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

This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any NTP determination or policy.

Peer Review Date: October 1-2, 2012
Table of Contents

Table of Contents .............................................................................................................................. I

List of Tables ..................................................................................................................................... III

List of Figures .................................................................................................................................... III

Abbreviations ....................................................................................................................................... VI

1.0 Executive Summary .................................................................................................................. 1

2.0 Introduction ............................................................................................................................. 1

3.0 Methods ......................................................................................................................................... 3

3.1 Search methods for identification of studies ............................................................................. 3

3.2 Criteria for considering studies for this evaluation ................................................................. 4

3.3 Data Collection and Analysis ................................................................................................. 10

4.0 Cancer Diagnosed during Pregnancy: Background information on seven frequently diagnosed cancers .................................................................................................................. 11

4.1 Breast Cancer & Pregnancy ......................................................................................................... 12

4.2 Cervical Cancer & Pregnancy ................................................................................................. 19

4.3 Hodgkin Lymphoma & Pregnancy .......................................................................................... 22

4.4 Non-Hodgkin Lymphoma & Pregnancy ............................................................................... 25

4.5 Leukemia & Pregnancy ........................................................................................................... 30

4.6 Ovarian Cancer & Pregnancy ............................................................................................... 33

4.7 Melanoma & Pregnancy ......................................................................................................... 36

5.0 Cancer Chemotherapeutic Agents Administered during Pregnancy: Overall Analysis and Agent Specific Summaries ........................................................................................................ 39

5.1 OVERALL ANALYSIS BASED ON ANY CHEMOTHERAPY EXPOSURE .................................. 40

5.2 5-FLUOROURACIL ..................................................................................................................... 49

5.3 6-MERCAPTOPURINE ............................................................................................................. 54

5.4 6-THIOGUANINE ...................................................................................................................... 58

5.5 ACTINOMYCIN D ..................................................................................................................... 62

5.6 ALL-TRANS RETINOIC ACID ................................................................................................. 64

5.7 BLEOMYCIN ........................................................................................................................... 68

5.8 BUSULFAN ............................................................................................................................... 71

5.9 CARBOPLATIN ......................................................................................................................... 74

July 30, 2012
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.10</td>
<td>CISPLATIN</td>
<td>77</td>
</tr>
<tr>
<td>5.11</td>
<td>CYCLOPHOSPHAMIDE</td>
<td>82</td>
</tr>
<tr>
<td>5.12</td>
<td>CYTARABINE (Cytosine arabinoside)</td>
<td>90</td>
</tr>
<tr>
<td>5.13</td>
<td>DACARBAZINE</td>
<td>97</td>
</tr>
<tr>
<td>5.14</td>
<td>DAUNORUBICIN</td>
<td>100</td>
</tr>
<tr>
<td>5.15</td>
<td>DOCETAXEL</td>
<td>105</td>
</tr>
<tr>
<td>5.16</td>
<td>DOXORUBICIN</td>
<td>108</td>
</tr>
<tr>
<td>5.17</td>
<td>EPIRUBICIN</td>
<td>114</td>
</tr>
<tr>
<td>5.18</td>
<td>ETOPOSIDE</td>
<td>117</td>
</tr>
<tr>
<td>5.19</td>
<td>HYDROXYUREA</td>
<td>120</td>
</tr>
<tr>
<td>5.20</td>
<td>IDARUBICIN</td>
<td>124</td>
</tr>
<tr>
<td>5.21</td>
<td>IFOSFAMIDE</td>
<td>127</td>
</tr>
<tr>
<td>5.22</td>
<td>IMATINIB</td>
<td>130</td>
</tr>
<tr>
<td>5.23</td>
<td>INTERFERON ALPHA</td>
<td>134</td>
</tr>
<tr>
<td>5.24</td>
<td>METHOTREXATE</td>
<td>137</td>
</tr>
<tr>
<td>5.25</td>
<td>MITOXANTRONE</td>
<td>141</td>
</tr>
<tr>
<td>5.26</td>
<td>NITROGEN MUSTARD (Mechlorethamine)</td>
<td>144</td>
</tr>
<tr>
<td>5.27</td>
<td>PACLITAXEL</td>
<td>147</td>
</tr>
<tr>
<td>5.28</td>
<td>PROCARBAZINE</td>
<td>150</td>
</tr>
<tr>
<td>5.29</td>
<td>RITUXIMAB</td>
<td>153</td>
</tr>
<tr>
<td>5.30</td>
<td>TAMOXIFEN</td>
<td>156</td>
</tr>
<tr>
<td>5.31</td>
<td>TRASTUZUMAB</td>
<td>160</td>
</tr>
<tr>
<td>5.32</td>
<td>VINBLASTINE</td>
<td>164</td>
</tr>
<tr>
<td>5.33</td>
<td>VINCIRISTINE</td>
<td>168</td>
</tr>
<tr>
<td>5.34</td>
<td>VINORELBINE</td>
<td>173</td>
</tr>
<tr>
<td>6.0</td>
<td>Long-term evaluations of growth and development</td>
<td>174</td>
</tr>
<tr>
<td>7.0</td>
<td>Pregnancy outcomes of medical personnel exposed to cancer chemotherapeutics</td>
<td>176</td>
</tr>
<tr>
<td>8.0</td>
<td>Discussion</td>
<td>177</td>
</tr>
<tr>
<td>9.0</td>
<td>References</td>
<td>183</td>
</tr>
<tr>
<td>10.0</td>
<td>Errata</td>
<td>214</td>
</tr>
</tbody>
</table>
List of Tables

Table 1. Types of studies included in the NTP monograph on developmental effects associated with cancer chemotherapy use during pregnancy. .......................................................... 4

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.......................................................... 6

Table 3 Estimated new cases and deaths from breast cancer in the United States in 2010........................................ 12

Table 4 Chemotherapy agents used to treat breast cancer reviewed in the NTP monograph.................. 18

Table 5 Estimated new cases and deaths from cervical (uterine cervix) cancer in the United States in 2010: ......................................................................................................................... 19

Table 6 Chemotherapy agents used to treat cervical cancer reviewed in the NTP monograph .......... 21

Table 7 Estimated new cases and deaths from Hodgkin lymphoma in the United States in 2010 .......... 22

Table 8 Chemotherapy agents used to treat Hodgkin lymphoma reviewed in the NTP monograph ...... 24

Table 9 Estimated new cases and deaths from non-Hodgkin lymphoma in the United States in 2010.... 25

Table 10 Chemotherapy agents used to treat non-Hodgkin lymphoma reviewed in the NTP monograph ......................................................................................................................... 29

Table 11 Estimated new cases and deaths from Leukemia in the United States in 2010............. 30

Table 12 Chemotherapy agents used to treat leukemia reviewed in the NTP monograph ............. 31

Table 13 Estimated new cases and deaths from ovarian cancer in the United States in 2010....... 33

Table 14 Chemotherapy agents used to treat ovarian cancer reviewed in the NTP monograph ...... 35

Table 15 Estimated new cases and deaths from melanoma in the United States in 2010.............. 36

Table 16 Chemotherapy agents used to treat melanoma reviewed in the NTP monograph............. 38

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. ............. 39

Table 18 Pooled pregnancy outcome data associated with cancer chemotherapy use during pregnancy. ................................................................................................................................. 40

Table 19 Incidence of spontaneous abortiona and stillbirthb following cancer chemotherapy use during pregnancy to any cancer chemotherapy or individual agents (singly or in combination therapy) .......... 45

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. 46

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. .......... 47

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. .................. 48

July 30, 2012
List of Figures

Figure 1 Apparent rates of major congenital malformations (± 95% confidence interval) reported following cancer chemotherapy use during the pregnancy. Data are presented as any chemotherapy exposure or by individual agent, singly or in combination therapy. ............. Error! Bookmark not defined.
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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>doxorubicin (also called adriamycin), bleomycin, vinblastine, and dacarbazine</td>
</tr>
<tr>
<td>AGL</td>
<td>acute granulocytic leukemia; same as acute myelogenous leukemia</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>ALL (acute lymphocytic)</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloblastic leukemia</td>
</tr>
<tr>
<td>AMML</td>
<td>acute myelomonocytic leukemia</td>
</tr>
<tr>
<td>AMSA</td>
<td>amascrine</td>
</tr>
<tr>
<td>APL</td>
<td>acute promyelocytic leukemia</td>
</tr>
<tr>
<td>ATRA</td>
<td>all-trans retinoic acid</td>
</tr>
<tr>
<td>BEACOPP</td>
<td>bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone</td>
</tr>
<tr>
<td>Behenoyl-araC</td>
<td>behenoyl cytosine arabinoside</td>
</tr>
<tr>
<td>bw</td>
<td>body weight</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control and Prevention</td>
</tr>
<tr>
<td>CGL</td>
<td>chronic granulocytic leukemia; same as chronic myelogenous leukemia</td>
</tr>
<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>CML (chronic myeloid leukemia)</td>
<td></td>
</tr>
<tr>
<td>C-section</td>
<td>Caesarean-section</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
</tr>
<tr>
<td>IT</td>
<td>intrathecal</td>
</tr>
<tr>
<td>IU</td>
<td>international units</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine growth retardation</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>µg</td>
<td>microgram</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>m²</td>
<td>meter cubed</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NCCN</td>
<td>The National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NIEHS</td>
<td>National Institute of Environmental Health Sciences</td>
</tr>
<tr>
<td>NS</td>
<td>not specified</td>
</tr>
<tr>
<td>NTP</td>
<td>National Toxicology Program</td>
</tr>
<tr>
<td>OHAT</td>
<td>Office of Health Assessment and Translation</td>
</tr>
<tr>
<td>PC</td>
<td>period of conception</td>
</tr>
<tr>
<td>Pt</td>
<td>patient</td>
</tr>
<tr>
<td>SLL</td>
<td>small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Stanford V</td>
<td>doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone</td>
</tr>
</tbody>
</table>
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, 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 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

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 chemotherapeutic 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.

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 chemotherapeutic 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 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. 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?

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. **Is cancer chemotherapy use during pregnancy associated with an increased risk of spontaneous abortions or stillbirth?**

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. **Is cancer chemotherapy use during pregnancy associated with pregnancy complications?**

**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. **Is cancer chemotherapy use during pregnancy associated with effects on newborn weight and health?**

**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 anthracyclines 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 cyclophosphamide 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. Is cancer chemotherapy use associated with adverse effects on infant growth and development at follow up evaluation?

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:

---

July 30, 2012
• **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 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

---

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

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.

<table>
<thead>
<tr>
<th>Study types</th>
<th>Number of studies</th>
<th>Number of conceptuses per study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>case reports</td>
<td>321</td>
<td>335</td>
</tr>
<tr>
<td>case series</td>
<td>84</td>
<td>385</td>
</tr>
<tr>
<td>case series, retrospective</td>
<td>9</td>
<td>93</td>
</tr>
<tr>
<td>cohort, retrospective</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>survey, registry</td>
<td>1</td>
<td>160</td>
</tr>
<tr>
<td>survey, retrospective</td>
<td>13</td>
<td>267</td>
</tr>
<tr>
<td>Total</td>
<td>431</td>
<td>1271</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Chemotherapeutic agent</th>
<th>Number of reported conceptuses</th>
<th>Location in this review</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>175</td>
<td>Text section 5.2, Appendix C Table 1</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>84</td>
<td>Text section 5.3, Appendix C Table 2</td>
</tr>
<tr>
<td>6-Thioguanine</td>
<td>49</td>
<td>Text section 5.4, Appendix C Table 3</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>13</td>
<td>Text section 5.5, Appendix C Table 4</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>29</td>
<td>Text section 5.6, Appendix C Table 5</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>2</td>
<td>Appendix D Table 1</td>
</tr>
<tr>
<td>Behenoyl cytosine arabinoside</td>
<td>3</td>
<td>Appendix D Table 2</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>95</td>
<td>Text section 5.7, Appendix C Table 6</td>
</tr>
<tr>
<td>Busulfan</td>
<td>31</td>
<td>Text section 5.8, Appendix C Table 7</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1</td>
<td>Appendix D Table 3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>17</td>
<td>Text section 5.9, Appendix C Table 8</td>
</tr>
<tr>
<td>Carmustine</td>
<td>3</td>
<td>Appendix D Table 4</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>10</td>
<td>Appendix D Table 5</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>101</td>
<td>Text section 5.10, Appendix C Table 9</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>408</td>
<td>Text section 5.11, Appendix C Table 10</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>151</td>
<td>Text section 5.12, Appendix C Table 11</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>57</td>
<td>Text section 5.13, Appendix C Table 12</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>3</td>
<td>Appendix D Table 6</td>
</tr>
<tr>
<td>Chemotherapeutic agent</td>
<td>Number of reported conceptuses</td>
<td>Location in this review</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>106</td>
<td>Text section 5.14, Appendix C Table 13</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>20</td>
<td>Text section 5.15, Appendix C Table 14</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>420</td>
<td>Text section 5.16, Appendix C Table 15</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>69</td>
<td>Text section 5.17, Appendix C Table 16</td>
</tr>
<tr>
<td>Etoposide</td>
<td>42</td>
<td>Text section 5.18, Appendix C Table 17</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>2</td>
<td>Appendix D Table 7</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>3</td>
<td>Appendix D Table 8</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>68</td>
<td>Text section 5.19, Appendix C Table 18</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>22</td>
<td>Text section 5.20, Appendix C Table 19</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>11</td>
<td>Text section 5.21, Appendix C Table 20</td>
</tr>
<tr>
<td>Imatinib</td>
<td>157</td>
<td>Text section 5.21, Appendix C Table 21</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>43</td>
<td>Text section 0, Appendix C Table 22</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>2</td>
<td>Appendix D Table 9</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1</td>
<td>Appendix D Table 10</td>
</tr>
<tr>
<td>Lomustine</td>
<td>1</td>
<td>Appendix D Table 11</td>
</tr>
<tr>
<td>Methyl-GAG</td>
<td>3</td>
<td>Appendix D Table 12</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>83</td>
<td>Text section 5.24, Appendix C Table 23</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>17</td>
<td>Text section 5.25, Appendix C Table 24</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1</td>
<td>Appendix D Table 13</td>
</tr>
<tr>
<td>Nimustine</td>
<td>1</td>
<td>Appendix D Table 14</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>30</td>
<td>Text section 5.26, Appendix C Table 25</td>
</tr>
<tr>
<td>Oxalplatin</td>
<td>5</td>
<td>Appendix D Table 15</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>31</td>
<td>Text section 5.27, Appendix C Table 26</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>31</td>
<td>Text section 5.28, Appendix C Table 27</td>
</tr>
<tr>
<td>Rituximab</td>
<td>24</td>
<td>Text section 5.29, Appendix C Table 28</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>1</td>
<td>Appendix D Table 16</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>14</td>
<td>Text section 5.30, Appendix C Table 29</td>
</tr>
<tr>
<td>Teniposide</td>
<td>2</td>
<td>Appendix D Table 17</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>20</td>
<td>Text section 5.31, Appendix C Table 30</td>
</tr>
<tr>
<td>Triethylenemelamine</td>
<td>6</td>
<td>Appendix D Table 18</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>73</td>
<td>Text section 5.32, Appendix C Table 31</td>
</tr>
<tr>
<td>Vincristine</td>
<td>223</td>
<td>Text section 5.33, Appendix C Table 32</td>
</tr>
<tr>
<td>Vindesine</td>
<td>1</td>
<td>Appendix D Table 19</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>15</td>
<td>Text section 5.34, Appendix C Table 33</td>
</tr>
</tbody>
</table>
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:
  - Intrauterine growth restriction
  - Reduced/absent amniotic fluid
  - 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 defects 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 gestational 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>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Cases</td>
<td>207,090</td>
<td>1,970</td>
</tr>
<tr>
<td>Deaths</td>
<td>39,840</td>
<td>390</td>
</tr>
</tbody>
</table>


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 breast 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.

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

<table>
<thead>
<tr>
<th>Chemotherapy agent</th>
<th>Number of studies*</th>
<th>Number of cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil, Appendix C Table 1</td>
<td>27</td>
<td>149</td>
</tr>
<tr>
<td>Capecitabine, Appendix D Table 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carboplatin, Appendix C Table 8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide, Appendix C Table 10</td>
<td>36</td>
<td>258</td>
</tr>
<tr>
<td>Docetaxel, Appendix C Table 14</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Doxorubicin, Appendix C Table 15</td>
<td>39</td>
<td>246</td>
</tr>
<tr>
<td>Epirubicin, Appendix C Table 16</td>
<td>17</td>
<td>59</td>
</tr>
<tr>
<td>Lapatinib, Appendix D Table 11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate, Appendix C Table 22</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Mitoxantrone, Appendix C Table 23</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Paclitaxel, Appendix C Table 25</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Tamoxifen, Appendix C Table 28</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Trastuzumab, Appendix C Table 29</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vinorelbine, Appendix C Table 32</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

*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 website (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  |


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>
<thead>
<tr>
<th>Chemotherapy agent</th>
<th>Number of studies*</th>
<th>Number of cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil, Appendix C Table 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bleomycin, Appendix C Table 6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carboplatin, Appendix C Table 8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cisplatin, Appendix C Table 9</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>Cytarabine, Appendix C Table 11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel, Appendix C Table 25</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th>Table 7 Estimated new cases and deaths from Hodgkin lymphoma in the United States in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cases</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Number of Studies*</th>
<th>Number of Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine, Appendix C Table 2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bleomycin, Appendix C Table 6</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Chlorambucil, Appendix D Table 5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cisplatin, Appendix C Table 9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide, Appendix C Table 10</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Cytarabine, Appendix C Table , 11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dacarbazine, Appendix C Table 12</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Doxorubicin, Appendix C Table 13</td>
<td>13</td>
<td>51</td>
</tr>
<tr>
<td>Epirubicin, Appendix C Table 16</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Etoposide, Appendix C Table 17</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Interferon alpha, Appendix C Table 21</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lomustine, Appendix D Table 12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nitrogen Mustard, Appendix C Table 24</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Procarbazine, Appendix C Table 26</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Rituximab, Appendix C Table 27</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Triethylenemelamine, Appendix D Table 19</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Vinblastine, Appendix C Table 30</td>
<td>24</td>
<td>66</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td>15</td>
<td>26</td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th>Table 9 Estimated new cases and deaths from non-Hodgkin lymphoma in the United States in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cases</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
</tbody>
</table>

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+carboplatin+etoposide; 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, denileukin 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

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Number of Studies*</th>
<th>Number of Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine, Appendix C Table 2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bleomycin, Appendix C Table 6</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Chlorambucil, Appendix D Table 5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cisplatin, Appendix C Table 9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cyclophosphamide, Appendix C Table 10</td>
<td>37</td>
<td>70</td>
</tr>
<tr>
<td>Cytarabine, Appendix C Table , 11</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Doxorubicin, Appendix C Table 15</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>Epirubicin, Appendix C Table 16</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Etoposide, Appendix C Table 17</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Hydroxyurea, Appendix C Table 18</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ifosfamide, Appendix D Table 9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Methotrexate, Appendix C Table 22</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Mitoxantrone, Appendix C Table 23</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Procarbazine, Appendix C Table 26</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab, Appendix C Table 27</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Teniposide, Appendix D Table 18</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Triethylenemelamine, Appendix D Table 19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td>34</td>
<td>68</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>New Cases</th>
<th>207,090</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>39,840</td>
</tr>
</tbody>
</table>


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**

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Number of Studies*</th>
<th>Number of Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Mercaptopurine, Appendix C Table 2</td>
<td>44</td>
<td>78</td>
</tr>
<tr>
<td>6-Thioguanine, Appendix C Table 3</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>All-trans retinoic acid, Appendix C Table 5</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Amsacrine, Appendix D Table 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Behenoyl cytosine arabinoside, Appendix D Table 2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Busulfan, Appendix C Table 7</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>Chlorambucil, Appendix D Table 5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cyclophosphamide, Appendix C Table 10</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Cytarabine, Appendix C Table 11</td>
<td>72</td>
<td>134</td>
</tr>
<tr>
<td>Dasatinib, Appendix D Table 6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Daunorubicin, Appendix C Table 13</td>
<td>55</td>
<td>108</td>
</tr>
<tr>
<td>Doxorubicin, Appendix C Table 15</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>Drug</td>
<td>Table</td>
<td>1</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------</td>
<td>----</td>
</tr>
<tr>
<td>Epirubicin, Appendix C Table 16</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Etoposide, Appendix C Table 17</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Fludarabine, Appendix D Table 7</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hydroxyurea, Appendix C Table 18</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Idarubicin, Appendix C Table 19</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Imatinib, Appendix C Table 20</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Interferon alpha, Appendix C Table 21</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Methotrexate, Appendix C Table 22</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Methyl-GAG, Appendix D Table 13</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Mitoxantrone, Appendix C Table 23</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Nilotinib, Appendix D Table 14</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Nitrogen mustard, Appendix C Table 24</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Triethylenemelamine, Appendix D Table 19</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Vindesine, Appendix D Table 20</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New cases</td>
<td>21,880</td>
</tr>
<tr>
<td>Deaths</td>
<td>13,850</td>
</tr>
</tbody>
</table>


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 et al. 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 63) 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**

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Number of Studies*</th>
<th>Number of Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin D, Appendix C Table 4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Bleomycin, Appendix C Table 6</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Carboplatin, Appendix C Table 8</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Cisplatin, Appendix C Table 9</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>Cyclophosphamide, Appendix C Table 10</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Docetaxel, Appendix C Table 14</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin, Appendix C Table 15</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Etoposide, Appendix C Table 17</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Irinotecan, Appendix D Table 10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel, Appendix C Table 25</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Vinblastine, Appendix C Table 30</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

*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            |


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

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Number of Studies*</th>
<th>Number of Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine, Appendix D Table 4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cisplatin, Appendix C Table 9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dacarbazine, Appendix C Table 12</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Interferon alpha, Appendix C Table 21</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Nimustine, Appendix D Table 15</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tamoxifen, Appendix C Table 28</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vincristine, Appendix C Table 31</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*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, behenyl 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/cross-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.

<table>
<thead>
<tr>
<th>Anti-metabolites</th>
<th>DNA intercalating/cross-linking agents</th>
<th>Topoisomerase II inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluourouracil</td>
<td>Actinomycin D</td>
<td>Etoposide</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Carboplatin</td>
<td></td>
</tr>
<tr>
<td>6-Thioguanine</td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Epirubicin</td>
<td></td>
</tr>
<tr>
<td>DNA alkylating agents</td>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Busulfan&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Epirubicin</td>
<td></td>
</tr>
<tr>
<td>Nitrogen mustard&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Idarubicin</td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Mitoxantrone&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>DNA intercalating/cross-linking agents</td>
<td>Actinomycin D</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Carboplatin</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Epirubicin</td>
<td></td>
</tr>
</tbody>
</table>

July 30, 2012
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. |
|---------------------------------------------------|------------------|------------------|------------------|------------------|
| **Number of conceptuses** | **Overall total** | **Trimester Exposed** | **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 | 703 | 133 | 539 | 31 |

*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 of 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

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 use during pregnancy. Data are presented as any chemotherapy exposure or by individual agent, singly or in combination therapy.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trimester Exposed</th>
<th>% Malformed (±95th CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Chemotherapy Agent</td>
<td>1st</td>
<td>9.8 ± 2.9 (40/410)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>2.7 ± 1.1 (22/823)</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>1st</td>
<td>26.7 ± 2.2.4 (4/15)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>1.3 ± 1.7 (2/160)</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>1st</td>
<td>5.3 ± 7.1 (2/38)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/42)</td>
</tr>
<tr>
<td>6-Thioguanine</td>
<td>1st</td>
<td>33.3 ± 37.7 (2/6)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/43)</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>1st</td>
<td>NA (0 of 13)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/24)</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>1st</td>
<td>0.0 ± 0.0 (0/5)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/24)</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>1st</td>
<td>6.7 ± 12.6 (1/15)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>1.3 ± 2.5 (1/78)</td>
</tr>
<tr>
<td>Busulfan</td>
<td>1st</td>
<td>15.0 ± 15.6 (3/20)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>20.0 ± 35.1 (1/5)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>1st</td>
<td>NA (0 of 17)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/101)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>1st</td>
<td>0.0 ± 0.0 (0/4)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>1.0 ± 1.9 (1/101)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1st</td>
<td>15.2 ± 10.4 (7/46)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.8 ± 0.9 (3/360)</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1st</td>
<td>12.5 ± 11.5 (4/32)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/118)</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>1st</td>
<td>11.1 ± 20.5 (1/9)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/48)</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>1st</td>
<td>5.6 ± 10.6 (1/18)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.0 ± 0.0 (0/84)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>1st</td>
<td>0.0 ± 0.0 (0/1)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>5.3 ± 10.0 (1/19)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1st</td>
<td>9.5 ± 8.9 (4/42)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>0.5 ± 0.7 (3/378)</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>1st</td>
<td>14.3 ± 25.9 (1/7)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>3.3 ± 4.5 (2/61)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>1st</td>
<td>0.0 ± 0.0 (0/3)</td>
</tr>
<tr>
<td></td>
<td>2nd and/or 3rd Only</td>
<td>2.6 ± 5.0 (1/39)</td>
</tr>
</tbody>
</table>
Figure 1. (cont’d) Apparent rates of major congenital malformations.

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

---

*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).

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

\(^a\)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.
Reducions 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.

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

<sup>a</sup>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.

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

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

<sup>a</sup>Includes 7 pregnancies with transient preterm spontaneous labor (Section 5.1)

<sup>b</sup>Preterm birth includes spontaneous and induced vaginal births, and Caesarian-section births.

<sup>c</sup>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 LD50) (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 transferred 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. Hemihypertrophy 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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester exposure and co-exposure to doxorubicin and cyclophosphamide. One infant had a bilateral small protuberance on phalanx 5 following exposure in the 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 seizures 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 {Berry, 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 1\textsuperscript{st} trimester, major congenital malformations were observed in two infants and two fetuses terminated by induced abortion. One newborn with 1\textsuperscript{st} 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), hemangiom (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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} trimester chemotherapy exposure. Therefore, a revised occurrence of major malformations possibly attributed to 5-fluorouracil exposure in the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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). Gardner 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 microphthalmia 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., 1\textsuperscript{st} trimester exposure), then to busulfan from 1\textsuperscript{st} and 3\textsuperscript{rd} trimesters with the addition of 6-mercaptopurine again in the 3\textsuperscript{rd} 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 1\textsuperscript{st} through 3\textsuperscript{rd} 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 2\textsuperscript{nd} trimester and co-treated with vincristine, cyclophosphamide, asparaginase, daunorubicin, and radiation therapy; and was previously exposed to vincristine and intrathecal methotrexate in the 1\textsuperscript{st} trimester (Okun et al. 1979). There were no malformations in infants exposed to 6-mercaptopurine during the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 known as antimetabolites. It is a metabolite of azathioprine 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 myelogenous 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/8x10^8 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 of four mothers treated with daily oral doses of azathioprine (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, 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 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 secundum-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 parvulus. 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 known 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 omphalocoele, micrognathia or agnathia, microcephaly, 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
anhidramnios and fetal growth restriction 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 abnormalities (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 accurately 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. (Taikitani 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 1\textsuperscript{st} trimester in 5 pregnancies and in the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 1\textsuperscript{st} 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 3\textsuperscript{rd} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester and co-exposed to idarubicin (Carradice et al. 2002) and the other infant was exposed in the 3\textsuperscript{rd} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 Potter 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/m² 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/m² 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 sets 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 was exposed following pregnancy (n=2 pregnancies) (Ghaemmaghami et al. 2007), fetal growth retardation (n=1 pregnancy) (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 hypoplasias (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 WKHA/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 Japanese 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 conceptions). 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/m²) 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/m² 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 embroyolethal 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: gastrochosisis, 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/m²) 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/m² (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/m² (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 LD50S 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; these 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 transplacental 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
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 hypoplasia, 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 microphthalmia 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 (Benhaim, 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. Microphthalmia, 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

80 July 30, 2012
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’Incalti et al. (D’Incalti 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/m² 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/mm³ and 270,000/mm³ to 3,200/mm³ and 47,000/mm³, 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, ectodactyly, 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, encephaly, kinky tail, polydactyly, syndactyly, ectodactyly, 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 ectodysontactyly 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 (Lyczette, 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 (Lyczette, 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-exposure 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; Lyctee, 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; Ginopoulo, 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 (Chegoum 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}.

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 hypopcapnia 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
atria, 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/m² 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/m² basis). In rats administered single intraperitoneally doses of 50 mg/kg (about 10 times the recommended human dose on mg/m² 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/m² 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/m² 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, microcystic renal changes, and retinal dysplasia. Percy et al. (Percy 1975) reports that treatment of pregnant ICR Swiss mice and Sprague-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 microcystic 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, renouretal 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 Jc1: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 cytarabine/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), erythroleukemia (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) (Chelgoum 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 bruising 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 cyclophosphamide, 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). Hypoplasdias 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 experienced a 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 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 cytarabine 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 2010, Price et al. 2010).
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 hypotremia; 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 1\textsuperscript{st} trimester in 9 pregnancies, and in the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 2\textsuperscript{nd} 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 1\textsuperscript{st} trimester and co-treated with nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, and vinblastine. Induced abortion terminated two additional pregnancies following 2\textsuperscript{nd} trimester exposure (d’Incalci et al. 1983) (Zemlickis, 1992 #576); no fetal data were provided. Intrauterine fetal death occurred in the 8\textsuperscript{th} month of pregnancy following 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 1\textsuperscript{st} trimester and co-exposed to bleomycin, doxorubicin, and vinblastine. Another infant had syndactyly of the 4\textsuperscript{th} and 5\textsuperscript{th} fingers with exposure in the 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 1\textsuperscript{st} and 2\textsuperscript{nd} 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 1\textsuperscript{st} 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) (Fadliah 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 enterocolitis (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 microphthalmia) 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 myelogenous 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 daunorubicin. 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). Polyhydramnios 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 hydrotic, 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

102 July 30, 2012
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, Matsu 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 hypocalcemic (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 (Matsu 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, Lilleman 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/m² 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/m² basis). Docetaxel did not induce teratogenic effects in fetuses, even at the highest doses intravenously administered to rat (1.8 mg/m²/d) or rabbit dams (1.2 mg/m²/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 intraterine 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 cytotoxic 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/m² 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/m²] 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 Gillick 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-esophageal 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 myelogenous leukemia (n=15 cases) and acute promyelocogenous 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, vincblastine, 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, vincblastine, 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, colpocephaly, 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 cyclophosphamide, 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 plagiocephy 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}{Willems, 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 {Willems 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 leucopenia 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 bronchitis (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).
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; Ustaaligolu, 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 transferred 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

July 30, 2012

115
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 syndactyly 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 anophthalmia 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 intravenously 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),

July 30, 2012
lungs 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-exposed 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 {Benajipibal, 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, Benajipibal 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 thrombocytopenia (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). Thauvin-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/m²/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/m²/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, brachnial 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 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-treatment with 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 arteriosus 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 macrogathia (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), meylowsuppression (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/m³ 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/m² on gestation days 6 to 15 caused embryolethal effects, and embryotoxic effects were observed following doses of 18 mg/m² over the same dosing period. In mice, administration of 30 mg ifosfamide/m² 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/m²/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 organogenesis. In rabbits, administration of ifosfamide during organogenesis at a dose of 20 mg/kg [bw] resulted in ectrodactyly (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 gestation, 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, Gleevec 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 PDGFRA (Apperley, 2009 #46). PDGFRA plays an important role in mammalian organogenesis (Hoch and Soriano 2003). Of note, mice engineered with mutated, nonfunctional PDGFRA 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). Imatinib 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 a 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 gastrochisis (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 meningoele (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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 dihydrofolate 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 fungoides, 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 $1.86 \times 10^{-9}$ M following delivery by a woman who was on weekly methotrexate therapy (20 mg/m²). 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 µg/L; the reference substance) was injected as a 100 µL 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/m² (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 ectodactyly 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

July 30, 2012
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). Methotrexate 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, asparaginase 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 our 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}{Willems, 1990 #573}, including two cases with both premature rupture of membranes 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 restriction thought 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, Willems 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 hypodip with abdominal distension and was treated for congenital heart failure {Okun, 1979 #691}. Other health effects in newborns included: asystole which accompanied apnea (Willems 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 methotrexate 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 express difficulty, 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 erythroid 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 mitoxantrone may occur as there are data demonstrating limited placental transport of other anthracyline intercalating drugs (e.g., doxorubicin and epirubicin) in humans (O’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 mitoxantrone were present in breast milk at 21 and 28 days post-administration of 6 mg/m² 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 mixoxantrone is designated a human teratogen based on its mechanism of action and the development effects of other anthracyline 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 mitoxantrone 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 mitoxantrone 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-exposed 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, etrodactylyous, 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 bronchoscooped 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/B16J 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 embryolethal 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/m² basis) (Bristol-Myers Squibb 2010). In a review by Shepard et al. (Shepard, 2004 #871), paclitaxel 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, Cremophor 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 paclitaxel 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 procarbazine 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; accephaly and omphalocole. 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, hemangiomia, 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 malformation 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 IgG1 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 tachyypnea 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/m² 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 acetalbar 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. Atelactasis (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, chorioamnionitis 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 2009).
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 microphthalmia 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 oligohydramnios, 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 embroyolethal 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 genes.
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 tachyypnea 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 dysraphism 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 sepsisemia, 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 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 bronchitis, 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 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, rhabdomyosarcoma, neuroblastoma, Wilms tumor, and non-Hodgkin lymphomas (histiocytic, 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. 2000). Of 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 talipes (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 fetuses) in three strains of mice (C3H, DBA/2J and Swiss ICR/Ha strains) (Joneja and Unthavorn 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 (Wilms 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 dacarbazone. 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 cyclophosphamide, 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 excavatum following 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;Willems, 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; \[however, age at delivery and the definition of prematurity were not specified
so they are not included in the tally.\] 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,
Veneri et al. 1996, Willemsen 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
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
days three with treatment (Achtari and Hohlfeld 2000) and asystole (in addition to apnea, then
respiratory distress) on day of birth {Willemsen 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}{Willemsen, 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 haemangioma (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 Mechanisms 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/m² to mice and 5.5 mg/m² 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 2\textsuperscript{nd} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} or 3\textsuperscript{rd} 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), including one 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 1\textsuperscript{st} trimester: one newborn had cleft palate, tracheoesophageal 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 1\textsuperscript{st} 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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} trimester only, so the total occurrence of major malformations following exposure to vinorelbine in the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 1\textsuperscript{st} 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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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 1\textsuperscript{st} trimester or the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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, daunorubicin, idarubicin, and epirubicin).
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 Hospital 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, meningocoele, 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
caued 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 (PDGFs). 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 PDGFs 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 a 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**

July 30, 2012

179
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 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 anthracyclines 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 cyclophosphamide 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) gestationally 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, epirubicin, 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](http://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](http://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 arthritis 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


Bristol-Myers Squibb. 2010. TAXOL® (paclitaxel) INJECTION full product label. Bristol-Myers Squibb Company Princeton, NJ 08543 USA.


(http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s105256lbl.pdf; accessed on May 103730, 102011).

(http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103705s105344lbl.pdf; accessed on August 103704, 102011).


Gilead Sciences. 2002. DaunoXome Product Label DAUNORUBICIN. San Dimas, CA 91773 USA


http://pharmacycode.com/fda/HN2 this one is for the 1999 year pdf

Whitehouse Station, NJ, USA.


NCCN Guidelines. 2010. Hodgkin Lymphoma

Clinical Practice Guidelines in Oncology (NCCN Guidelines).


Clinical Practice Guidelines in Oncology (NCCN Guidelines).


Clinical Practice Guidelines in Oncology (NCCN Guidelines).
NCCN Guidelines. 2011. Ovarian Cancer  
Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Acute Myeloid Leukemia  
Clinical Practice Guidelines in Oncology (NCCN Guidelines).

Clinical Practice Guidelines in Oncology (NCCN Guidelines).

NCCN Guidelines. 2011. Melanoma  
Clinical Practice Guidelines in Oncology (NCCN Guidelines).


Novartis. 2009. Gleevec Full Prescribing Information. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey  

Accessed June 15, 2011


Hoffmann-La Roche Inc. Nutley, New Jersey 07110.


Sigma-tau. 2004. Matulane (procarbazine hydrochloride capsules) complete product label. Pharmaceuticals, Gaithersburg, MD 20877.


SkyePharma. 2006. DEPOCYT (cytarabine liposome injection) for intrathecal use only Complete Product label. San Diego, CA 92121.


Sotiropoulos D, Adamidou D. 2004. Two Pregnancies Resulting in a Healthy Newborn in a CML Patient Treated with Imatinib. ABSTRACT from ASH Annual Meeting


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:


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.