foot, hemi-hypertrophy of lower extremities, polycystic kidney, pyloric stenosis, and ventriculomegaly. Exclusion of preexisting malformations or malformations not likely caused by exposed in the second and/or third trimester did not appreciably change the rate of malformations in the first trimester and it decreased the rate of malformations in the second trimester (data not shown).

The rate of malformations following gestational exposure to the targeted therapies was variable (Figure 1). Targeted therapies are designed to target specific receptors and cell-signalling pathways in an effort to increase efficacy of the treatment and decrease the systemic side effects often observed with the cytotoxic chemotherapy agents. The targeted agents are commonly administered as a single drug therapy, which makes it easier to identify the drugs' potential developmental effects. The targeted therapies reviewed in the NTP monograph include: all-trans retinoic acid, rituximab, interferon alpha, tamoxifen, imatinib, and trastuzumab. The apparent rate of major congenital malformations following first trimester exposure to imatinib was 8.1% (12/149 conceptuses), which was similar to the overall apparent rate of major malformation following exposure to any cancer chemotherapy during the first trimester 9.8% (40/410 conceptuses). Imatinib is a tyrosine kinases inhibitor that slow the proliferation of chronic myeloid leukemia cells, but can target other receptors including platelet-derived growth factors (PDGFRs).   It has been hypothesized that the incidence of exomphalos and/or skeletal system defects in infants exposed to imatinib during pregnancy may be due to effects mediated via the platelet-derived growth factor receptors as PDGFRs are know to play an important role in mammalian organogenesis {Apperley, 2009 #46}{Hoch, 2003 #954}. Imatinib is also know to be anti-angiogenic in animal models through inhibitory effects on PDGFR, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Higher apparent rates of major malformations were observed following exposure during the first trimester to rituximab at 16.7% (1/6 conceptuses) and tamoxifen at 27.3 % (3/11 conceptuses); however, these rates are based on very few published reports and may not accurately represent the risk of malformation of these agents. Rituximab is a genetically engineered

chimeric murine/human IgG 1 monoclonal antibody that is directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, and developmental toxicity studies in cynomolgus monkeys did not observe any embryotoxicity or fetal malformations {Genentech, 2011 #1016;Vaidyanathan, 2011 #1060}. In contrast, there were no published report of malformations following exposure during the first trimester exposure to all-trans retinoic acid (n=5 conceptuses), interferon (n=21 conceptuses) or trastuzumab (n=14 conceptuses). However, the manufacturers reported that gestational exposure to trastuzumab may result in skeletal abnormalities consistent with oligohydramnios sequence {Genentech, 2010 #929}{Christianson, 1999 #1343}. None of the targeted therapies were associated with major congenital malformation following exposure during the second and/or third trimester only, with the exception of all trans retinoic acid. However, the two major congenital malformations that were reported for exposure to all-trans retinoic acid in the second and/or third trimester were likely not due to cancer chemotherapy exposure: one infant with Potter syndrome diagnosed prior to chemotherapy {Sham, 1996 #627} and an infant with atrial septal defects {Siu, 2002 #410} (Appendix A Table 1) (2/24 conceptuses).

Spontaneous fetal death

The apparent rate of early spontaneous pregnancy loss (≤22 weeks of gestation) following in utero exposure to any cancer chemotherapy (3.6%; 46/1271 conceptuses) appeared to be lower than a pooled estimate of spontaneous abortion in healthy women of 13% (95% CI = 10% to 16%) (Wilcox 2010). In contrast, the apparent rate of late spontaneous fetal death (>22 weeks of gestation) following in utero exposure to any cancer chemotherapy (1.8%; 23/1271 conceptuses) was higher than rates of late spontaneous fetal loss for the general population in the United States from 1990 to 2004 (0.3 to 0.4%) (MacDorman 2005, Martin 2011). When the data were evaluated by individual chemotherapy agent (administered either singly or in combination therapy), late spontaneous fetal loss occurred most frequently following exposure to cytarabine in combination with an anthracycline antibiotic (e.g. daunorubicin, doxorubicin, idarubicin or mitoxantrone); the apparent rate of late fetal loss for cytarabine was 8.6% (13/151 conceptuses). Twelve of 13 of the intrauterine fetal deaths occurred in pregnancies exposed to cytarabine and co-exposed to anthracycline antibiotics daunorubicin in combination therapies (n=8 conceptuses), doxorubicin (n=2 conceptuses), or idarubicin (n=2 conceptuses).

Reduction in amniotic fluid

Of the 1128 pregnancies evaluated in this monograph resulting in stillbirths and live births, the apparent rate of moderate to severe reductions in amniotic fluid (e.g., oligohydramnios and anhydramnios, respectively) was 2.9% (33/1128 pregnancies) for pregnancies gestationally exposed to any cancer chemotherapy. This apparent rate of occurrence of reduction in amniotic fluid is similar to the prevalence of oligohydramnios in the general population, which is reported to occur at a rate of 2.3 to 4% of all pregnancies (Casey *et al.* 2000, March of Dimes 2010). Of interest, 42% of the total pregnancies reporting moderate to severe reductions in amniotic fluid were exposed to trastuzumab (13 of 33 total pregnancies reporting oligohydramnios). Among the pregnancies exposed to trastuzumab that resulted in stillbirths and live births, the apparent rate of oligohydramnios was 68.4% (13/19 pregnancies). The severity of oligohydramnios appeared to increase with continued exposure to trastuzumab; however, this condition also appeared to be reversible if administration of the agent was discontinued until birth (Azim *et al.* 2009).

Spontaneous preterm labor

Preterm birth (<37 weeks gestation) occurred for a majority of the patients administered chemotherapy during pregnancy evaluated in this monograph; these births include spontaneous and induced vaginal deliveries as well as Caesarean-section deliveries. Of these preterm births, spontaneous preterm labor did not appear to be the primary cause of preterm births (apparent rate of spontaneous preterm labor was 5.1%; 58/1138 pregnancies resulting in live births and stillbirths). As a point of comparison, the spontaneous preterm labor rate in the general population of the United States is approximately 8.4% (based on a preterm birth rate of 12% and an estimation that 70% of preterm births are caused by spontaneous preterm labor (Iams and Donovan 2011). Thus, spontaneous preterm labor does not appear to be associated with cancer chemotherapy use.

Newborn health issues

Small for gestational age infants: Small for gestational age (<10th percentile body weight for gestational age) was reported by the authors for 24 newborns out of 1097 liveborn infants evaluated in this monograph. It was not possible to compare the birth weights reported in the literature to a common growth scale due to the international nature of the patient population (e.g., differences in geographical location and ethnicity) as well as temporal differences (e.g., the data reviewed in the NTP monograph were collected from 1950-2012). Intrauterine fetal growth restriction was not always a predictor of a small for gestational age newborn. Intrauterine fetal growth restriction was observed in Intrauterine fetal growth restriction was observed in 36 of 1136 total conceptuses of stillbirths and live births evaluated in this monograph. However, only 2 fetuseswith intrauterine growth restriction yielded a small for gestational age newborn. It is possible that when the chemotherapy regime is discontinued 2 to 3 weeks prior to birth, the intrauterine growth rate has a chance to catch up.

Transient myelosuppression. Transient myelosuppression was reported in 50 of 1112 newborns gestationally exposed to cancer chemotherapy evaluated in this monograph. This myelosuppression generally resolved within the first 2 to 3 weeks of life; myelosuppression resolved without treatment in the majority of cases. It has been suggested that transient myelosuppression may be avoided if administration of cancer chemotherapy is halted three weeks prior to birth (Sorosky *et al.* 1997). The occurrence of myelosuppression at birth in the general population is not known, because complete blood counts are not regularly evaluated in healthy newborns (Christensen *et al.* 2009).

Fetal/neonatal cardiotoxicity. Some chemotherapeutic agents are known to induce cardiovascular complications in patients directly administered these drugs, such as anthracycline antibiotics (i.e., doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone) (reviewed in (Gziri *et al.* 2012)). The apparent rate of fetal/neonatal cardiotoxicity (e.g., arrhythmia, cardiomyopathy, tachycardia and heart failure) following gestational exposure to any cancer chemotherapy was 0.6% (7/1136 total conceptuses, including stillbirths and live born infants). These cases of cardiotoxicity did not appear to limited to one class of chemotherapeutic agents: 3 pregnancies were exposed to anthyracyclines in combination therapies {Baumgartner, 2009 #151;Garcia, 1999 #69;Okun, 1979 #691}, 3 pregnancies were exposed to all-trans retinoic acid {Harrison, 1994 #631;Leong, 2000 #252;Takitani, 2005 #525}, and the remaining pregnancy was exposed to cyclosphophamide and cisplatin {King, 1991 #137}. All-trans retinoic acid chemotherapy has also been reported to cause cardiotoxicity in cancer patient directly administered the drug {Roche, 2008 #968}. This overt cardiotoxicity appears to resolve at birth or following treatment shortly after birth as there was no evidence of congenital heart failure at follow-up evaluation of any of these 6 infants.

Newborn health issues associated with preterm birth

Many of the other health effects were reported in newborns exposed gestationally to cancer chemotherapy may have been due to the high incidence of preterm births among pregnant women

undergoing cancer chemotherapy, either by spontaneous or induced (vaginal or Casearian delivery). A birth is considered preterm when the infant is born at less than 37 weeks of gestation. In 2006, the Institute of Medicine issued a report that discusses the acute complications of preterm births in the general population (Institute of Medicine 2007). Complications often observed in preterm infants include: respiratory distress syndrome and other lung disorders (e.g., chronic lung disease), apnea, gastrointestinal disorders (e.g., necrotizing enterocolitis and gastroesophageal reflux), immune system disorders, cardiovascular problems (e.g., patent ductus arteriosus), anemia, hearing impairments, visual impairments, and central nervous system disorders (e.g., intraventricular hemorrhage and bleeding into the germinal matrix). The risk for developing these complications, as well as for the occurrence of neonatal/infant death, increases with decreasing gestational age at birth. Many of these complications were reported for preterm infants in the cases reviewed in the current NTP draft evaluation. Thus, the complications were likely due to prematurity rather than to exposure to cancer chemotherapeutic agents in the womb.

Growth and development of children

In addition to the possibility of the induction of grossly observable congenital malformations at birth, there is concern that other adverse health effects might be induced by exposure to cancer chemotherapy that may not become apparent until a later life stage. The detection of such effects would require monitoring the health of the exposed individuals into adulthood and, perhaps, throughout their lives. Areas of possible concern include physical growth, development of the central nervous system, reproductive system, vision, and hematopoietic system, as well as cardiotoxicity, cancer, and mutations in the germ cells.

In particular, exposure to cancer chemotherapy in the second and/third trimesters may cause functional deficits to several organs systems including the ear, eye, heart, nervous system, and reproductive system {Moore, 2003 #1216}. Of the studies reviewed in the NTP monograph, follow up data were available for 63% of the infants (703/1116 live born children) gestaionally exposed to cancer chemotherapy, and normal growth and development were reported for a majority of these children. For example, 97.2% of children exposed in utero to cyclophosphamide had normal growth and development at ages ranging from 6 months to 22 years old (their age at their last follow up evaluation; n=274/282 children) (Section 5.11.4, Appendix C Table 10). There was only one report of a child (a male twin) developing cancer following exposure to cancer chemotherapy; the mother was administered cyclophosphamide during the period of conception and throughout pregnancy, and his female twin had normal growth and development (Zemlickis *et al.* 1993).

While the results of follow up examinations are often reported for children exposed to chemotherapy in utero, most of these reports are limited to the first few months or years of life. For example, there were 100 children who were gestationally-exposed to cyclophosphamide for which individual age at follow-up evaluation was reported (Appendix C Table 10). Of these children, 42 children (42%) were less than 2 years of age at last reported follow-up evaluation, while 27 children (27%) were 2 to 4 years of age, 13 children (13%) were 5 to 12 years of age, 6 children were 12-16 years old, and 3% (3 children) were 18-22 years of age at last follow-up evaluation.

Limitations to the approach

There are a number of limitations to the NTP's interpretation of the published reports on pregnancy outcomes, mostly stemming from the necessity of relying on case reports or case series, which limit the ability to reach conclusions with confidence. Specific limitations include:

- **Lack of referent group**. Many studies did not have the pregnancy outcomes for a reference group of cancer patients who elected not to receive cancer chemotherapy during pregnancy as a more direct point of comparison for the patient population. Thus, the ability to conduct statistical analyses was limited. General population rates, when available, were provided as a point of reference to help interpret the NTP's examination of the compiled data.
- **Small number of cases for most chemotherapeutic agents.** In most instances, the number of cases treated with a single agent or common combination therapies was small. This limits the ability to reach conclusions with confidence or to conduct sub-analyses that clinicians and patients might find useful (e.g., assessments of health outcome stratified by cancer type and cancer chemotherapeutic agents/combination therapies). In addition, an estimated 113 cancer chemotherapeutic agents are currently in use (Perry 2008); however, published data were only identified for 52 agents.
- **Lack of long-term follow-up evaluations**. The types of major malformations that occur following first trimester exposure to chemotherapeutic agents relate to organogenesis and are often more easily detected at birth compared to morphological and/or functional deficits that may result from exposure in the second or third trimesters of pregnancy (Buekers and Lallas 1998). Thus, the lack of long-term assessment of these children is a barrier to more fully understanding the potential consequences of exposure that occur after the first trimester.
- **Publication bias**. It is possible that data based on case reports and case series may be influenced by publication bias as adverse pregnancy outcomes are more likely to be reported, while normal pregnancy outcomes may be less likely to be published.

Closing comments and Research Needs

The NTP recognizes that the decision on how to manage cancer during pregnancy is made on a case-by-case basis by the patient and her clinical team. The overall goal of this NTP monograph is to summarize the reports of effects of gestational exposure to cancer chemotherapy on pregnancy outcomes to serve as a resource for those discussions. The NTP Monograph examined the pregnancy outcomes literature for effects of any cancer chemotherapy exposure during pregnancy or by individual agent (administered singly or in combination) to evaluate possible trends in exposure to certain agents. Recent publications have also examined the pregnancy outcomes of common chemotherapy regimen on solid tumor and hematological cancers {Azim, 2010 #61}{Azim, 2010 #1057}. The appendix tables provided in the NTP monograph include the individual studies results that may also be mined to observe the pregnancy outcomes of common chemotherapy regimens. For example, there were 109 pregnant patients treated for breast cancer with 5-fluorouracil, doxorubicin, and cyclophosphamide summarized in Appendix C Table 1 (5-Fluorouracil). Similarly, there were 20 pregnant patient treated with 5-fluorouracil, epirubucin, and cyclophosphamide also summarized in Appendix C Table 1.

Broader participation in registries of cancer during pregnancy, prospective studies of the pregnancy outcomes of women receiving chemotherapy for cancer treatment, and studies evaluating the likelihood of late onset adverse health outcomes of the children exposed in utero to cancer chemotherapy are needed to more thoroughly assess the risks of gestational exposure to cancer chemotherapy. There are at least two registries of patients with cancer during pregnancy in the United States: Cooper University Hospital in Camden, New Jersey coordinated by Dr. Elyce Cardonick (www.cancerandpregnancy.com) and University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma coordinated by Dr. John Mulvihill. In addition, there are at least two registries for such patients outside of the United States: the Toronto Hospital of Sick Children in Ontario, Canada (www.MotherRisk.com) and the University of Frankfurt and German Breast Group

(http://www.germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft/english-summary-.html). There are also several ongoing clinical trials include prospective studies of pregnancy outcomes at institutions in the United States and internationally; some of the clinical trials are listed in NTP Monograph Appendix D.

This area of study may benefit from evaluating the pregnancy outcomes and long-term evaluations of gestationally exposed offspring of other populations exposed to cancer chemotherapy, including medical professionals who administer these agents as well as pregnant patients treated with cancer chemotherapeutic agents for other non-cancer medical conditions. Other non-cancerous medical conditions frequently treated with cancer chemotherapeutics include blood diseases (e.g., sickle cell anemia, essential thrombocythemia) {Thauvin-Robinet, 2001 #430} and autoimmune disorders (e.g., rheumatoid arthyritis and systemic lupus erythematosus) {Ebert, 1997 #220}{Lloyd, 1999 #902}.

Ultimately, these data on pregnancy outcomes and development of children exposed in utero to cancer chemotherapy will be useful in the development and continued improvement of consensus guidelines for the diagnosis, staging, and treatment of cancer of pregnant women. International consensus guidelines have been developed for the diagnosis, staging, and treatment of cancer of pregnant women for some of these cancers: breast cancer (Loibl *et al.* 2006), (Amant *et al.* 2010), cervical cancer (Morice *et al.* 2009), and gynecological cancers (Amant *et al.* 2009). Consensus guidelines have yet to be developed for the hematological cancers and melanoma among more frequently diagnosed cancers in pregnant patients.

9.0 References

AAP Pharmaceuticals. 2010. Mitoxantrone. *http://www.drugs.com/pro/mitoxantrone.html?printable=1* (accessed 08/16/2011).

Abellar RG, Pepperell JR, Greco D, Gundogan F, Kostadinov S, Schwartz J, Tantravahi U, De Paepe ME. 2009. Effects of chemotherapy during pregnancy on the placenta. Pediatr Dev Pathol 12(1): 35-41.

Abramovici A, Shaklai M, Pinkhas J. 1978. Myeloschisis in a six weeks embryo of a leukemic woman treated by busulfan. Teratology 18(2): 241-246.

Achtari C, Hohlfeld P. 2000. Cardiotoxic transplacental effect of idarubicin administered during the second trimester of pregnancy. American journal of obstetrics and gynecology 183(2): 511-512.

Addar MH. 2004. Methotrexate embryopathy in a surviving intrauterine fetus after presumed diagnosis of ectopic pregnancy: case report. J Obstet Gynaecol Can 26(11): 1001-1003.

Aige-Gil V, Simkiss K. 1991. Sterilisation of avian embryos with busulphan. Research in veterinary science 50(2): 139-144.

Al-Saleh E, Al-Harmi J, Al-Rashdan I, Al-Shammari M, Nandakumaran M. 2007. Maternal-fetal transport kinetics of methotrexate in perfused human placenta: in vitro study. J Matern Fetal Neonatal Med 20(5): 411-418.

Al Bahar S, Pandita R, Nath SV. 2004. Pregnancy in chronic myeloid leukemia patients treated with alpha interferon. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 85(3): 281-282.

Ali R, Ozkalemkas F, Ozcelik T, Ozkocaman V, Ozan U, Kimya Y, Tunali A. 2003. Maternal and fetal outcomes in pregnancy complicated with acute leukemia: a single institutional experience with 10 pregnancies at 16 years. Leukemia research 27(5): 381-385.

Ali R, Ozkalemkas F, Kimya Y, Koksal N, Ozkan H, Ozkocaman V, Hoyrazli A, Cetinkaya M, Tunali A. 2009. Acute leukemia and pregnancy. Leukemia research 33(3): e26-28.

Ali R, Ozkalemkas F, Kimya Y, Koksal N, Ozkocaman V, Gulten T, Yorulmaz H, Tunali A. 2009. Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Archives of gynecology and obstetrics 280(2): 169-175.

Ali SA, Gupta S, Sehgal R, Vogel V. 2012. Survival outcomes in pregnancy associated breast cancer: a retrospective case control study. The breast journal 18(2): 139-144.

AlKindi S, Dennison D, Pathare A. 2005. Imatinib in pregnancy. Eur J Haematol 74(6): 535-537.

Allen DG, Planner RS, Tang PT, Scurry JP, Weerasin T. 1995. Invasive Cervical Cancer in Pregnancy. Aust N Z J Obstet Gynecol 35: 408-412.

Amant F, Van Calsteren K, Halaska MJ, Beijnen J, Lagae L, Hanssens M, Heyns L, Lannoo L, Ottevanger NP, Vanden Bogaert W, Ungar L, Vergote I, du Bois A. 2009. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. Int J Gynecol Cancer 19 Suppl 1: S1-12.

Amant F, Van Calsteren K, Halaska MJ, Gziri MM, Hui W, Lagae L, Willemsen MA, Kapusta L, Van Calster B, Wouters H, Heyns L, Han SN, Tomek V, Mertens L, Ottevanger PB. 2012. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. The lancet oncology 13(3): 256-264.

Amant F, Deckers S, Van Calsteren K, Loibl S, Halaska M, Brepoels L, Beijnen J, Cardoso F, Gentilini O, Lagae L, Mir O, Neven P, Ottevanger N, Pans S, Peccatori F, Rouzier R, Senn HJ, Struikmans H, Christiaens MR, Cameron D, Du Bois A. 2010. Breast cancer in pregnancy: Recommendations of an international consensus meeting. European journal of cancer (Oxford, England : 1990).

Amato D, Niblett JS. 1977. Neutropenia from cyclophosphamide in breast milk. The Medical journal of Australia 1(11): 383-384.

American Academy of Pediatrics. 2001. Transfer of drugs and other chemicals into human milk. Pediatrics 108(3): 776-789.

Anderson C. 2008. Systemic Therapy for Advanced Melanoma (Chapter 30). In The Chemotherapy Source Book, Fourth Edition. Perry M, ed. Philadelphia, PA: Lippincott, Williams, and Wilkins. 305-310.

Andreadis C, Charalampidou M, Diamantopoulos N, Chouchos N, Mouratidou D. 2004. Combined chemotherapy and radiotherapy during conception and first two trimesters of gestation in a woman with metastatic breast cancer. Gynecologic oncology 95(1): 252-255.

Antonelli NM, Dotters DJ, Katz VL, Kuller JA. 1996. Cancer in pregnancy: A review of the literature. Part I. Obstetrical and Gynecological Survey 51(2): 125-134.

APP Pharmaceuticals. 2010. Mitoxantrone hydrochloride product information. APP Pharmaceuticals LLC, Schaumburg, Illinois, (http://www.drugs.com/pro/mitoxantrone.html?printable=1, accessed on August 16, 2011).

Apperley J. 2009. Issues of imatinib and pregnancy outcome. J Natl Compr Canc Netw 7(10): 1050-1058.

Arango HA, Kalter CS, Decesare SL, Fiorica JV, Lyman GH, Spellacy WN. 1994. Management of chemotherapy in a pregnancy complicated by a large neuroblastoma. Obstet Gynecol 84(4 Pt 2): 665-668.

Armitage JO, Feagler JR, Skoog DP. 1977. Burkitt lymphoma during pregnancy with bilateral breast involvement. Jama 237(2): 151.

Artlich A, Moller J, Tschakaloff A, Schwinger E, Kruse K, Gortner L. 1994. Teratogenic effects in a case of maternal treatment for acute myelocytic leukaemia--neonatal and infantile course. Eur J Pediatr 153(7): 488-491.

Au-Yong R, Collins P, Young J. 1972. Acute Myeloblastic Leukaemia during Pregnancy. British medical journal 4(5838): 493.

Auger N, Giraud J, Daniel M. 2009. The joint influence of area income, income inequality, and immigrant density on adverse birth outcomes: a population-based study. BMC Public Health 9: 237.

Ault P, Kantarjian H, O'Brien S, Faderl S, Beran M, Rios MB, Koller C, Giles F, Keating M, Talpaz M, Cortes J. 2006. Pregnancy among patients with chronic myeloid leukemia treated with imatinib. J Clin Oncol 24(7): 1204-1208.

Aviles A, Niz J. 1988. Long-term follow-up of children born to mothers with acute leukemia during pregnancy. Medical and pediatric oncology 16(1): 3-6.

Aviles A, Diaz-Maqueo JC, Torras V, Garcia EL, Guzman R. 1990. Non-Hodgkin's lymphomas and pregnancy: presentation of 16 cases. Gynecologic oncology 37(3): 335-337.

Aviles A, Diaz-Maqueo JC, Talavera A, Guzman R, Garcia EL. 1991. Growth and development of children of mothers treated with chemotherapy during pregnancy: current status of 43 children. American journal of hematology 36(4): 243-248.

Aviles A, Neri N. 2001. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. Clin Lymphoma 2(3): 173-177.

Aviles A, Neri N, Nambo MJ. 2006. Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. Ann Oncol 17(2): 286-288.

Awidi AS, Tarawneh MS, Shubair KS, Issa AA, Dajani YF. 1983. Acute leukemia in pregnancy: report of five cases treated with a combination which included a low dose of adriamycin. European journal of cancer & clinical oncology 19(7): 881-884.

Azim HA, Jr., Peccatori FA, Scarfone G, Acaia B, Rossi P, Cascio R, Goldhirsch A. 2008. Anthracyclines for gestational breast cancer: course and outcome of pregnancy. Ann Oncol 19(8): 1511-1512.

Azim HA, Jr., Del Mastro L, Scarfone G, Peccatori FA. 2010. Treatment of breast cancer during pregnancy: Regimen selection, pregnancy monitoring and more. Breast (Edinburgh, Scotland).

Azim Jr HA, Botteri E, Renne G, Dell'orto P, Rotmensz N, Gentilini O, Sangalli C, Pruneri G, Di Nubila B, Locatelli M, Sotiriou C, Piccart M, Goldhirsch A, Viale G, Peccatori FA. 2011. The biological features and prognosis of breast cancer diagnosed during pregnancy: A case-control study. Acta oncologica.

Azuno Y, Kaku K, Fujita N, Okubo M, Kaneko T, Matsumoto N. 1995. Mitoxantrone and etoposide in breast milk. American journal of hematology 48(2): 131-132.

Bader AA, Petru E, Winter R. 2007. Long-term follow-up after neoadjuvant chemotherapy for high-risk cervical cancer during pregnancy. Gynecologic oncology 105(1): 269-272.

Bader AA, Schlembach D, Tamussino KF, Pristauz G, Petru E. 2007. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. The lancet oncology 8(1): 79-81.

Baer MR, Ozer H, Foon KA. 1992. Interferon-a therapy during pregnancy

in chronic myelogenous leukaemia and hairy cell leukaemia. british Journal of Haematology 81: 167-169.

Baltzer J, Regenbrecht ME, Kopcke W, Zander J. 1990. Carcinoma of the cervix and pregnancy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 31(4): 317-323.

Barni S, Ardizzoia A, Zanetta G, Strocchi E, Lissoni P, Tancini G. 1992. Weekly doxorubicin chemotherapy for breast cancer in pregnancy. A case report. Tumori 78(5): 349-350.

Barry RM, Diamond HD, Craver LF. 1962. Influence of pregnancy on the course of Hodgkin's disease. American journal of obstetrics and gynecology 84: 445-454.

Bartsch HH, Meyer D, Teichmann AT, Speer Ch P. 1988. Treatment of promyelocytic leukemia during pregnancy. A case report and review of the literature. Blut 57(1): 51-54.

Bartz D, Goldberg A. 2009. Medication abortion. Clinical obstetrics and gynecology 52(2): 140-150.

Baumgartner AK, Oberhoffer R, Jacobs VR, Ostermayer E, Menzel H, Voigt M, Schneider KT, Pildner von Steinburg S. 2009. Reversible foetal cerebral ventriculomegaly and cardiomyopathy under chemotherapy for maternal AML. Onkologie 32(1-2): 40-43.

Bawle EV, Conard JV, Weiss L. 1998. Adult and two children with fetal methotrexate syndrome. Teratology 57(2): 51-55.

Baxter. 2009. Cyclophosphamide.

Bayhan G, Aban M, Yayla M, Gul T, Yaldiz M, Erden AC. 1999. Cis-platinum combination chemotherapy during pregnancy for mucinous cystadenocarcinoma of the ovary. Case report. European journal of gynaecological oncology 20(3): 231-232.

Beadle BM, Woodward WA, Middleton LP, Tereffe W, Strom EA, Litton JK, Meric-Bernstam F, Theriault RL, Buchholz TA, Perkins GH. 2009. The impact of pregnancy on breast cancer outcomes in women<or=35 years. Cancer 115(6): 1174-1184.

Beale JM, Tuohy J, McDowell SJ. 2009. Herceptin (trastuzumab) therapy in a twin pregnancy with associated oligohydramnios. American journal of obstetrics and gynecology 201(1): e13-14.

Bedford. 2008. CERUBIDINE (Daunorubicin HCl) FOR INJECTION product label. Bedford Laboratories, Bedford, Ohio.

Bedford Laboratories. 2004. Carboplatin

Bedford Laboratories. 2007. Dacarbazine Product Insert.

Behtash N, Karimi Zarchi M, Modares Gilani M, Ghaemmaghami F, Mousavi A, Ghotbizadeh F. 2008. Ovarian carcinoma associated with pregnancy: A clinicopathologic analysis of 23 cases and review of the literature. BMC Pregnancy and Childbirth 8.

Bekisz J, Schmeisser H, Hernandez J, Goldman ND, Zoon KC. 2004. Human interferons alpha, beta and omega. Growth factors (Chur, Switzerland) 22(4): 243-251.

Ben-Baruch G, Menczer J, Goshen R, Kaufman B, Gorodetsky R. 1992. Cisplatin excretion in human milk. Journal of the National Cancer Institute 84(6): 451-452.

Ben Venue Laboratories. 2001. VinBLAStine Sulfate for Injection USP. Ben Venue Laboratories, Bedford, OH 44146.

Benjapibal M, Chaopotong P, Leelaphatanadit C, Jaishuen A. 2010. Ruptured ovarian endodermal sinus tumor diagnosed during pregnancy: case report and review of the literature. The journal of obstetrics and gynaecology research 36(5): 1137-1141.

Berger JC, Clericuzio CL. 2008. Pierre Robin sequence associated with first trimester fetal tamoxifen exposure. Am J Med Genet A 146A(16): 2141-2144.

Bergstrom SK, Altman AJ. 1998. Pregnancy during therapy for childhood acute lymphoblastic leukemia: two case reports and a review of the literature. J Pediatr Hematol Oncol 20(2): 154-159.

Berrebi A, Schattner A, Mogilner BM. 1983. Disseminated Burkitt's lymphoma during pregnancy. Acta Haematol 70(2): 139-140.

Berry DL, Theriault RL, Holmes FA, Parisi VM, Booser DJ, Singletary SE, Buzdar AU, Hortobagyi GN. 1999. Management of breast cancer during pregnancy using a standardized protocol. J Clin Oncol 17(3): 855-861.

Berveiller P, Mir O, Sauvanet E, Antoine EC, Goldwasser F. 2008. Ectopic pregnancy in a breast cancer patient receiving trastuzumab. Reproductive toxicology (Elmsford, N.Y 25(2): 286-288.

Bienengraber V, Malek F, Fanghanel J, Kundt G. 1999. Disturbances of palatogenesis and their prophylaxis in animal experiments. Ann Anat 181(1): 111-115.

Biener DM, Gossing G, Kuehnl A, Cremer M, Dudenhausen JW. 2009. Diagnosis and treatment of maternal acute myeloid leukemia during pregnancy imitating HELLP syndrome. Journal of perinatal medicine 37(6): 713-714.

Bierman P, Armitage J. 2008. Non-Hodgkin's Lymphoma (Chapter 43). In The Chemotherapy Source Book, Fourth Edition. Perry M, ed. Philadelphia, PA: Lippincott, Williams, and Wilkins. 518-533.

BioPharma P. 2007. Busulfex (busulfan) Injection.

Bladstrom A, Anderson H, Olsson H. 2003. Worse survival in breast cancer among women with recent childbirth: results from a Swedish population-based register study. Clin Breast Cancer 4(4): 280-285.

Blatt J, Mulvihill JJ, Ziegler JL, Young RC, Poplack DG. 1980. Pregnancy outcome following cancer chemotherapy. The American journal of medicine 69(6): 828-832.

Boggs DR, Wintrobe MM, Cartwright GE. 1962. The acute leukemias. Analysis of 322 cases and review of the literature. Medicine 41: 163-225.

Boike GM, Deppe G, Young JD, Malone JM, Jr., Malviya VK, Sokol RJ. 1989. Chemotherapy in a pregnant rat model. 2.5-fluorouracil: nonlinear kinetics and placental transfer. Gynecologic oncology 34(2): 191-194.

Boland J. 1951. Clinical experience with nitrogen mustard in Hodgkin's disease. The British journal of radiology 24(285): 513-515.

Bonnier P, Romain S, Dilhuydy JM, Bonichon F, Julien JP, Charpin C, Lejeune C, Martin PM, Piana L. 1997. Influence of pregnancy on the outcome of breast cancer: a case-control study. Societe Francaise de Senologie et de Pathologie Mammaire Study Group. Int J Cancer 72(5): 720-727.

Boros SJ, Reynolds JW. 1977. Intrauterine growth retardation following third-trimester exposure to busulfan. American journal of obstetrics and gynecology 129(1): 111-112.

Bowen RA, Olson PN, Young S, Withrow SJ. 1988. Efficacy and toxicity of tamoxifen citrate for prevention and termination of pregnancy in bitches. American journal of veterinary research 49(1): 27-31.

Boyd A, Cowie V, Gourley C. 2009. The use of cisplatin to treat advanced-stage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a case and review of the literature. Int J Gynecol Cancer 19(2): 273-276.

Briggs GG, Freeman RK, Yaffe SJ. 2008. A Reference guide to drugs in Pregnancy and Lactation, Eighth Edition. Lippincott Williams & Wilkins.

Bristol-Myers-Squibb. 2010. Hydrea (hydroxyurea capsules, USP) prescribing information. Bristol-Myers Squibb Company, Princeton, New Jersey. (http://packageinserts.bms.com/pi/pi_hydrea.pdf, accessed pm November 23, 2010.)

Bristol-Myers Squibb. 2010. TAXOL® (paclitaxel) INJECTION full product label. Bristol-Myers Squibb Company

Princeton, NJ 08543 USA.

Bristol-Myers Squibb. 2010. Platinol (cisplatin for injection, USP) product information. Bristol-Myers Squibb Company, Princeton, New Jersey. May 2010. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018057s079lbl.pdf; accessed on May 25, 2011)

Bristol-Myers Squibb. 2010. Blenoxane® (bleomycin sulfate) INJECTION full product label. Bristol-Myers Squibb Company

Princeton, NJ 08543 USA.

Bristol-Myers Squibb. 2011. Etopophos (etoposide phosphate) for Injection product information. . Bristol-Myers Squibb Company, Princeton, NJ.

Brudie LA, Ahmad S, Radi MJ, Finkler NJ. 2011. Metastatic choriocarcinoma in a viable intrauterine pregnancy treated with EMA-CO in the third trimester: a case report. The Journal of reproductive medicine 56(7-8): 359-363.

Brunel P, Renault J, Guitin P, Lerman S, Clark R, Nohynek G. 1995. Reproductive and developmental toxicity studies of a novel anticancer, Docetaxel. Teratology 51: 21A.

Buekers TE, Lallas TA. 1998. Chemotherapy in pregnancy. Obstetrics and gynecology clinics of North America 25(2): 323-329.

Buller RE, Darrow V, Manetta A, Porto M, DiSaia PJ. 1992. Conservative surgical management of dysgerminoma concomitant with pregnancy. Obstet Gynecol 79(5 (Pt 2)): 887-890.

Caligiuri MA, Mayer RJ. 1989. Pregnancy and leukemia. Seminars in oncology 16(5): 388-396.

Cantini E, Yanes B. 1984. Acute myelogenous leukemia in pregnancy. Southern medical journal 77(8): 1050-1052.

Cardonick E, Usmani A, Ghaffar S. 2010. Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. Am J Clin Oncol 33(3): 221-228.

Carradice D, Austin N, Bayston K, Ganly PS. 2002. Successful treatment of acute promyelocytic leukaemia during pregnancy. Clinical and laboratory haematology 24(5): 307-311.

Catanzarite VA, Ferguson JE, 2nd. 1984. Acute leukemia and pregnancy: a review of management and outcome, 1972-1982. Obstetrical & gynecological survey 39(11): 663-678.

Chakravarty EF, Murray ER, Kelman A, Farmer P. 2011. Pregnancy outcomes following maternal exposure to rituximab. Blood.

Chalas E, Valea FA. 1996. Malignancies diagnosed in pregnancy. Primary Care Update for Ob/Gyns 3(2): 69-74.

Chard T. 1989. Interferon in pregnancy. Journal of Developmental Physiology 11(5): 271-276.

Chaube S, Kreis W, Uchida K, Murphy ML. 1968. The teratogenic effects of the recent drugs active in cancer chemotherapy. 3: 181-237.

Chaube S, Murphy ML. 1969. Fetal malformations produced in rats by N-isopropyl-alpha-(2-methylhydrazino)-p-toluamide hydrochloride (procarbazine). Teratology 2(1): 23-31.

Chaube S. 1973. Protective effects of thymidine, 5-aminoimidazolecarboxamide, and riboflavin against fetal abnormalities produced in rats by 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide. Cancer research 33(10): 2231-2240.

Chelghoum Y, Vey N, Raffoux E, Huguet F, Pigneux A, Witz B, Pautas C, de Botton S, Guyotat D, Lioure B, Fegueux N, Garban F, Saad H, Thomas X. 2005. Acute leukemia during pregnancy: a report on 37 patients and a review of the literature. Cancer 104(1): 110-117.

Cheung CY. 2004. Vascular endothelial growth factor activation of intramembranous absorption: a critical pathway for amniotic fluid volume regulation. Journal of the Society for Gynecologic Investigation 11(2): 63-74.

Choudhary DR, Mishra P, Kumar R, Mahapatra M, Choudhry VP. 2006. Pregnancy on imatinib: fatal outcome with meningocele. Ann Oncol 17(1): 178-179.

Claahsen HL, Semmekrot BA, van Dongen PW, Mattijssen V. 1998. Successful fetal outcome after exposure to idarubicin and cytosine-arabinoside during the second trimester of pregnancy--a case report. Am J Perinatol 15(5): 295-297.

Cohlan SQ, Kitay D. 1965. The Teratogenic Effect of Vincaleukoblastine in the Pregnant Rat. The Journal of pediatrics 66: 541-544.

Colbourn DS, Nathanson L, Belilos E. 1989. Pregnancy and malignant melanoma. Seminars in oncology 16(5): 377-387.

Connor TH, McDiarmid MA. 2006. Preventing occupational exposures to antineoplastic drugs in health care settings. CA: a cancer journal for clinicians 56(6): 354-365.

Connor TH, DeBord DG, Pretty JR, Oliver MS, Roth TS, Lees PS, Krieg EF, Jr., Rogers B, Escalante CP, Toennis CA, Clark JC, Johnson BC, McDiarmid MA. 2010. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. J Occup Environ Med 52(10): 1019-1027.

Corapcioglu F, Dillioglugil O, Sarper N, Akansel G, Caliskan M, Arisoy AE. 2004. Spinal cord compression and lung metastasis of Wilms' tumor in a pregnant adolescent. Urology 64(4): 807-810.

Cordeiro A, Machado AI, Borges A, Alves MJ, Frade MJ. 2009. Burkitt's lymphoma related to Epstein-Barr virus infection during pregnancy. Archives of gynecology and obstetrics 280(2): 297-300.

Cordoba O, Llurba E, Cortes J, Sabadell MD, Lirola JL, Ferrer Q, Xercavins J. 2010. Complete pathological remission in a patient with hormone-receptor positive and c-erbB-2 expression-negative breast cancer treated with FAC chemotherapy during pregnancy. Tumori 96(4): 629-632.

Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. 2007. Reporting birth defects surveillance data 1968-2003. Birth defects research 79(2): 65-186.

Cortes J, O'Brien SG, Ault P, Borthakur G, al e. 2008. Pregnancy Outcomes among patients with Chronic Myeloid Leukemia Treated with Dasatinib. Blood (ASH Annual Meeting Abstracts) 112(Abstract #3230).

Coulam CB, Moyer TP, Jiang NS, Zincke H. 1982. Breast-feeding after renal transplantation. Transplant Proc 14(3): 605-609.

Courtney KD, Valerio DA. 1968. Teratology in the Macaca mulatta. Teratology 1(2): 163-172.

Cullins SL, Pridjian G, Sutherland CM. 1994. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. Jama 271(24): 1905-1906.

Cuvier C, Espie M, Extra JM, Marty M. 1997. Vinorelbine in pregnancy. Eur J Cancer 33(1): 168-169.

Cybulsky AV, Goodyer PR, McTavish AJ. 1994. Epidermal growth factor receptor activation in developing rat kidney. The American journal of physiology 267(3 Pt 2): F428-436.

D'Emilio A, Dragone P, De Negri G, Montaldi A, Stella M, Battista R. 1989. Acute myelogenous leukemia in pregnancy. Haematologica 74(6): 601-604.

D'Incalci M, Sessa C, Colombo N, de Palo G, Semprini AE, Pardi G. 1982. Transplacental passage of cyclophosphamide. Cancer treatment reports 66(8): 1681-1682.

d'Incalci M, Broggini M, Buscaglia M, Pardi G. 1983. Transplacental passage of doxorubicin. Lancet 1(8314-5): 75.

Dagg CP. 1960. Sensitive stages for the production of developmental abnormalities in mice with 5-fluorouracil. The American journal of anatomy 106: 89-96.

Dagg CP, Doerr A, Offutt C. 1966. Incorporation of 5-fluorouracil-2-C-14 by mouse embryos. Biol Neonat 10(1): 32-46.

Daly H, McCann SR, Hanratty TD, Temperley IJ. 1980. Successful pregnancy during combination chemotherapy for Hodgkin's disease. Acta Haematologica 64(3): 154-156.

Dara P, Slater LM, Armentrout SA. 1981. Successful pregnancy during chemotherapy for acute leukemia. Cancer 47(5): 845-846.

de Boer NK, Van Elburg RM, Wilhelm AJ, Remmink AJ, Van Vugt JM, Mulder CJ, Van Bodegraven AA. 2005. 6-Thioguanine for Crohn's disease during pregnancy: thiopurine metabolite measurements in both mother and child. Scandinavian journal of gastroenterology 40(11): 1374-1377.

De Carolis S, Grimolizzi F, Garofalo S, Fatigante G, Ferrazzani S, Carducci B, Caruso A. 2006. Cancer in pregnancy: Results of a series of 32 patients. Anticancer Res 26(3 B): 2413-2418.

de Vries EG, van der Zee AG, Uges DR, Sleijfer DT. 1989. Excretion of platinum into breast milk. Lancet 1(8636): 497.

Decker M, Rothermundt C, Hollander G, Tichelli A, Rochlitz C. 2006. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. The lancet oncology 7(8): 693-694.

Deininger M, Buchdunger E, Druker BJ. 2005. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood 105(7): 2640-2653.

Delgado-Lamas JL, Garces-Ruiz OM. 2000. Malignancy: Case Report: Acute Promyelocytic Leukemia in Late Pregnancy. Successful Treatment with All-Trans-Retinoic Acid (ATRA) and Chemotherapy. Hematology (Amsterdam, Netherlands) 4(5): 415-418.

Delmer A, Rio B, Bauduer F, Ajchenbaum F, Marie JP, Zittoun R. 1992. Pregnancy during myelosuppressive treatment for chronic myelogenous leukemia. Br J Haematol 82(4): 783-784.

Demyer W. 1964. Vinblastine-Induced Malformations of Face and Nervous System in Two Rat Strains. Neurology 14: 806-808.

DeSesso JM, Goeringer GC. 1990. The nature of the embryo-protective interaction of propyl gallate with hydroxyurea. Reproductive toxicology (Elmsford, N.Y 4(2): 145-152.

DeSesso JM, Goeringer GC. 1992. Methotrexate-induced developmental toxicity in rabbits is ameliorated by 1-(p-tosyl)-3,4,4-trimethylimidazolidine, a functional analog for tetrahydrofolate-mediated one-carbon transfer. Teratology 45(3): 271-283.

Deshaies I, Cherenfant J, Gusani NJ, Jiang Y, Harvey HA, Kimchi ET, Kaifi JT, Staveley-O'Carroll KF. 2010. Gastrointestinal stromal tumor (GIST) recurrence following surgery: review of the clinical utility of imatinib treatment. Therapeutics and clinical risk management 6: 453-458.

Deuschle KW, Wiggins WS. 1953. The use of nitrogen mustard in the management of two pregnant lymphoma patients. Blood 8(6): 576-579.

Dgani R, Shoham Z, Atar E, Zosmer A, Lancet M. 1989. Ovarian carcinoma during pregnancy: a study of 23 cases in Israel between the years 1960 and 1984. Gynecologic oncology 33(3): 326-331.

Diamond I, Anderson MM, McCreadie SR. 1960. Transplacental transmission of busulfan (myleran) in a mother with leukemia. Production of fetal malformation and cytomegaly. Pediatrics 25: 85-90.

Dilek I, Topcu N, Demir C, Bay A, Uzun K, Gul A, Faik Oner A, Ugras S. 2006. Hematological malignancy and pregnancy: a single-institution experience of 21 cases. Clinical and laboratory haematology 28(3): 170-176.

Dolai TK, Bhargava R, Mahapatra M, Mishra P, Seth T, Pati HP, Saxena R. 2009. Is imatinib safe during pregnancy? Leukemia research 33(4): 572-573.

Doll DC, Ringenberg QS, Yarbro JW. 1988. Management of cancer during pregnancy. Arch Intern Med 148:2058-2064,1988 Tax - Homo Sapiens.

Doll DC, Ringenberg QS, Yarbro JW. 1989. Antineoplastic agents and pregnancy. Seminars in oncology 16(5): 337-346.

Doney KC, Kraemer KG, Shepard TH. 1979. Combination chemotherapy for acute myelocytic leukemia during pregnancy: three case reports. Cancer treatment reports 63(3): 369-371.

Dranitsaris G, Johnston M, Poirier S, Schueller T, Milliken D, Green E, Zanke B. 2005. Are health care providers who work with cancer drugs at an increased risk for toxic events? A systematic review and meta-analysis of the literature. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners 11(2): 69-78.

Dreicer R, Love RR. 1991. High total dose 5-fluorouracil treatment during pregnancy. Wis Med J 90(10): 582-583.

Duggan B, Muderspach LI, Roman LD, Curtin JP, d'Ablaing G, 3rd, Morrow CP. 1993. Cervical cancer in pregnancy: reporting on planned delay in therapy. Obstet Gynecol 82(4 Pt 1): 598-602.

Durodola JI. 1979. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. Journal of the National Medical Association 71(2): 165-166.

Earll JM, May RL. 1965. Busulfan Therapy of Myelocytic Leukemia During Pregnancy. American journal of obstetrics and gynecology 92: 580-581.

Ebert U, Loffler H, Kirch W. 1997. Cytotoxic therapy and pregnancy. Pharmacology & therapeutics 74(2): 207-220.

Eedarapalli P, Biswas N, Coleman M. 2007. Epirubicin for breast cancer during pregnancy: a case report. J Reprod Med 52(8): 730-732.

Egan PC, Costanza ME, Dodion P, Egorin MJ, Bachur NR. 1985. Doxorubicin and cisplatin excretion into human milk. Cancer treatment reports 69(12): 1387-1389.

Egberts F, Lischner S, Russo P, Kampen WU, Hauschild A. 2006. Diagnostic and therapeutic procedures for management of melanoma during pregnancy: Risks for the fetus? Case report and review of the literature. Diagnostische und therapeutische maÃŸnahmen in der behandlung des malignen melanoms wÃ¤hrend der schwangerschaft: Risiko fÃ¼r den fetus? Fallbericht und literatur-Ã¼berblick 4(9): 717-720.

Elis J, DiPaolo JA. 1970. The alteration of actinomycin D teratogenicity by hormones and nucleic acids. Teratology 3(1): 33-38.

Elit L, Bocking A, Kenyon C, Natale R. 1999. An endodermal sinus tumor diagnosed in pregnancy: Case report and review of the literature. Gynecologic oncology 72(1): 123-127.

Endo A, Sakai N, Ohwada K. 1987. Analysis of diurnal difference in teratogen (Ara-C) susceptibility in mouse embryos by a progressive phase-shift method. Teratogenesis, carcinogenesis, and mutagenesis 7(5): 475-482.

Fadilah SA, Leong CF, Jamil MY, Cheong SK, Rozilaila R. 2006. Pregnancy complicated by Hodgkin's disease. Med J Malaysia 61(3): 358-360.

Fanale MA, Uyei AR, Theriault RL, Adam K, Thompson RA. 2005. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. Clin Breast Cancer 6(4): 354-356.

Fantel AG, Shepard TH, Newell-Morris LL, Moffett BC. 1977. Teratogenic effects of retinoic acid in pigtail monkeys (Macaca nemestrina). I. General features. Teratology 15(1): 65-71.

Fassas A, Kartalis G, Klearchou N, Tsatalas K, Sinacos Z, Mantalenakis S. 1984. Chemotherapy for acute leukemia during pregnancy. Five case reports. Nouv Rev Fr Hematol 26(1): 19-24.

Feliu J, Juarez S, Ordonez A, Garcia-Paredes ML, Gonzalez-Baron M, Montero JM. 1988. Acute leukemia and pregnancy. Cancer 61(3): 580-584.

Ferm VH. 1963. Congenital malformations in hamster embryos after treatment with vinblastine and vincristine. Science (New York, N.Y 141: 426.

Ferm VH. 1966. Severe developmental malformations. . Arch Path 81: 174-177.

Fernandez H, Diallo A, Baume D, Papiernik E. 1989. Anhydramnios and cessation of fetal growth in a pregnant mother with polychemotherapy during the second trimester. Prenat Diagn 9(9): 681-682.

Ferrantini M, Capone I, Belardelli F. 2007. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. Biochimie 89(6-7): 884-893.

Fogliatto L, Brum C. 2005. Pregnancy during Treatment with Imatinib: A Case Report. ABSTRACT from ASH Annual Meeting

Freedman HL, Magagnini A, Glass M. 1962. Pregnancies following chemically treated choriocarcinoma. American journal of obstetrics and gynecology 83: 1637-1641.

Friedrichs B, Tiemann M, Salwender H, Verpoort K, Wenger MK, Schmitz N. 2006. The effects of rituximab treatment during pregnancy on a neonate. Haematologica 91(10): 1426-1427.

Fritz H, Hess R. 1971. Effects of cyclophosphamide on embryonic development in the rabbit. Agents and actions 2(2): 83-86.

Fritz H, Hess R. 1980. Effects of hydroxyurea on postnatal growth and behaviour of rats. Agents and actions 10(4): 389-393.

Furr BJ, Jordan VC. 1984. The pharmacology and clinical uses of tamoxifen. Pharmacology & therapeutics 25(2): 127-205.

Gambacorti-Passerini CB, Tornaghi L, Marangon E, Franceschino A, Pogliani EM, D'Incalci M, Zucchetti M. 2007. Imatinib concentrations in human milk. Blood 109(4): 1790.

Gambino A, Gorio A, Carrara L, Agoni L, Franzini R, Lupi GP, Maggino T, Romagnolo C, Sartori E, Pecorelli S. 2011. Cancer in pregnancy: maternal and fetal implications on decision-making. European journal of gynaecological oncology 32(1): 40-45.

Ganzitti L, Fachechi G, Driul L, Marchesoni D. 2010. Acute promyelocytic leukemia during pregnancy. Fertility and sterility 94(6): 2330.e2335-2336.

Garber JE. 1989. Long-term follow-up of children exposed in utero to antineoplastic agents. Seminars in oncology 16(5): 437-444.

Garcia-Gonzalez J, Cueva J, Lamas MJ, Curiel T, Grana B, Lopez-Lopez R. 2008. Paclitaxel and cisplatin in the treatment of metastatic non-small-cell lung cancer during pregnancy. Clin Transl Oncol 10(6): 375-376.

Garcia-Manero M, Royo MP, Espinos J, Pina L, Alcazar JL, Lopez G. 2009. Pregnancy associated breast cancer. Eur J Surg Oncol 35(2): 215-218.

Garcia L, Valcarcel M, Santiago-Borrero PJ. 1999. Chemotherapy during pregnancy and its effects on the fetus-- neonatal myelosuppression: two case reports. J Perinatol 19(3): 230-233.

Gardiner SJ, Gearry RB, Roberts RL, Zhang M, Barclay ML, Begg EJ. 2006. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. British journal of clinical pharmacology 62(4): 453-456.

Garrett MJ. 1974. Teratogenic effects of combination chemotherapy. Annals of internal medicine 80(5): 667.

Gelb AB, van de Rijn M, Warnke RA, Kamel OW. 1996. Pregnancy-associated lymphomas. A clinicopathologic study. Cancer 78(2): 304-310.

Genentech. 2010. Herceptin product information. Genentech, Inc., South San Francisco, CA. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s105256lbl.pdf; accessed on May 103730, 102011).

Genentech. 2011. Rituzan (Rituzimab) product information. Genentech, Inc., South San Francisco, CA. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103705s105344lbl.pdf; accessed on August 103704, 102011).

Germann N, Goffinet F, Goldwasser F. 2004. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. Ann Oncol 15(1): 146-150.

Germann N, Haie-Meder C, Morice P, Lhomme C, Duvillard P, Hacene K, Gerbaulet A. 2005. Management and clinical outcomes of pregnant patients with invasive cervical cancer. Annals of Oncology 16(3): 397-402.

Ghaemmaghami F, Abbasi F, Abadi AG. 2009. A favorable maternal and neonatal outcome following chemotherapy with etoposide, bleomycin, and cisplatin for management of grade 3 immature teratoma of the ovary. J Gynecol Oncol 20(4): 257-259.

Giacalone PL, Laffargue F, Benos P. 1999. Chemotherapy for breast carcinoma during pregnancy: A French national survey. Cancer 86(11): 2266-2272.

Giannakopoulou C, Manoura A, Hatzidaki E, Korakaki E, Froudarakis G, Koumandakis E. 2000. Multimodal cancer chemotherapy during the first and second trimester of pregnancy: a case report. European journal of obstetrics, gynecology, and reproductive biology 91(1): 95-97.

Gibson JE, Becker BA. 1968. The teratogenicity of cyclophosphamide in mice. Cancer research 28(3): 475-480.

Gilead Sciences. 2002. DaunoXome Product Label DAUNORUBICIN. San Dimas, CA 91773 USA

http://rxdrugsinfo.com/drug-info-label/daunoxome accessed 07/01/2011.

Gillick J, Mortell A, Dawrant M, Giles S, Bannigan J, Puri P. 2008. The Adriamycin rat/mouse model and its importance to the paediatric surgeon. Pediatr Surg Int 24(1): 113-118.

Ginopoulos PV, Michail GD, Kourounis GS. 2004. Pregnancy associated breast cancer: a case report. European journal of gynaecological oncology 25(2): 261-263.

GlaskoSmithKline. 2004. Tabloid brand Thioguanine.

GlaxoSmithKline. 2002. Navelbine. (*http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20388S014lbl.pdf*).

GlaxoSmithKline. 2003. Myleran.

Gondo H, Hamasaki Y, Nakayama H, Kondo T, Mitsuuchi J, Kawaga Y, Taniguchi S, Harada M, Niho Y. 1990. Acute leukemia during pregnancy. Association with immune-mediated thrombocytopenia in mother and infant. Acta Haematol 83(3): 140-144.

Goodyer MJ, Ismail JR, O'Reilly SP, Moylan EJ, Ryan CA, Hughes PA, O'Connor A. 2009. Safety of trastuzumab (Herceptin) during pregnancy: two case reports. Cases J 2: 9329.

Goodyer PR, Cybulsky A, Goodyer C. 1993. Expression of the epidermal growth factor receptor in fetal kidney. Pediatric nephrology (Berlin, Germany) 7(5): 612-615.

Goto T, Endo A. 1987. Dose- and stage-related sex difference in the incidence of cytosine arabinoside induced digit anomalies in the mouse fetus. Teratology 35(1): 35-40.

Gottschalk N, Jacobs VR, Hein R, Fischer T, Schneider KTM, von Steinburg SP. 2009. Advanced Metastatic Melanoma during Pregnancy: A Multidisciplinary Challenge. Onkologie 32(12): 748-751.

Greenberg LH, Tanaka KR. 1964. Congenital Anomalies Probably Induced by Cyclophosphamide. Jama 188: 423-426.

Greenlund LJ, Letendre L, Tefferi A. 2001. Acute leukemia during pregnancy: a single institutional experience with 17 cases. Leukemia & lymphoma 41(5-6): 571-577.

Gulati SC, Vega R, Gee T, Koziner B, Clarkson B. 1986. Growth and development of children born to patients after cancer therapy. Cancer Invest 4(3): 197-205.

Gurumurthy M, Koh P, Singh R, Bhide A, Satodia P, Hocking M, Anbarasu A, Wood LE. 2009. Metastatic non-small-cell lung cancer and the use of gemcitabine during pregnancy. J Perinatol 29(1): 63-65.

Gutterman J, Huang A, Hochstein P. 1969. Studies on the mode of action of N-isopropy-(2-methylhydrazine)-p-toluamide. Proc Soc Exp Biol Med 130: 797-799.

Haas JF. 1984. Pregnancy in association with a newly diagnosed cancer: a population-based epidemiologic assessment. Int J Cancer 34(2): 229-235.

Hacker NF, Berek JS, Lagasse LD. 1982. Carcinoma of the cervix associated with pregnancy. Obstetrics and Gynecology 59(6): 735-746.

Haerr RW, Pratt AT. 1985. Multiagent chemotherapy for sarcoma diagnosed during pregnancy. Cancer 56(5): 1028-1033.

Haggstrom J, Adriansson M, Hybbinette T, Harnby E, Thorbert G. 1996. Two cases of CML treated with alpha-interferon during second and third trimester of pregnancy with analysis of the drug in the new-born immediately postpartum [1]. European Journal of Haematology 57(1): 101-102.

Hahn KM, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M, Yang W, Perkins G, Hortobagyi GN, Theriault RL. 2006. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 107(6): 1219-1226.

Halakivi-Clarke L, Cho E, Onojafe I, Liao DJ, Clarke R. 2000. Maternal exposure to tamoxifen during pregnancy increases carcinogen-induced mammary tumorigenesis among female rat offspring. Clin Cancer Res 6(1): 305-308.

Halaska MJ, Pentheroudakis G, Strnad P, Stankusova H, Chod J, Robova H, Petruzelka L, Rob L, Pavlidis N. 2009. Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: a matched controlled study. Breast J 15(5): 461-467.

Hallett JS, Wentworth BC. 1991. The effects of busulfan on gonadal differentiation and development in Japanese quail (Coturnix coturnix japonica). Poultry science 70(7): 1619-1623.

Han JY, Nava-Ocampo AA, Kim TJ, Shim JU, Park CT. 2005. Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases. Reproductive toxicology (Elmsford, N.Y 19(4): 557-561.

Hansen WF, Fretz P, Hunter SK, Yankowitz J. 2001. Leukemia in pregnancy and fetal response to multiagent chemotherapy. Obstet Gynecol 97(5 Pt 2): 809-812.

Harrison P, Chipping P, Fothergill GA. 1994. Successful use of all-trans retinoic acid in acute promyelocytic leukaemia presenting during the second trimester of pregnancy. British Journal of Haematology 86(3): 681-682.

Hassan M, Oberg G, Ehrsson H, Ehrnebo M, Wallin I, Smedmyr B, Totterman T, Eksborg S, Simonsson B. 1989. Pharmacokinetic and metabolic studies of high-dose busulphan in adults. European journal of clinical pharmacology 36(5): 525-530.

Heartin E, Walkinshaw S, Clark RE. 2004. Successful outcome of pregnancy in chronic myeloid leukaemia treated with imatinib. Leukemia & lymphoma 45(6): 1307-1308.

Heller RH, Jones HW, Jr. 1964. Production of Ovarian Dysgenesis in the Rat and Human by Busulphan. American journal of obstetrics and gynecology 89: 414-420.

Henderson CE, Elia G, Garfinkel D, Poirier MC, Shamkhani H, Runowicz CD. 1993. Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. Gynecologic oncology 49(1): 92-94.

Hendrickx AG, Hummler H. 1992. Teratogenicity of all-trans retinoic acid during early embryonic development in the cynomolgus monkey (Macaca fascicularis). Teratology 45(1): 65-74.

Hensley ML, Ford JM. 2003. Imatinib treatment: specific issues related to safety, fertility, and pregnancy. Semin Hematol 40(2 Suppl 2): 21-25.

Herbst RS, Khuri FR. 2003. Mode of action of docetaxel - a basis for combination with novel anticancer agents. Cancer treatment reviews 29(5): 407-415.

Herold M, Schnohr S, Bittrich H. 2001. Efficacy and safety of a combined rituximab chemotherapy during pregnancy. J Clin Oncol 19(14): 3439.

Hoch RV, Soriano P. 2003. Roles of PDGF in animal development. Development (Cambridge, England) 130(20): 4769-4784.

Holstein S, Hohl R. 2008. Chemotherapy of Gynecologic Cancers (Chapter 38). In The Chemotherapy Source Book, Fourth Edition. Perry M, ed. Philadelphia, PA: Lippincott, Williams, and Wilkins. 447-463.

Hoover BA, 2nd, Schumacher HR. 1966. Acute leukemia in pregnancy. American journal of obstetrics and gynecology 96(3): 316-320.

Hopkins MP, Morley GW. 1992. The prognosis and management of cervical cancer associated with pregnancy. Obstet Gynecol 80(1): 9-13.

Horbelt D, Delmore J, Meisel R, Cho S, Roberts D, Logan D. 1994. Mixed germ cell malignancy of the ovary concurrent with pregnancy. Obstetrics and Gynecology 84(4 II SUPPL.): 662-664.

Hospira. 2008. Cytarabine Injection Complete product label. Hospira, Inc., Lake Forest, IL. *http://www.hospira.com/_docs/Cytarabine%20483176-PROMOWEB.pdf* (Accessed on June 9, 2011).

Hospira. 2008. VinCRIStine Sulfate Injection, USP: prescribing information. . Hospira, Inc., Lake Forest, IL. <*http://www.hospira.com/_docs/VinCRIStine-482805-PROMOWEB.pdf*> (Accessed on June 9, 2011).

.

Hospira. 2008. Methotrexate Sodium for Injections. *http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7158* accessed 08/29/2011 Hospira, Inc., Lake Forest, IL. .

Houghton AN, Flannery J, Viola MV. 1981. Malignant melanoma of the skin occurring during pregnancy. Cancer 48(2): 407-410.

Hsu KF, Chang CH, Chou CY. 1995. Sinusoidal fetal heart rate pattern during chemotherapy in a pregnant woman with acute myelogenous leukemia. J Formos Med Assoc 94(9): 562-565.

Hubalek M, Smekal-Schindelwig C, Zeimet AG, Sergi C, Brezinka C, Mueller-Holzner E, Marth C. 2007. Chemotherapeutic treatment of a pregnant patient with ovarian dysgerminoma. Archives of gynecology and obstetrics 276(2): 179-183.

Hudis CA. 2007. Trastuzumab--mechanism of action and use in clinical practice. The New England journal of medicine 357(1): 39-51.

Ibrahim EM, Ezzat AA, Baloush A, Hussain ZH, Mohammed GH. 2000. Pregnancy-associated breast cancer: A case-control study in a young population with a high-fertility rate. Medical Oncology 17(4): 293-300.

Ibrahim N, Saadeddin A, Al Sabbah T. 2006. TAC chemotherapy during the first trimester of pregnancy-the first case report. J Oncol Pham Practice 12(1): 25.

Incerpi MH, Miller DA, Posen R, Byrne JD. 1997. All-trans retinoic acid for the treatment of acute promyelocytic leukemia in pregnancy. Obstetrics and Gynecology 89(5 II SUPPL.): 826-828.

Institute of Medicine. 2007. Preterm Birth: Causes, Consequences, and Prevention, Committee on Understanding Premature Birth and

Assuring Healthy Outcomes. Washington, DC: The National Academies Press. 790.

Isaacs RJ, Hunter W, Clark K. 2001. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy-- case report and literature review. Gynecologic oncology 80(3): 405-408.

Ishida I, Yamaguchi Y, Tanemura A, Hosokawa K, Itami S, Morita A, Katayama I. 2009. Stage III melanoma treated with chemotherapy after surgery during the second trimester of pregnancy. Arch Dermatol 145(3): 346-348.

Ishida T, Yokoe T, Kasumi F, Sakamoto G, Makita M, Tominaga T, Simozuma K, Enomoto K, Fujiwara K, Nanasawa T, et al. 1992. Clinicopathologic characteristics and prognosis of breast cancer patients associated with pregnancy and lactation: analysis of case-control study in Japan. Jpn J Cancer Res 83(11): 1143-1149.

Ives AD, Saunders CM, Semmens JB. 2005. The Western Australian gestational breast cancer project: a population-based study of the incidence, management and outcomes. Breast (Edinburgh, Scotland) 14(4): 276-282.

Izumi HM. 1956. Myleran in pregnancy; report of a case. Journal of the American Medical Association 161(10): 969.

Jacobs AJ, Marchevsky A, Gordon RE, Deppe G, Cohen CJ. 1980. Oat cell carcinoma of the uterine cervix in a pregnant woman treated with cis-diamminedichloroplatinum. Gynecologic oncology 9(3): 405-410.

Jameel A, Jamil SN. 2007. Safety of cytotoxic chemotherapy during pregnancy. J Pak Med Assoc 57(9): 449-452.

Janne PA, Rodriguez-Thompson D, Metcalf DR, Swanson SJ, Greisman HA, Wilkins-Haug L, Johnson BE. 2001. Chemotherapy for a patient with advanced non-small-cell lung cancer during pregnancy: a case report and a review of chemotherapy treatment during pregnancy. Oncology 61(3): 175-183.

Janov AJ, Anderson J, Cella DF, Zuckerman E, Kornblith AB, Holland JC, Kantor AF, Li FP. 1992. Pregnancy outcome in survivors of advanced Hodgkin disease. Cancer 70(3): 688-692.

Jansz GF, Pomerantz DK. 1985. The effect of prenatal treatment with busulfan on in vitro androgen production by testes from rats of various ages. Canadian journal of physiology and pharmacology 63(9): 1155-1158.

Jeppesen JB, Osterlind K. 2011. Successful Twin Pregnancy Outcome After In Utero Exposure to FOLFOX for Metastatic Colon Cancer: A Case Report and Review of the Literature. Clinical colorectal cancer.

Johansson AL, Andersson TM, Hsieh CC, Cnattingius S, Lambe M. 2011. Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum. Cancer Epidemiol Biomarkers Prev.

Johns DG, Rutherford LD, Leighton PC, Vogel CL. 1972. Secretion of methotrexate into human milk. American journal of obstetrics and gynecology 112(7): 978-980.

Johnson IR, Filshie GM. 1977. Hodgkin's disease diagnosed in pregnancy, case report. British journal of obstetrics and gynaecology 84(10): 791-792.

Johnson JM, Thompson DJ, Haggerty GC, Dyke IL, Lower CE. 1985. The effect of prenatal procarbazine treatment on brain development in the rat. Teratology 32(2): 203-212.

Joneja M, Ungthavorn S. 1969. Teratogenic effects of vincristine in three lines of mice. Teratology 2(3): 235-240.

Kai S, Kohmura H, Ishikawa K, Makihara Y, Ohta S, Kawano S, Takahashi N. 1989. Teratogenic effects of carboplatin, an oncostatic drug, administered during the early organogenetic period in rats. The Journal of toxicological sciences 14(2): 115-130.

Kaplan-Kraicer R, Kostovetsky I, Bardin CW, Shalgi R. 1996. Tamoxifen and RU39411 synergize with mifepristone to produce preimplantation pregnancy loss by increasing embryo transport (rat). Contraception 53(6): 367-373.

Karam A, Feldman N, Holschneider CH. 2007. Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy. Nat Clin Pract Oncol 4(6): 375-380.

Kardinal C, Cole J. 2008. Breast Cancer (Chapter 34). In The Chemotherapy Source Book, Fourth Edition. Perry M, ed. Philadelphia, PA: Lippincott, Williams, and Wilkins. 363-407.

Karnofsky DA, Lacon CR. 1966. The effects of 1-beta-d-arabinofuransyl-cytosine on the developing chick embryo. Biochemical pharmacology 15: 1435-1442.

Karp GI, von Oeyen P, Valone F, Khetarpal VK, Israel M, Mayer RJ, Frigoletto FD, Garnick MB. 1983. Doxorubicin in pregnancy: possible transplacental passage. Cancer treatment reports 67(9): 773-777.

Kato H, Ogino T, Minami A, Ohshio I. 1990. Experimental study of radial ray deficiency. Journal of hand surgery (Edinburgh, Scotland) 15(4): 470-476.

Kawamura S, Yoshiike M, Shimoyama T, Suzuki Y, Itoh J, Yamagata K, Fukushima K, Ogasawara H, Saitoh S, Tsushima K, Sawada Y, Sakata Y, Yoshida Y. 1994. Management of acute leukemia during pregnancy: From the results of a nationwide questionnaire survey and literature survey. Tohoku Journal of Experimental Medicine 174(2): 167-175.

Keller KA, Aggarwal SK. 1983. Embryotoxicity of cisplatin in rats and mice. Toxicology and applied pharmacology 69(2): 245-256.

Kerr JR. 2005. Neonatal effects of breast cancer chemotherapy administered during pregnancy. Pharmacotherapy 25(3): 438-441.

Khosrotehrani K, Nguyen Huu S, Prignon A, Avril MF, Boitier F, Oster M, Mortier L, Richard MA, Maubec E, Kerob D, Mansard S, Merheb C, Moguelet P, Nassar D, Guegan S, Aractingi S. 2011. Pregnancy promotes melanoma metastasis through enhanced lymphangiogenesis. The American journal of pathology 178(4): 1870-1880.

Khurshid M, Saleem M. 1978. Acute leukaemia in pregnancy. Lancet 2(8088): 534-535.

Kim JH, Kim HS, Sung CW, Kim KJ, Kim CH, Lee KY. 2008. Docetaxel, gemcitabine, and cisplatin administered for non-small cell lung cancer during the first and second trimester of an unrecognized pregnancy. Lung cancer (Amsterdam, Netherlands) 59(2): 270-273.

Kimby E, Sverrisdottir A, Elinder G. 2004. Safety of rituximab therapy during the first trimester of pregnancy: a case history. Eur J Haematol 72(4): 292-295.

King LA, Nevin PC, Williams PP, Carson LF. 1991. Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy. Gynecologic oncology 41(1): 78-80.

King MT, Wild D. 1979. Transplacental mutagenesis: the micronucleus test on fetal mouse blood. Human genetics 51(2): 183-194.

Kjems E, Krag C. 1993. Melanoma and pregnancy. A review. Acta oncologica (Stockholm, Sweden) 32(4): 371-378.

Klepfish A, Schattner A, Shtalrid M, Shvidel L, Berrebi A, Bentwich Z. 2000. Advanced Hodgkin's disease in a pregnant HIV seropositive woman: favorable mother and baby outcome following combined anticancer and antiretroviral therapy. American journal of hematology 63(1): 57-58.

Kobayashi S, Sakai T, Dalrymple PD, Wood SG, Chasseaud LF. 1993. Disposition of the novel anticancer agent vinorelbine ditartrate following intravenous administration in mice, rats and dogs. Arzneimittelforschung 43(12): 1367-1377.

Koc ON, McFee M, Reed E, Gerson SL. 1994. Detection of platinum-DNA adducts in cord blood lymphocytes following in utero platinum exposure. Eur J Cancer 30A(5): 716-717.

Kopf-Maier P, Merker HJ. 1983. Effects of the cytostatic drug cis-platinum on the developing neocortex of the mouse. Teratology 28(2): 189-199.

Kopf-Maier P, Erkenswick P, Merker HJ. 1985. Lack of severe malformations versus occurrence of marked embryotoxic effects after treatment of pregnant mice with cis-platinum. Toxicology 34(4): 321-331.

Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. 2004. Medical methods for first trimester abortion. Cochrane Database Syst Rev(2): CD002855.

Kumar AR, Hale TW, Mock RE. 2000. Transfer of interferon alfa into human breast milk. J Hum Lact 16(3): 226-228.

Lam MS. 2006. Treatment of Burkitt's lymphoma during pregnancy. Ann Pharmacother 40(11): 2048-2052.

Lambert J, Wijermans PW, Dekker GA, Ossenkoppele GJ. 1991. Chemotherapy in non-Hodgkin's lymphoma during pregnancy. Neth J Med 38(1-2): 80-85.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW, Jr., Lott IT, et al. 1985. Retinoic acid embryopathy. The New England journal of medicine 313(14): 837-841.

Lawson CC, Rocheleau CM, Whelan EA, Lividoti Hibert EN, Grajewski B, Spiegelman D, Rich-Edwards JW. 2011. Occupational exposures among nurses and risk of spontaneous abortion. American journal of obstetrics and gynecology.

Lazar R, Conran PC, Damjanov I. 1979. Embryotoxicity and teratogenicity of Cis-diamminedichloroplatinum. Experientia 35(5): 647-648.

Leachman SA, Jackson R, Eliason MJ, Larson AA, Bolognia JL. 2007. Management of melanoma during pregnancy. Dermatology nursing / Dermatology Nurses' Association 19(2).

Lee KF, Simon H, Chen H, Bates B, Hung MC, Hauser C. 1995. Requirement for neuregulin receptor erbB2 in neural and cardiac development. Nature 378(6555): 394-398.

Lee RA, Johnson CE, Hanlon DG. 1962. Leukemia during pregnancy. American journal of obstetrics and gynecology 84: 455-458.

Leiserowitz GS, Xing G, Cress R, Brahmbhatt B, Dalrymple JL, Smith LH. 2006. Adnexal masses in pregnancy: how often are they malignant? Gynecologic oncology 101(2): 315-321.

Lens MB, Rosdahl I, Ahlbom A, Farahmand BY, Synnerstad I, Boeryd B, Bishop JAN. 2004. Effect of pregnancy on survival in women with cutaneous malignant melanoma. Journal of Clinical Oncology 22(21): 4369-4375.

Leong KW, Teh A, Bosco JJ. 2000. Tretinoin in pregnancy complicated with acute promyelocytic leukaemia. Med J Malaysia 55(2): 277-279.

Lergier JE, Jimenez E, Maldonado N, Veray F. 1974. Normal pregnancy in multiple myeloma treated with cyclophosphamide. Cancer 34(4): 1018-1022.

Leslie KK. 2002. Chemotherapy and pregnancy. Clinical obstetrics and gynecology 45(1): 153-164.

Leslie KK, Koil C, Rayburn WF. 2005. Chemotherapeutic drugs in pregnancy. Obstetrics and gynecology clinics of North America 32(4): 627-640.

Leyder M, Laubach M, Breugelmans M, Keymolen K, De Greve J, Foulon W. 2010. Specific Congenital Malformations after Exposure to Cyclophosphamide, Epirubicin and 5-Fluorouracil during the First Trimester of Pregnancy. Gynecologic and obstetric investigation.

Li FP, Jaffe N. 1974. Progeny of childhood-cancer survivors. Lancet 2(7882): 707-709.

Li J, Wang LJ, Zhang BZ, Peng YP, Lin ZQ. 2011. Neoadjuvant chemotherapy with paclitaxel plus platinum for invasive cervical cancer in pregnancy: two case report and literature review. Archives of gynecology and obstetrics.

Li RH, Tam WH, Ng PC, Mok TS, Tam B, Lau TK. 2007. Microphthalmos associated with Dartmouth combination chemotherapy in pregnancy: a case report. J Reprod Med 52(6): 575-576.

Lilleyman JS, Hill AS, Anderton KJ. 1977. Consequences of acute myelogenous leukemia in early pregnancy. Cancer 40(3): 1300-1303.

Lipovsky MM, Biesma DH, Christiaens GCML, Petersen EJ. 1996. Successful treatment of acute promyelocytic leukaemia with all-trans-retinoic-acid during late pregnancy. British Journal of Haematology 94(4): 699-701.

Lipscomb GH. 2007. Medical therapy for ectopic pregnancy. Semin Reprod Med 25(2): 93-98.

Lishner M, Zemlickis D, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. 1992. Maternal and foetal outcome following Hodgkin's disease in pregnancy. British journal of cancer 65(1): 114-117.

Lishner M, Zemlickis D, Sutcliffe SB, Koren G. 1994. Non-Hodgkin's lymphoma and pregnancy. Leukemia & lymphoma 14(5-6): 411-413.

Liu H, Zheng Z, Wintour EM. 2008. Aquaporins and fetal fluid balance. Placenta 29(10): 840-847.

Loibl S, von Minckwitz G, Gwyn K, Ellis P, Blohmer JU, Schlegelberger B, Keller M, Harder S, Theriault RL, Crivellari D, Klingebiel T, Louwen F, Kaufmann M. 2006. Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer 106(2): 237-246.

Loibl S. 2007. Treatment of Pregnant Breast Cancer Patients and Outcomes of Children Exposed to Chemotherapy In Utero. Breast Diseases 18(2): 203.

Longley DB, Harkin DP, Johnston PG. 2003. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer 3(5): 330-338.

Lowenthal RM, Marsden KA, Newman NM, Baikie MJ, Campbell SN. 1978. Normal infant after treatment of acute myeloid leukaemia in pregnancy with daunorubicin. Aust N Z J Med 8(4): 431-432.

Lundbeck Inc. 2012. Cosmegen® for Injection (dactinomycin for injection) (Actinomycin D). Lundbeck Inc

Deerfield, IL 60015 USA.

Lycette JL, Dul CL, Munar M, Belle D, Chui SY, Koop DR, Nichols CR. 2006. Effect of pregnancy on the pharmacokinetics of paclitaxel: a case report. Clin Breast Cancer 7(4): 342-344.

MacDorman MFaK, Sharon 2005. Fetal and Perinatal Mortality, United States, 2005. Natl Vital Stat Rep 57(8).

Machado F, Vegas C, Leon J, Perez A, Sanchez R, Parrilla JJ, Abad L. 2007. Ovarian cancer during pregnancy: Analysis of 15 cases. Gynecologic oncology 105(2): 446-450.

MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N. 1991. Lack of effect of pregnancy on outcome of melanoma. For The World Health Organisation Melanoma Programme. Lancet 337(8742): 653-655.

Magloire LK, Pettker CM, Buhimschi CS, Funai EF. 2006. Burkitt's lymphoma of the ovary in pregnancy. Obstet Gynecol 108(3 Pt 2): 743-745.

Malek FA, Moritz KU, Fanghanel J. 2003. Effects of prenatal procarbazine administration on intrauterine development in rats. Ann Anat 185(2): 117-119.

Malhotra N, Sood M. 2000. Ovarian germ cell neoplasm in pregnancy. European journal of gynaecological oncology 21(4): 396.

Malone JM, Gershenson DM, Creasy RK, Kavanagh JJ, Silva EG, Stringer CA. 1986. Endodermal sinus tumor of the ovary associated with pregnancy. Obstet Gynecol 68(3 Suppl): 86S-89S.

Mandrawa CL, Stewart J, Fabinyi GC, Walker SP. 2011. A case study of trastuzumab treatment for metastatic breast cancer in pregnancy: fetal risks and management of cerebral metastases. The Australian & New Zealand journal of obstetrics & gynaecology 51(4): 372-376.

Mantovani G, Gramignano G, Mais V, Melis GB, Parodo G, Carrucciu GM. 2007. Use of chemotherapy for ovarian cancer during human pregnancy: case report and literature review. European journal of obstetrics, gynecology, and reproductive biology 131(2): 238-239.

Markman M. 2009. An update on the use of intraperitoneal chemotherapy in the management of ovarian cancer. Cancer journal (Sudbury, Mass 15(2): 105-109.

Markowitz CE. 2007. Interferon-beta: mechanism of action and dosing issues. Neurology 68(24 Suppl 4): S8-11.

Marnitz S, Schmittel A, Bolbrinker J, Schmidt FP, Fons G, Kalache K, Schneider A, Kohler C. 2009. The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum. Fertility and sterility 92(5): 1748 e1741-1744.

Marnitz S, Kohler C, Oppelt P, Schmittel A, Favero G, Hasenbein K, Schneider A, Markman M. 2010. Cisplatin application in pregnancy: first in vivo analysis of 7 patients. Oncology 79(1-2): 72-77.

Martin JAH, B.E.; Ventura, S.J.; Osterman, MJK; Kirmeyer, S; Mathews, TJ; Wilson, EA. 2011. Births: Final Data for 2009. National Vital Statistics Reports 60(1).

Masala A, Delitala G, Lo Dico G, Stoppelli I, Alagna S, Devilla L. 1978. Inhibition of lactation and inhibition of prolactin release after mechanical breast stimulation in puerperal women given tamoxifen or placebo. British journal of obstetrics and gynaecology 85(2): 134-137.

Matsouka C, Marinopoulos S, Barbaroussi D, Antsaklis A. 2008. Acute lymphoblastic leukemia during gestation. Med Oncol 25(2): 190-193.

Matsuo K, Shimoya K, Ueda S, Wada K, Koyama M, Murata Y. 2004. Idarubicin administered during pregnancy: its effects on the fetus. Gynecologic and obstetric investigation 58(4): 186-188.

Maurer LH, Forcier RJ, McIntyre OR, Benirschke K. 1971. Fetal group C trisomy after cytosine arabinoside and thioguanine. Annals of internal medicine 75(5): 809-810.

Mavrommatis CG, Daskalakis GJ, Papageorgiou IS, Antsaklis AJ, Michalas SK. 1998. Non-Hodgkin's lymphoma during pregnancy--case report. European journal of obstetrics, gynecology, and reproductive biology 79(1): 95-97.

Mayne. 2006. Epirubicin hydrochloride for injection product information. Mayne. 2006. Epirubicin hydrochloride for injection product information. Mayne Pharma Limited, Mulgrave, Australia. (*http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/050807lbl.pdf*, accessed on August 16, 2011).

McClure HM, Wilk AL, Horigan EA, Pratt RM. 1979. Induction of craniofacial malformations in rhesus monkeys (Macaca mulatta) with cyclophosphamide. Cleft Palate J 16(3): 248-256.

McConnell JB, Bhoola R. 1973. A neonatal complication of maternal leukaemia treated with 6-mercaptopurine. Postgraduate medical journal 49(569): 211-213.

McManamny DS, Moss AL, Pocock PV, Briggs JC. 1989. Melanoma and pregnancy: a long-term follow-up. British journal of obstetrics and gynaecology 96(12): 1419-1423.

Meera V, Jijina F, Shrikande M, Madkaikar M, Ghosh K. 2008. Twin pregnancy in a patient of chronic myeloid leukemia on imatinib therapy. Leukemia research 32(10): 1620-1622.

Menegola E, Broccia ML, Prati M, Ricolfi R, Giavini E. 1997. Comparative embryotoxicity of four anthracyclines: In Vitro study on their effects on glutathione status. Toxicol In Vitro 11(1-2): 33-41.

Menegola E BM, Renzo FD. 2001. Teratogenic effects of Doxorubicin in rats at midgestation and term. Teratog Carcinogen Mutagen 21(4): 283-293.

Mennuti MT, Shepard TH, Mellman WJ. 1975. Fetal renal malformation following treatment of Hodgkin's disease during pregnancy. Obstet Gynecol 46(2): 194-196.

Merck. 2004. Triuration of MUSTARGEN. *http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=19281* this one is for the 2004

http://pharmacycode.com/fda/HN2 this one is for the 1999 year pdf

Whitehouse Station, NJ, USA.

Merimsky O, Le Chevalier T, Missenard G, Lepechoux C, Cojean-Zelek I, Mesurolle B, Le Cesne A. 1999. Management of cancer in pregnancy: a case of Ewing's sarcoma of the pelvis in the third trimester. Ann Oncol 10(3): 345-350.

Merskey C, Rigal W. 1956. Pregnancy in acute leukaemia treated with 6-mercaptopurine. Lancet 271(6955): 1268-1269.

Meyer-Wittkopf M, Barth H, Emons G, Schmidt S. 2001. Fetal cardiac effects of doxorubicin therapy for carcinoma of the breast during pregnancy: case report and review of the literature. Ultrasound Obstet Gynecol 18(1): 62-66.

Millicovsky G, DeSesso JM, Kleinman LI, Clark KE. 1981. Effects of hydroxyurea on hemodynamics of pregnant rabbits: a maternally mediated mechanism of embryotoxicity. American journal of obstetrics and gynecology 140(7): 747-752.

Mir O, Berveiller P, Ropert S, Goffinet F, Pons G, Treluyer JM, Goldwasser F. 2008. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol 19(4): 607-613.

Mir O, Berveiller P, Goffinet F, Treluyer JM, Serreau R, Goldwasser F, Rouzier R. 2010. Taxanes for breast cancer during pregnancy: a systematic review. Ann Oncol 21(2): 425-426.

Mirkes PE, Zwelling LA. 1990. Embryotoxicity of the intercalating agents m-AMSA and o-AMSA and the epipodophyllotoxin VP-16 in postimplantation rat embryos in vitro. Teratology 41(6): 679-688.

Molkenboer JF, Vos AH, Schouten HC, Vos MC. 2005. Acute lymphoblastic leukaemia in pregnancy. Neth J Med 63(9): 361-363.

Moore KLP, T.V.N., ed. 2003. The developing human: clinically oriented embryology, 7th edition. Philadelphia, PA: Saunders. 1-560.

Moreira WB, Brandao EC, Soares AN, Lucena CE, Antunes CM. 2010. Prognosis for patients diagnosed with pregnancy-associated breast cancer: a paired case-control study. Sao Paulo medical journal = Revista paulista de medicina 128(3): 119-124.

Moretti ME, Verjee Z, Ito S, Koren G. 2006. Breast-feeding during maternal use of azathioprine. Ann Pharmacother 40(12): 2269-2272.

Morice P, Narducci F, Mathevet P, Marret H, Darai E, Querleu D. 2009. French recommendations on the management of invasive cervical cancer during pregnancy. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 19(9): 1638-1641.

Morishita S, Imai A, Kawabata I, Tamaya T. 1994. Acute myelogenous leukemia in pregnancy: fetal blood sampling and early effects of chemotherapy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 44(3): 273-277.

Morris JM, Van Wagenen G, Hurteau GD, Johnston DW, Carlsen RA. 1967. Compounds interfering with ovum implantation and development. I. Alkaloids and antimetabolites. Fertility and sterility 18(1): 7-17.

Morton J, Taylor K, Wright S. 1995. Successful maternal and fetal outcome following the use of ATRA for the induction of APML late in the first trimester. Blood 86(1 SUPPL.).

Moster D, Lie RT, Markestad T. 2008. Long-term medical and social consequences of preterm birth. The New England journal of medicine 359(3): 262-273.

Motegi M, Takakura S, Takano H, Tanaka T, Ochiai K. 2007. Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary. Obstet Gynecol 109(2 Pt2): 537-540.

Moudgal NR, Shetty G, Selvaraj N, Bhatnagar AS. 1996. Use of a specific aromatase inhibitor for determining whether there is a role for oestrogen in follicle/oocyte maturation, ovulation and preimplantation embryo development. Journal of reproduction and fertility 50: 69-81.

Mubarak AA, Kakil IR, Awidi A, Al-Homsi U, Fawzi Z, Kelta M, Al-Hassan A. 2002. Normal outcome of pregnancy in chronic myeloid leukemia treated with interferon-alpha in 1st trimester: report of 3 cases and review of the literature. American journal of hematology 69(2): 115-118.

Mulvihill JJ, McKeen EA, Rosner F, Zarrabi MH. 1987. Pregnancy outcome in cancer patients. Experience in a large cooperative group. Cancer 60(5): 1143-1150.

Munnell EW. 1963. Primary Ovarian Cancer Associated with Pregnancy. Clinical obstetrics and gynecology 30: 983-993.

Muranaka R-i, Fukishi Y, Tsuiki H, Hasegawa Y. 1995. Teratogenic Characteristics by Single Dosing of Antineoplastic Platinum Complexes in Rats. Cong Anom 35: 73-86.

Murphy ML, Del Moro A, Lacon C. 1958. The comparative effects of five polyfunctional alkylating agents on the rat fetus, with additional notes on the chick embryo. Annals of the New York Academy of Sciences 68(3): 762-781; discussion 781-762.

Murray CL, Reichert JA, Anderson J, Twiggs LB. 1984. Multimodal cancer therapy for breast cancer in the first trimester of pregnancy. A case report. Journal of the American Medical Association 252(18): 2607-2608.

Murray NA, Acolet D, Deane M, Price J, Roberts IA. 1994. Fetal marrow suppression after maternal chemotherapy for leukaemia. Archives of disease in childhood 71(3): F209-210.

Nagao T, Yoshimura S, Saito Y, Imai K. 1999. Developmental toxicity of the topoisomerase inhibitor, etoposide, in rabbits after intravenous administration. Teratogenesis, carcinogenesis, and mutagenesis 19(3): 233-241.

Nakajima W, Ishida A, Takahashi M, Hirayama M, Washino N, Ogawa M, Takahashi S, Okada K. 2004. Good outcome for infant of mother treated with chemotherapy for ewing sarcoma at 25 to 30 weeks' gestation. J Pediatr Hematol Oncol 26(5): 308-311.

Nakamura K, Dan K, Iwakiri R, Gomi S, Nomura T. 1995. Successful treatment of acute promyelocytic leukemia in pregnancy with all-trans retinoic acid [1]. Annals of Hematology 71(5): 263-264.

Nakamura Y, Harada K, Yamamoto I, Uemura Y, Okamoto K, Fukuda S, Hashimoto T. 1992. Human pulmonary hypoplasia. Statistical, morphological, morphometric, and biochemical study. Archives of pathology & laboratory medicine 116(6): 635-642.

Nantel S, Parboosingh J, Poon MC. 1990. Treatment of an aggressive non-Hodgkin's lymphoma during pregnancy with MACOP-B chemotherapy. Medical and pediatric oncology 18(2): 143-145.

Narbaitz R, Marino I. 1988. Experimental induction of microphthalmia in the chick embryo with a single dose of cisplatin. Teratology 37(2): 127-134.

Nau H. 2001. Teratogenicity of isotretinoin revisited: species variation and the role of all-trans-retinoic acid. Journal of the American Academy of Dermatology 45(5): S183-187.

NCCN Guidelines. 2010. Hodgkin Lymphoma

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 07/27/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Cervical Cancer

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 01/18/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Breast Cancer

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 02/2/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Ovarian Cancer

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 07/27/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Acute Myeloid Leukemia

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 04/11/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Non-Hodgkin's Lymphomas

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 03/18/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Melanoma

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed 01/7/2011). National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

Neu LT, Jr. 1962. Leukemia complicating pregnancy. Missouri medicine 59: 220-221.

Nicholson HO. 1968. Cytotoxic drugs in pregnancy. Review of reported cases. The Journal of obstetrics and gynaecology of the British Commonwealth 75(3): 307-312.

Nicholson HO. 1968. Leukaemia and pregnancy. A report of five cases and discussion of management. The Journal of obstetrics and gynaecology of the British Commonwealth 75(5): 517-520.

Niedermeier DM, Frei-Lahr DA, Hall PD. 2005. Treatment of acute myeloid leukemia during the second and third trimesters of pregnancy. Pharmacotherapy 25(8): 1134-1140.

Nishimura N, Furukawa Y, Sutheesophon K, Nakamura M, Kishi K, Okuda K, Sato Y, Kano Y. 2003. Suppression of ARG kinase activity by STI571 induces cell cycle arrest through up-regulation of CDK inhibitor p18/INK4c. Oncogene 22(26): 4074-4082.

Novartis. 2009. Gleevec Full Presecribing Information. . Novartis Pharmaceuticals Corporation, East Hanover, New Jersey
<http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021588s030s031lbl.pdf>.

Accessed June 15, 2011

Nulman I, Laslo D, Fried S, Uleryk E, Lishner M, Koren G. 2001. Neurodevelopment of children exposed in utero to treatment of maternal malignancy. British journal of cancer 85(11): 1611-1618.

O'Donnell R, Costigan C, O'Connell LG. 1979. Two cases of acute leukaemia in pregnancy. Acta Haematol 61(5): 298-300.

O'Leary J, Bepko F. 1963. Obstetrical Clinics:Acute Leukemia and Pregnancy. Georgetown Med Bull 16: 162-164.

O'Meara AT, Cress R, Xing G, Danielsen B, Smith LH. 2005. Malignant melanoma in pregnancy. A population-based evaluation. Cancer 103(6): 1217-1226.

Ohzu E, Shoji R. 1965. Preliminary Notes on Abnormalities Induced by Velban in Devloping Mouse Embryos. Proc Jap Acad 41: 321-325.

Okechukwu CN, Ross J. 1998. Hodgkin's lymphoma in a pregnant patient with acquired immunodeficiency syndrome. Clinical oncology (Royal College of Radiologists (Great Britain)) 10(6): 410-411.

Okun DB, Groncy PK, Sieger L, Tanaka KR. 1979. Acute leukemia in pregnancy: transient neonatal myelosuppression after combination chemotherapy in the mother. Medical and pediatric oncology 7(4): 315-319.

Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. 2010. New intrauterine growth curves based on United States data. Pediatrics 125(2): e214-224.

Ono T, Miyaki M, Taguchi T, Ohashi M. 1976. Actions of bleomycin on DNA ligase and polymerases. Prog Biochem Pharmacol 11: 48-58.

Ortega A, Puig M, Domingo JL. 1991. Maternal and developmental toxicity of low doses of cytosine arabinoside in mice. Teratology 44(4): 379-384.

Ortega J. 1977. Multiple agent chemotherapy including bleomycin of non-Hodgkin's lymphoma during pregnancy. Cancer 40(6): 2829-2835.

OSHA. 1999. Occupational Safety and Health Administration (OSHA) Technical Manual (OTM), Section VI: Chapter 2 Controlling Occupational Exposure to Hazardous Drugs. Directive number: TED 01-00-015, January 20, 1999. United States Department of Labor. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html#2, accessed April 10, 2012).

Ozumba BC, Obi GO. 1992. Successful pregnancy in a patient with chronic myeloid leukemia following therapy with cytotoxic drugs [1]. International Journal of Gynecology and Obstetrics 38(1): 49-50.

Pack GT, Scharnagel IM. 1951. The prognosis for malignant melanoma in the pregnant woman. Cancer 4(2): 324-334.

Pages C, Robert C, Thomas L, Maubec E, Sassolas B, Granel-Brocard F, Chevreau C, De Raucourt S, Leccia MT, Fichet D, Khammari A, Boitier F, Stoebner PE, Dalac S, Celerier P, Aubin F, Viguier M. 2009. Management and outcome of metastatic melanoma during pregnancy. The British journal of dermatology.

Pant S, Landon MB, Blumenfeld M, Farrar W, Shapiro CL. 2008. Treatment of breast cancer with trastuzumab during pregnancy. J Clin Oncol 26(9): 1567-1569.

Papantoniou N, Daskalakis G, Marinopoulos S, Anastasakis E, Mesogitis S, Antsaklis A. 2008. Management of pregnancy in adolescence complicated by acute lymphoblastic leukemia. Fetal diagnosis and therapy 23(2): 164-167.

Parekh J, Shah K, Sharma R. 1959. Acute Leukaemia in Pregnancy. Journal of J.J. Group of Hospitals: 49-51.

Parente JT, Amsel M, Lerner R, Chinea F. 1988. Breast cancer associated with pregnancy. Obstet Gynecol 71(6 Pt 1): 861-864.

Partridge AH, Garber JE. 2000. Long-term outcomes of children exposed to antineoplastic agents in utero. Seminars in oncology 27(6): 712-726.

Paşa S, Altintaş A, Çil T, Ayyildiz O. 2009. Fetal loss in a patient with acute myeloblastic leukemia associated with FLAG-IDA regime. UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi 19(2): 110-112.

Paskulin GA, Gazzola Zen PR, de Camargo Pinto LL, Rosa R, Graziadio C. 2005. Combined chemotherapy and teratogenicity. Birth defects research 73(9): 634-637.

Patel M, Dukes IAF, Hull JC. 1991. Use of hydroxyurea in chronic myeloid leukemia during pregnancy: A case report. American journal of obstetrics and gynecology 165(3): 565-566.

Pavlidis NA. 2002. Coexistence of pregnancy and malignancy. The oncologist 7(4): 279-287.

Pawliger DF, McLean FW, Noyes WD. 1971. Normal fetus after cytosine arabinoside therapy. Annals of internal medicine 74(6): 1012.

Peccatori FA, Azim HA, Jr., Scarfone G, Gadducci A, Bonazzi C, Gentilini O, Galimberti V, Intra M, Locatelli M, Acaia B, Rossi P, Cinieri S, Calabrese L, Goldhirsch A. 2009. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast cancer research and treatment 115(3): 591-594.

Pentsuk N, van der Laan JW. 2009. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. Birth Defects Res B Dev Reprod Toxicol 86(4): 328-344.

Percy DH. 1975. Taratogenic effects of the pyrimidine analogues 5-iododeoxyuridine and cytosine arabinoside in late fetal mice and rats. Teratology 11(1): 103-117.

Pereg D, Koren G, Lishner M. 2008. Cancer in pregnancy: gaps, challenges and solutions. Cancer treatment reviews 34(4): 302-312.

Peres RM, Sanseverino MT, Guimaraes JL, Coser V, Giuliani L, Moreira RK, Ornsten T, Schuler-Faccini L. 2001. Assessment of fetal risk associated with exposure to cancer chemotherapy during pregnancy: a multicenter study. Braz J Med Biol Res 34(12): 1551-1559.

Peretz B, Peretz T. 2003. The effect of chemotherapy in pregnant women on the teeth of offspring. Pediatr Dent 25(6): 601-604.

Perry MC. 2008. Appendix I. In The Chemotherapy Source Book 4th Edition. McKinney Pa, ed. Philadelphia, PA. : Lippincott Williams & Wilkins. 600-601.

Peterson B. 2008. Chemotherapy of Hodgkin Lymphoma (Chapter 42). In The Chemotherapy Source Book, Fourth Edition. Perry M, ed. Philadelphia, PA: Lippincott, Williams, and Wilkins. 499-517.

Peterson C, Lester DR, Jr., Sanger W. 2010. Burkitt's lymphoma in early pregnancy. J Clin Oncol 28(9): e136-138.

Petit AM, Rak J, Hung MC, Rockwell P, Goldstein N, Fendly B, Kerbel RS. 1997. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. The American journal of pathology 151(6): 1523-1530.

Petrek J, Seltzer V. 2003. Breast cancer in pregnant and postpartum women. J Obstet Gynaecol Can 25(11): 944-950.

Petrek JA. 1994. Breast cancer during pregnancy. Cancer 74(1 Suppl): 518-527.

Petrere JA, Kim SN, Anderson JA, Fitzgerald JE, de la Iglesia FA, Schardein JL. 1986. Teratology studies of ametantrone acetate in rats and rabbits. Teratology 34(3): 271-278.

Pettersson BF, Andersson S, Hellman K, Hellstrom AC. 2010. Invasive carcinoma of the uterine cervix associated with pregnancy: 90 years of experience. Cancer 116(10): 2343-2349.

Pharmaceutical Partners of Canada Inc. 2009. Vinorelbine. http://www.ppcdrugs.com/en/products/product_inserts/EN_WebInsert_Vinorelbine.pdf).

Pharmacia & UpJohn Company. 2010. Doxorubicin Hydrochloride for Injection, USP. Division of Pfizer Inc. NY NY 10017.

Pierro LJ. 1961. Teratogenic action of actinomycin D in the embryonic chick. J Exp Zool 147: 203-210.

Pilkington T, Brogden RN. 1992. Acitretin. A review of its pharmacology and therapeutic use. Drugs 43(4): 597-627.

Pizzuto J, Aviles A, Noriega L, Niz J, Morales M, Romero F. 1980. Treatment of acute leukemia during pregnancy: presentation of nine cases. Cancer treatment reports 64(4-5): 679-683.

Plows CW. 1982. Acute myelomonocytic leukemia in pregnancy: report of a case. American journal of obstetrics and gynecology 143(1): 41-43.

Polifka JE, Friedman JM. 2002. Teratogen update: Azathioprine and 6-mercaptopurine. Teratology 65(5): 240-261.

Pons JC, Lebon P, Frydman R, Delfraissy JF. 1995. Pharmacokinetics of interferon-alpha in pregnant women and fetoplacental passage. Fetal diagnosis and therapy 10(1): 7-10.

Potluri V, Lewis D, Burton GV. 2006. Chemotherapy with taxanes in breast cancer during pregnancy: case report and review of the literature. Clin Breast Cancer 7(2): 167-170.

Potter JF, Schoeneman M. 1970. Metastasis of maternal cancer to the placenta and fetus. Cancer 25(2): 380-388.

Press MF, Cordon-Cardo C, Slamon DJ. 1990. Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. Oncogene 5(7): 953-962.

Pye SM, Cortes J, Ault P, Hatfield A, Kantarjian H, Pilot R, Rosti G, Apperley JF. 2008. The effects of imatinib on pregnancy outcome. Blood 111(12): 5505-5508.

Rabaiotti E, Sigismondi C, Montoli S, Mangili G, Candiani M, Vigano R. 2010. Management of locally advanced cervical cancer in pregnancy: a case report. Tumori 96(4): 623-626.

Raffles A, Williams J, Costeloe K, Clark P. 1989. Transplacental effects of maternal cancer chemotherapy. Case report. British journal of obstetrics and gynaecology 96(9): 1099-1100.

Raghunath G, Shashi R. 2006. A case of pregnancy with epithelial ovarian carcinoma. J Obstet Gynecol India 56(5): 446-448.

Rahman ME, Ishikawa H, Watanabe Y, Endo A. 1994. Carpal and tarsal bone anomalies in mice induced by maternal treatment of Ara-C. Reproductive toxicology (Elmsford, N.Y 8(1): 41-47.

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. 2003. Guidelines for case classification for the National Birth Defects Prevention Study. Birth defects research 67(3): 193-201.

Reed W, Hannisdal E, Skovlund E, Thoresen S, Lilleng P, Nesland JM. 2003. Pregnancy and breast cancer: a population-based study. Virchows Arch 443(1): 44-50.

Reintgen DS, McCarty KS, Jr., Vollmer R, Cox E, Seigler HF. 1985. Malignant melanoma and pregnancy. Cancer 55(6): 1340-1344.

Requena A, Velasco JG, Pinilla J, Gonzalez-Gonzalez A. 1995. Acute leukemia during pregnancy: Obstetric management and perinatal outcome of two cases. European Journal of Obstetrics Gynecology and Reproductive Biology 63(2): 139-141.

Reynoso EE, Shepherd FA, Messner HA, Farquharson HA, Garvey MB, Baker MA. 1987. Acute leukemia during pregnancy: the Toronto Leukemia Study Group experience with long-term follow-up of children exposed in utero to chemotherapeutic agents. J Clin Oncol 5(7): 1098-1106.

Reynoso EE, Huerta F. 1994. Acute leukemia and pregnancy--fatal fetal outcome after exposure to idarubicin during the second trimester. Acta oncologica (Stockholm, Sweden) 33(6): 709-710.

Ring AE, Smith IE, Ellis PA. 2005. Breast cancer and pregnancy. Ann Oncol 16(12): 1855-1860.

Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. 2005. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol 23(18): 4192-4197.

Ritter EJ. 1984. Potentiation of teratogenesis. Fundam Appl Toxicol 4(3 Pt 1): 352-359.

Rizack T, Mega A, Legare R, Castillo J. 2009. Management of hematological malignancies during pregnancy. American journal of hematology 84(12): 830-841.

Rizzo R, Lammer EJ, Parano E, Pavone L, Argyle JC. 1991. Limb reduction defects in humans associated with prenatal isotretinoin exposure. Teratology 44(6): 599-604.

Roberts NJ, Auld BJ. 2010. Trastuzamab (Herceptin)-related cardiotoxicity in pregnancy. Journal of the Royal Society of Medicine 103(4): 157-159.

Robova H, Rob L, Hrehorcak M, Zoban P, Prusa R. 2007. Endodermal sinus tumor diagnosed in pregnancy: a case report. Int J Gynecol Cancer 17(4): 914-916.

Roboz J, NGleicher N, Wu K, Chahinian P, Kerenyi T, Holland J. 1979. DOES DOXORUBICIN CROSS THE PLACENTA? The Lancet 22(29): 1382.

Roche. 2008. Vesnoid (tretinoin) capsules. Complete product information. Roche Laboratories, Nutley, New Jersey. *http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=18446*

(accessed on June 22, 2011).

.

Roche Pharmaceuticals. 2004. ROFERON-A (Interferon alfa-2a, recombinant) Full Product Label Hoffmann-La Roche Inc. Nutley, New Jersey 07110(http://www.gene.com/gene/products/information/roferon-a/pdf/pi.pdf; accessed on July 28, 2011)

Hoffmann-La Roche Inc. Nutley, New Jersey 07110.

Rodriguez AO, Chew H, Cress R, Xing G, McElvy S, Danielsen B, Smith L. 2008. Evidence of poorer survival in pregnancy-associated breast cancer. Obstet Gynecol 112(1): 71-78.

Rosenzweig AI, Crews QE, Jr., Hopwood HG. 1964. Vinblastine Sulfate in Hodgkin's Disease in Pregnancy. Annals of internal medicine 61: 108-112.

Roth MS, Foon KA. 1986. Alpha interferon in the treatment of hematologic malignancies. The American journal of medicine 81(5): 871-882.

Rothberg H, Conrad ME, Cowley RG. 1959. Acute granulocytic leukemia in pregnancy: report of four cases, with apparent acceleration by prednisone in one. The American journal of the medical sciences 237(2): 194-204.

Rouzi AA, Sahly NN, Sahly NF, Alahwal MS. 2009. Cisplatinum and docetaxel for ovarian cancer in pregnancy. Archives of gynecology and obstetrics 280(5): 823-825.

Roy V, Gutteridge CN, Nysenbaum A, Newland AC. 1989. Combination chemotherapy with conservative obstetric management in the treatment of pregnant patients with acute myeloblastic leukaemia. Clinical and laboratory haematology 11(3): 171-178.

Ruiz Reyes G, Tamayo Perez R. 1961. Leukemia and pregnancy: observation of a case treated with busulfan (myleran). Blood 18: 764-768.

Russell MA, Carpenter MW, Akhtar MS, Lagattuta TF, Egorin MJ. 2007. Imatinib mesylate and metabolite concentrations in maternal blood, umbilical cord blood, placenta and breast milk. J Perinatol 27(4): 241-243.

Saarikoski S, Seppala M. 1973. Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus. American journal of obstetrics and gynecology 115(8): 1100-1106.

Sahasranaman S, Howard D, Roy S. 2008. Clinical pharmacology and pharmacogenetics of thiopurines. European journal of clinical pharmacology 64(8): 753-767.

Sandoz. 2011. Fluorouracil Injection, Product Information. Fluorouracil Injection, Product Information. SANDOZ, Princeton, NJ. (*http://www.drugs.com/pro/fluorouracil-injection.html?printable=1;* accessed on August 3, 2011)

sanofi-aventis. 2010. Taxotere (docetaxol) product information. sanofi-aventis U.S. LLC, Bridgewater, NJ. . *http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020449s059lbl.pdf*

accessed on July 4, 2011).

Sanyal MK, Kitchin KT, Dixon RL. 1981. Rat conceptus development in vitro: comparative effects of alkylating agents. Toxicology and applied pharmacology 57(1): 14-19.

Sau A, Clarke S, Bass J, Kaiser A, Marinaki A, Nelson-Piercy C. 2007. Azathioprine and breastfeeding: is it safe? Bjog 114(4): 498-501.

Savient. 2006. SOLTAMOX (Tamoxifen citrate) Oral Solution. Savient Pharmaceuticals,Brunswick, NJ 08816. *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistoryEast* (accessed 08/31/2011).

Sayedur Rahman M, Al-Sibai MH, Rahman J, Al-Suleiman SA, El-Yahia AR, Al-Mulhim AA, Al-Jama F. 2002. Ovarian carcinoma associated with pregnancy. A review of 9 cases. Acta obstetricia et gynecologica Scandinavica 81(3): 260-264.

Schafer AI. 1981. Teratogenic effects of antileukemic chemotherapy. Archives of internal medicine 141(4): 514-515.

Scherf C, Price J. 1996. Severe fetal anaemia following maternal chemotherapy for acute myeloid leukaemia. Journal of Obstetrics and Gynaecology 16(1): 39-40.

Schering Corporation. 2007. INTRON A interferon alfa-2b, recombinant for injection (product information). Kenilworth, NJ 07033.

Schleuning M, Clemm C. 1987. Chromosomal aberrations in a newborn whose mother received cytotoxic treatment during pregnancy. New England Journal of Medicine 317(26): 1666-1667.

Schmid BP. 1984. Monitoring of organ formation in rat embryos after in vitro exposure to azathioprine, mercaptopurine, methotrexate or cyclosporin A. Toxicology 31(1): 9-21.

Scialli AR, DeSesso JM, Rahman A, Husain SR, Goeringer GC. 1995. Embryotoxicity of free and liposome-encapsulated taxol in the chick. Pharmacology 51(3): 145-151.

Scialli AR, Waterhouse TB, Desesso JM, Rahman A, Goeringer GC. 1997. Protective effect of liposome encapsulation on paclitaxel developmental toxicity in the rat. Teratology 56(5): 305-310.

Sekar R, Stone PR. 2007. Trastuzumab use for metastatic breast cancer in pregnancy. Obstet Gynecol 110(2 Pt 2): 507-510.

Shaaban MM. 1975. Suppression of lactation by an antiestrogen, tamoxifen. European journal of obstetrics, gynecology, and reproductive biology 4(5): 167-169.

Sham RL. 1996. All-trans retinoic acid-induced labor in a pregnant patient with acute promyelocytic leukemia [5]. American journal of hematology 53(2): 145.

Shamkhani H, Anderson LM, Henderson CE, Moskal TJ, Runowicz CD, Dove LF, Jones AB, Chaney SG, Rice JM, Poirier MC. 1994. DNA adducts in human and patas monkey maternal and fetal tissues induced by platinum drug chemotherapy. Reproductive toxicology (Elmsford, N.Y 8(3): 207-216.

Sharma JB, Pushparaj M, Kumar S, Roy KK, Raina V, Malhotra N. 2009. Successful pregnancy outcome with 5-flurouracil, epirubicin, cyclophosphamide chemotherapy, and hemostatic radiotherapy with abdominal shielding for metastatic invasive intraductal breast carcinoma. Archives of gynecology and obstetrics 279(3): 415-417.

Shepard TH. 1979. Teratogenicity of therapeutic agents. Curr Probl Pediatr 10(2): 1-42.

Shepard TH, Lemire RJ. 2004. Catalog of Teratogenic Agents, Eleventh Edition. The Johns Hopkins University Press, Baltimore and London.

Sherman JL, Jr., Locke RV. 1958. Use of busulfan in myelogenous leukemia during pregnancy. The New England journal of medicine 259(6): 288-289.

Shieh MP, Mehta RS. 2011. Oligohydramnios associated with administration of weekly paclitaxel for triple-negative breast cancer during pregnancy. Annals of Oncology.

Shrim A, Garcia-Bournissen F, Maxwell C, Farine D, Koren G. 2007. Favorable pregnancy outcome following Trastuzumab (Herceptin) use during pregnancy--Case report and updated literature review. Reproductive toxicology (Elmsford, N.Y 23(4): 611-613.

Sieber SM, Whang-Peng J, Botkin C, Knutsen T. 1978. Teratogenic and cytogenetic effects of some plant-derived antitumor agents (vincristine, colchicine, maytansine, VP-16-213 and VM-26) in mice. Teratology 18(1): 31-47.

Sigma-tau. 2004. Matulane (procarbazine hydrochloride capsules) complete product label. Pharmaceuticals, Gaithersburg, MD 20877.

Simister NE. 2003. Placental transport of immunoglobulin G. Vaccine 21(24): 3365-3369.

Simone MD, Stasi R, Venditti A, Del Poeta G, Aronica G, Bruno A, Masi M, Tribalto M, Papa G, Amadori S. 1995. All-trans retinoic acid (ATRA) administration during pregnancy in relapsed acute promyelocytic leukemia [1]. Leukemia 9(8): 1412-1413.

Siu BL, Alonzo MR, Vargo TA, Fenrich AL. 2002. Transient dilated cardiomyopathy in a newborn exposed to idarubicin and all-trans-retinoic acid (ATRA) early in the second trimester of pregnancy. Int J Gynecol Cancer 12(4): 399-402.

Skalko RG, Gold MP. 1974. Teratogenicity of methotrexate in mice. Teratology 9(2): 159-163.

SkyePharma. 2006. DEPOCYT (cytarabine liposome injection) for intrathecal use only Complete Product label. San Diago, CA 92121.

Slingluff CL, Jr., Reintgen DS, Vollmer RT, Seigler HF. 1990. Malignant melanoma arising during pregnancy. A study of 100 patients. Annals of surgery 211(5): 552-557; discussion 558-559.

Smit JW, Huisman MT, van Tellingen O, Wiltshire HR, Schinkel AH. 1999. Absence or pharmacological blocking of placental P-glycoprotein profoundly increases fetal drug exposure. The Journal of clinical investigation 104(10): 1441-1447.

Smith LH, Dalrymple JL, Leiserowitz GS, Danielsen B, Gilbert WM. 2001. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. American journal of obstetrics and gynecology 184(7): 1504-1512; discussion 1512-1503.

Smith LH, Danielsen B, Allen ME, Cress R. 2003. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. American journal of obstetrics and gynecology 189(4): 1128-1135.

Smith RB, Sheehy TW, Rothberg H. 1958. Hodgkin's disease and pregnancy; case reports and a discussion of the treatment of Hodgkin's disease and leukemia during pregnancy. AMA Arch Intern Med 102(5): 777-789.

Smith RS, Randall P. 1969. Melanoma during pregnancy. Obstet Gynecol 34(6): 825-829.

Sokal JE, Lessmann EM. 1960. Effects of cancer chemotherapeutic agents on the human fetus. Journal of the American Medical Association 172: 1765-1771.

Sood AK, Sorosky JI, Mayr N, Krogman S, Anderson B, Buller RE, Hussey DH. 1997. Radiotherapeutic management of cervical carcinoma that complicates pregnancy. Cancer 80(6): 1073-1078.

Soriano P. 1997. The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. Development (Cambridge, England) 124(14): 2691-2700.

Sorosky JI, Sood AK, Buekers TE. 1997. The use of chemotherapeutic agents during pregnancy. Obstetrics and gynecology clinics of North America 24(3): 591-599.

Sotiropoulos D, Adamidou D. 2004. Two Pregnancies Resulting in a Healthy Newborn in a CML Patient Treated with Imatinib. ABSTRACT from ASH Annual Meeting

Specenier PM, Vermorken JB. 2009. Current concepts for the management of head and neck cancer: chemotherapy. Oral Oncol 45(4-5): 409-415.

Stadler HE, Knowles J. 1971. Fluorouracil in pregnancy: effect on the neonate. Jama 217(2): 214-215.

Steiner-Salz D, Yahalom J, Samuelov A, Polliack A. 1985. Non-Hodgkin's lymphoma associated with pregnancy. A report of six cases, with a review of the literature. Cancer 56(8): 2087-2091.

Stensheim H, Moller B, van Dijk T, Fossa SD. 2009. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27(1): 45-51.

Stentoft J, Lanng Nielsen J, Hvidman LE. 1994. All-trans retinoic acid in acute promyelocytic leukemia in late pregnancy. Leukemia 8(SUPPL. 2): S77-S80.

Stephens JD, Golbus MS, Miller TR, Wilber RR, Epstein CJ. 1980. Multiple congenital anomalies in a fetus exposed to 5-fluorouracil during the first trimester. American journal of obstetrics and gynecology 137(6): 747-749.

Sylvester RK, Lobell M, Teresi ME, Brundage D, Dubowy R. 1987. Excretion of hydroxyurea into milk. Cancer 60(9): 2177-2178.

Takitani K, Hino N, Terada Y, Kurosawa Y, Koh M, Inoue A, Kawakami C, Kuno T, Tamai H. 2005. Plasma all-trans retinoic acid level in neonates of mothers with acute promyelocytic leukemia. Acta Haematol 114(3): 167-169.

Tamaki M, Sugawara T, Kameyama Y, Murakami U. 1966. Vincristine induced malformations in the rat embryo. Annual report of the Research Institute of Environmental Medicine, Nagoya University 15: 61-72.

Taylor G, Blom J. 1980. Acute leukemia during pregnancy. Southern medical journal 73(10): 1314-1315.

Telemo E, Hanson LA. 1996. Antibodies in milk. Journal of mammary gland biology and neoplasia 1(3): 243-249.

Terada Y, Shindo T, Endoh A, Watanabe M, Fukuya T, Yajima A. 1997. Fetal arrhythmia during treatment of pregnancy-associated acute promyelocytic leukemia with all-trans retinoic acid and favorable outcome [1]. Leukemia 11(3): 454-455.

Teva. 2009. Idarubicin hydrochloride product information. . Teva Parenteral Medicines, Inc., Irvine, CA. (*http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=39397*, accessed on August 17, 2011).

.

Teva. 2011. Purinethol (mercaptopurine) product information. Teva Pharmaceuticals USA, Sellersville, PA. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009053s032lbl.pdf; accessed August 10, 2011).

Tewari K, Bonebrake RG, Asrat T, Shanberg AM. 1997. Ambiguous genitalia in infant exposed to tamoxifen in utero. Lancet 350(9072): 183.

Thauvin-Robinet C, Maingueneau C, Robert E, Elefant E, Guy H, Caillot D, Casasnovas RO, Douvier S, Nivelon-Chevallier A. 2001. Exposure to hydroxyurea during pregnancy: a case series. Leukemia 15(8): 1309-1311.

Thiersch JB. 1957. Effect of 2-6 diaminopurine (2-6 DP): 6 chlorpurine (ClP) and thioguanine (ThG) on rat litter in utero. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine 94(1): 40-43.

Thomas L, Andes WA. 1982. Fetal anomaly associated with successful chemotherapy for Hodgkin's disease during the first trimester of pregnancy. Clinical Research 30(2).

Thomas PRM, Peckham MJ. 1976. The investigation and management of Hodgkin's disease in the pregnant patient. Cancer 38(3): 1443-1451.

Thompson DJ, Molello JA, Strebing RJ, Dyke IL. 1975. Reproduction and teratology studies with oncolytic agents in the rat and rabbit. II. 5-(3,3-dimethyl-l-triazeno)imidazole-4-carboxamide (DTIC). Toxicology and applied pharmacology 33(2): 281-290.

Thompson DJ, Molello JA, Strebing RJ, Dyke IL. 1978. Teratogenicity of adriamycin and daunomycin in the rat and rabbit. Teratology 17(2): 151-157.

Toledo TM, Harper RC, Moser RH. 1971. Fetal effects during cyclophosphamide and irradiation therapy. Annals of internal medicine 74(1): 87-91.

Travers RL, Sober AJ, Berwick M, Mihm MC, Jr., Barnhill RL, Duncan LM. 1995. Increased thickness of pregnancy-associated melanoma. The British journal of dermatology 132(6): 876-883.

Turchi JJ, Villasis C. 1988. Anthracyclines in the treatment of malignancy in pregnancy. Cancer 61(3): 435-440.

Udink ten Cate FE, ten Hove CH, Nix WM, de Vries JI, van de Loosdrecht AA, van Elburg RM. 2009. Transient neonatal myelosuppression after fetal exposure to maternal chemotherapy. Case report and review of the literature. Neonatology 95(1): 80-85.

Ushigome F, Takanaga H, Matsuo H, Yanai S, Tsukimori K, Nakano H, Uchiumi T, Nakamura T, Kuwano M, Ohtani H, Sawada Y. 2000. Human placental transport of vinblastine, vincristine, digoxin and progesterone: contribution of P-glycoprotein. European journal of pharmacology 408(1): 1-10.

Ustaalioglu BB, Gumus M, Unal A, Cayir K, Sever O, Elkiran ET, Karaca H, Benekli M, Karaoglu A, Seker M. 2010. Malignancies diagnosed during pregnancy and treated with chemotherapy or other modalities (review of 27 cases): multicenter experiences. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 20(5): 698-703.

Vaidyanathan A, McKeever K, Anand B, Eppler S, Weinbauer GF, Beyer JC. 2011. Developmental immunotoxicology assessment of rituximab in cynomolgus monkeys. Toxicol Sci 119(1): 116-125.

Valappil S, Kurkar M, Howell R. 2007. Outcome of pregnancy in women treated with all-trans retinoic acid; a case report and review of literature. Hematology (Amsterdam, Netherlands) 12(5): 415-418.

Van Calsteren K, Vergote I, Amant F. 2005. Cervical neoplasia during pregnancy: Diagnosis, management and prognosis. Best Practice & Research in Clinical Obstetrics & Gynaecology 19(4): 611-630.

Van Calsteren K, Berteloot P, Hanssens M, Vergote I, Amant F, Ganame J, Claus P, Mertens L, Lagae L, Delforge M, Paridaens R, Noens L, Humblet Y, Vandermeersch B, De Muylder X. 2006. In utero exposure to chemotherapy: effect on cardiac and neurologic outcome. J Clin Oncol 24(12): e16-17.

Van Calsteren K, Heyns L, De Smet F, Van Eycken L, Gziri MM, Van Gemert W, Halaska M, Vergote I, Ottevanger N, Amant F. 2010. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol 28(4): 683-689.

Van Calsteren K, Verbesselt R, Beijnen J, Devlieger R, De Catte L, Chai DC, Van Bree R, Heyns L, de Hoon J, Amant F. 2010. Transplacental transfer of anthracyclines, vinblastine, and 4-hydroxy-cyclophosphamide in a baboon model. Gynecologic oncology 119(3): 594-600.

Van Calsteren K, Verbesselt R, Devlieger R, De Catte L, Chai DC, Van Bree R, Heyns L, Beijnen J, Demarsin S, de Bruijn E, de Hoon J, Amant F. 2010. Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. Int J Gynecol Cancer 20(9): 1456-1464.

Van Calsteren K, Verbesselt R, Van Bree R, Heyns L, de Bruijn E, de Hoon J, Amant F. 2010. Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. Reproductive sciences (Thousand Oaks, Calif 18(1): 57-63.

Vandyke K, Fitter S, Dewar AL, Hughes TP, Zannettino AC. 2010. Dysregulation of bone remodeling by imatinib mesylate. Blood 115(4): 766-774.

Veneri D, Todeschini G, Pizzolo G, Franchini M, Ambrosetti A, Vassanelli A, Bressan F, Diani F. 1996. Acute leukemia and pregnancy. Case report. Clinical and experimental obstetrics & gynecology 23(2): 112-115.

Volkenandt M, Buchner T, Hiddemann W, van de Loo J. 1987. Acute leukaemia during pregnancy. Lancet 330(8574): 1521-1522.

Wagner VM, Hill JS, Weaver D, Baehner RL. 1980. Congenital abnormalities in baby born to cytarabine treated mother. Lancet 2(8185): 98-99.

Waller CF. 2010. Imatinib mesylate. Recent results in cancer research. Fortschritte der Krebsforschung 184: 3-20.

Warraich Q, Smith N. 2009. Herceptin therapy in pregnancy: continuation of pregnancy in the presence of anhydramnios. J Obstet Gynaecol 29(2): 147-148.

Watanabe R, Okamoto S, Moriki T, Kizaki M, Kawai Y, Ikeda Y. 1995. Treatment of acute promyelocytic leukemia with all-trans retinoic acid during the third trimester of pregnancy [9]. American journal of hematology 48(3): 210-211.

Watson WJ. 2005. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. Obstet Gynecol 105(3): 642-643.

Webb GA. 1980. The use of hyperalimentation and chemotherapy in pregnancy: a case report. American journal of obstetrics and gynecology 137(2): 263-266.

Weber-Schoendorfer C, Schaefer C. 2008. Trastuzumb exposure during pregnancy. Reproductive toxicology (Elmsford, N.Y 25(3): 390-391; author reply 392.

Wells JH, Marshall JR, Carbone PP. 1968. Procarbazine therapy for Hodgkin's disease in early pregnancy. Jama 205(13): 935-937.

White LG. 1962. Busulfan in pregnancy. Jama 179: 973-974.

Whitecar MP, Turner S, Higby MK. 1999. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. American journal of obstetrics and gynecology 181(1): 19-24.

Wiebe VJ, Sipila PE. 1994. Pharmacology of antineoplastic agents in pregnancy. Critical reviews in oncology/hematology 16(2): 75-112.

Wiernik PH, Duncan JH. 1971. Cyclophosphamide in human milk. Lancet 1(7705): 912.

Wiestler OD, Kleihues P, Rice JM, Ivankovic S. 1984. DNA methylation in maternal, fetal and neonatal rat tissues following perinatal administration of procarbazine. Journal of cancer research and clinical oncology 108(1): 56-59.

Wilcox AJ. 2010. Fertility and Pregnancy: An Epidemiologic Perspective, New York, New York: Oxford University Press.

Willemse PH, van der Sijde R, Sleijfer DT. 1990. Combination chemotherapy and radiation for stage IV breast cancer during pregnancy. Gynecologic oncology 36(2): 281-284.

Wilson JG, Scott WJ, Ritter EJ, Fradkin R. 1975. Comparative distribution and embryotoxicity of hydroxyurea in pregnant rats and rhesus monkeys. Teratology 11(2): 169-178.

Wisel MS, Datta JK, Saxena RN. 1994. Effects of anti-estrogens on early pregnancy in guinea pigs. International journal of fertility and menopausal studies 39(3): 156-163.

Witzel ID, Muller V, Harps E, Janicke F, Dewit M. 2008. Trastuzumab in pregnancy associated with poor fetal outcome. Ann Oncol 19(1): 191-192.

Yamasaki K, Noda S, Muroi T, Mitoma H, Takakura S, Sakamoto S. 2005. Effects of in utero and lactational exposure to tamoxifen in SD rats. Toxicology letters 156(2): 289-296.

Yarbro JW. 1992. Mechanism of action of hydroxyurea. Seminars in oncology 19(3 Suppl 9): 1-10.

Yucebilgin MS, Cagirgan S, Donmez A, Ozkinay E, Akercan F, Mgoyi L, Vural F. 2004. Acute myeloblastic leukemia in pregnancy: a case report and review of the literature. European journal of gynaecological oncology 25(1): 126-128.

Zamenhof S. 1985. Differential effects of antifolate on the development of brain parts in chick embryos. Growth 49(1): 28-33.

Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. 1991. Maternal and fetal outcome after invasive cervical cancer in pregnancy. J Clin Oncol 9(11): 1956-1961.

Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Burke B, Sutcliffe SB, Koren G. 1992. Maternal and fetal outcome after breast cancer in pregnancy. American journal of obstetrics and gynecology 166(3): 781-787.

Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. 1992. Fetal outcome after in utero exposure to cancer chemotherapy. Archives of internal medicine 152(3): 573-576.

Zemlickis D, Lishner M, Erlich R, Koren G. 1993. Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide. Teratogenesis, carcinogenesis, and mutagenesis 13(3): 139-143.

Zhao XY, Huang HF, Lian LJ, Lang JH. 2006. Ovarian cancer in pregnancy: A clinicopathologic analysis of 22 cases and review of the literature. International Journal of Gynecological Cancer 16(1): 8-15.

Zirvi KA, Gilani SH, Hill GJ. 1985. Embryotoxic effects of doxorubicin and N-trifluoroacetyladriamycin-14-valerate (AD-32). Teratology 31(2): 247-252.

Zoet AG. 1950. Pregnancy complicating Hodgkin's disease. Northwest medicine 49(6): 373-374.

Zuazu J, Julia A, Sierra J, Valentin MG, Coma A, Sanz MA, Batlle J, Flores A. 1991. Pregnancy outcome in hematologic malignancies. Cancer 67(3): 703-709.

Errata

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

August 12, 2012

1. The draft monograph is partially formatted. The full citation for all unformatted references can be found in the reference lists of the monograph and/or the appendices with the exception of two references. The two excluded references are:

   Bus, J.S., Gibson, J.E. 1973. Teratogenicity and neonatal toxicity of ifosfamide in mice. Proc Soc Exp Biol Med 143:965-970. (*reference #1344 in draft NTP monograph*)

   Christianson, C., Huff, D., and McPherson, E. 1999. Limb deformations in oligohydramnios sequence: Effects of gestational age and duration of oligohydramnios. Amer J Med Genet 86:430-433. *(reference #1343 in draft monograph)*

2. In the List of Figures, Figure 1 begins on page 43.

3. On page 2 of the Executive Summary, the superscript "d only" in the last sentence of the last paragraph should be removed.

4. Introduction (Section 2.0) should be page 7, instead of beginning again at page 1 after the Executive Summary.

5. On page 39, Table 17 should have two footnotes: [a]also, act as DNA intercalating/cross-linking agents and [b] also acts as a topoisomerase II inhibitor.

6. On page 46, Table 21 should have the following footnotes providing the descriptions for intrauterine growth restriction and small for gestational age: [a]Fetuses who are estimated to be less than the 10th percentile for growth per gestational age, and [b]Live born infants who are less than 10th percentile for body weight at birth as reported by the authors.

7. On page 178, the phrase "Table X for chemical –specific breakdown" should read "Appendix Table 1."

8. In References, there is a duplicate reference for mitoxantrone product information (AAP Pharmaceuticals, 2010).

9. In References, all product information citations will be made the same font size as the rest of the references and extra fields will be removed.