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

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

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ABBREVIATIONS

AGL	acute granulocytic leukemia
ALL	acute lymphocytic leukemia (also called acute lymphocytic leukemia)
AML	acute myelogenous leukemia (also called acute myeloid leukemia)
AMML	acute myelomonocytic leukemia
AMSA	amsacrine
APL	acute promyelocytic leukemia
ATRA	all-*trans* retinoic acid
Behenoyl-araC	behenoyl cytosine arabinoside
bw	body weight
CDC	Center for Disease Control and Prevention
CGL	chronic granulocytic leukemia
CLL	chronic lymphocytic leukemia
Cmax	time to reach maximal concentration in serum
CML	chronic myelogenous leukemia (also called chronic myeloid leukemia)
C-section	Cesarean-section
CSF	cerebral spinal fluid
FDA	Food and Drug Administration (United States)
IARC	International Agency for Research on Cancer
IM	intramuscular
IT	intrathecal
IU	international units
IUGR	intrauterine growth retardation
IV	intravenous
kg	kilogram
µg	microgram
mg	milligram
m^2	meter squared
NCCN	National Comprehensive Cancer Network
NIEHS	National Institute of Environmental Health Sciences
NS	not specified
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
pg	picogram
pt	patient
RoC	Report on Carcinogens
SC	subcutaneous
SLL	small lymphocytic lymphoma
Vd	volume of distribution
Vdss	volume of distribution at steady state

1.0 EXECUTIVE SUMMARY

1.1 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 treatment modalities 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 identified as known or suspected developmental toxicants with the evidence of risk to the fetus of chemotherapeutic agents usually based on 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 reports 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 more than 110 cancer chemotherapeutic agents currently in use (Perry and Mckinney 2008), the NTP monograph includes data on 56 agents for which pregnancy outcomes following gestational exposure were documented.

The NTP monograph focuses on the following health outcomes:

1. Major congenital malformations[1] 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., abnormally low levels of amniotic fluid and spontaneous preterm birth)

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

5. Growth and development of gestationally exposed children

[1] Major congenital malformations were identified using guidance from publications from the United States Center for Disease Control and Prevention (Rasmussen *et al.* 2003, Correa *et al.* 2007).

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

1.2 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 457 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 as well as a few papers published after this date brought to our attention by the expert panel peer reviewers. In total, the NTP monograph compiled data from 1247 female cancer patients with 1261 pregnancies and 1276 conceptuses treated with chemotherapy during pregnancy[2]. Collectively, a total of 56 cancer chemotherapeutic agents were administered, individually or in combination therapy, to the pregnant patients.

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 (Appendix C Tables 1 to 33 and Appendix D Tables 1 to 24). 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 (Section **5.2** to **5.34**). For agents with 10 or fewer cases, the data are organized into tables only (Appendix D Tables 1 to 24); no text summary of the pregnancy outcomes or background information on these agents is included.

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 by pooling results from all studies reporting treatment with chemotherapy for cancer during pregnancy. The data are presented for any chemotherapy exposure and by individual cancer chemotherapeutic

[2] A total of 1247 female cancer patients were identified from the 457 reports. Fifteen patients gave birth to twins and 15 patients received treatment with chemotherapy for cancer during two pregnancies each. The term conceptus is used to refer to a liveborn infant or an embryo or fetus from an induced abortion, spontaneous abortion, stillbirth or maternal/fetal death in order to tally the data compiled in the NTP monograph. Identical twins would have originated from the same conceptus; however, the NTP monograph did not adjust the total number conceptuses for reported twin births; most reports of twin births did not specify if they were monozygotic).

agents for which greater than 10 cases were identified. The purpose of examining the studies by individual chemotherapeutic agents (administered either singly (monotherapy) or in combination (polytherapy) 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 (75%; n=342/457 publications) and case series (20%; n=90/457 publications). These two types of reports comprised 57% of the total conceptuses exposed to chemotherapy (i.e., of 1276 total conceptuses, 357 conceptuses were reported in case reports and 371 conceptuses were reported in case series). 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 as identified by population studies (Haas 1984, Smith *et al.* 2003). 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, 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.

1.3 Findings

1. Are major congenital malformations more frequently associated with treatment with chemotherapy for cancer in the first trimester versus the second and/or third trimester only?

   Chemotherapy for treatment of cancer in the first trimester represents a higher apparent risk of major malformations than treatment only in the second or third trimesters. Among the reports reviewed in the NTP monograph, the apparent rate of major malformations was 14% (41/303 conceptuses) following exposure to any cancer chemotherapy during the first trimester compared to the apparent rate of 3% (21/826 conceptuses) of major malformations following exposure during the second and/or third trimester only; timing of exposure was not specified for 27 conceptuses and none of them were malformed. These data are consistent with the current medical practice 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.* 2010a). Exposure during the second and/or third trimester poses less risk of major malformations at birth, but may result in more functional deficits (Moore and Persaud 2003). The overall apparent rate of major malformations associated with treatment with chemotherapy for cancer at any time during pregnancy was 5% (62/1156 conceptuses based on 1118 liveborn infants and examinations of 38 fetuses of induced abortions, spontaneous fetal deaths, stillbirths and maternal/fetal deaths). 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).

   When reviewing the data by individual chemotherapeutic agent, the apparent rates of major malformations attributed to some agents were higher than others in the first trimester. For

example, the apparent rate of major malformations were higher following exposure to cyclophosphamide (18%; 7/39 conceptuses) and 5-fluorouracil (31%; 4/13 conceptuses) compared to interferon alpha (0%; 0/20 conceptuses). However, these data are challenging to interpret due to differences in the timing of exposure relate to the period of organogenesis, the small sample size, and the fact that combination therapies employ agents with various mechanisms of action. Generally, there were no increased rates of major malformations when comparing the data by classes of agents working via similar mechanisms of action (see **Table 76** to **Table 81**). Specific combinations of major malformations may be related to exposure to certain agents (e.g., imatinib (Pye *et al.* 2008, Vandyke *et al.* 2010)). For example, a pattern of cranio-facial and skeletal malformations has been observed in a small number of infants following exposure to cyclophosphamide, methotrexate or cytarabine during the period of organogenesis (Vaux *et al.* 2003) and are similar to the type of malformations observed in animal studies (Hyoun *et al.* 2012).

2. Is chemotherapy for treatment of cancer during pregnancy associated with an increased risk of spontaneous abortions or stillbirth?

   The apparent rate of spontaneous abortion (spontaneous fetal loss at <22 weeks of gestation) was 13% (42/327 conceptuses, not including induced abortions or maternal/fetal deaths) following exposure to any cancer chemotherapy during the first trimester. This apparent rate was similar to a pooled estimate of spontaneous abortion in healthy women of 13% (95% CI = 10% to 16%) (Wilcox 2010). However, the reported information in humans is insufficient to determine whether chemotherapy for treatment of cancer in the first trimester affects early spontaneous fetal loss (also called spontaneous abortion, <22 weeks of gestation).

   In contrast, the apparent rate of stillbirths (late spontaneous fetal death, ≥22 weeks of gestation) following exposure to any cancer chemotherapy during the second and/or third trimester only (2%; 20/836 conceptuses, not including induced abortions, maternal/fetal deaths or spontaneous abortions) 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 chemotherapeutic agent (administered either singly or in combination therapy), the apparent rates of stillbirth were highest with gestational exposure to chemotherapeutic agents used primarily to treat hematological cancers. For example, the apparent rate of stillbirth following second and/or third trimester only exposure to cytarabine, an agent used primarily to treat acute leukemia, was 8% (9/110 conceptuses) compared to an apparent rate of 1% (3/368 conceptuses) for cyclophosphamide, an agent used primarily to treat solid cancers. It is possible that the mother's disease may influence the rate of spontaneous abortion or stillbirth. For example, leukemia and other myeloproliferative neoplasias pose an increased risk of thrombosis, which can lead to spontaneous fetal death or intrauterine growth restriction (Brenner *et al.* 2012).

3. Is treatment with chemotherapy for cancer associated with pregnancy complications?

   Abnormally low levels of amniotic fluid. Abnormally low levels of amniotic fluid (i.e., oligohydramnios and anhydramnios) during development can lead to several adverse effects on the fetus, including pulmonary hypoplasia (Nakamura *et al.* 1992) and limb anomalies (Christianson *et al.* 1999). The apparent rate of abnormally low levels of amniotic fluid during pregnancy was 3% (33/1118 conceptuses based on liveborn infants) following gestational exposure to any cancer chemotherapy; this calculation included all cases reporting oligohydramnios, anhydramnios and any progressive reduction in amniotic fluid. This apparent rate of abnormally low 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 note, the majority of cases reporting abnormally low levels of amniotic fluid were exposed to trastuzumab (42%; 14/33 liveborn infants, including one set of twins). Among the liveborn infants gestationally exposed to trastuzumab, the apparent rate of abnormally low levels of amniotic fluid was 74% (14/19 liveborn infants, including one set of twins). 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.* 2009a). Abnormally low levels of amniotic fluid were not reported in pregnancies exposed to trastuzumab in the first trimester only or in pregnancies that occurred within 3 months of completing treatment with the drug (Azim *et al.* 2012). Thus, based on the available data, treatment with chemotherapy for cancer can result in abnormally low amniotic fluid levels that are primarily attributable to trastuzumab.

Spontaneous preterm birth: Chemotherapy for the treatment of cancer does not appear to be associated with spontaneous preterm birth. Preterm birth is defined as <37 weeks of gestation and is associated with number of medical issues in the newborn and later in life (Institute of Medicine 2007). The apparent rate of spontaneous preterm birth following gestational exposure to chemotherapy for the treatment of cancer was 9% (97/1118 liveborn infants). As a point of comparison, the rate of preterm births in the United States population in year 2009, which was 12% of 117,029 total births (Martin 2011). Of note, spontaneous preterm labor occurred at a rate of 8% (5/62 pregnancies with liveborn infants) in a large prospective study of cancer chemotherapy used during pregnancy (Van Calsteren *et al.* 2010a). Higher apparent rates of spontaneous preterm birth were observed following exposure to 6-mercaptopurine (23%, 17/74 infants) and 6-thioguanine (22%; 9/41 infants). However, the reason for this increased rate is not known.

Preterm birth can lead to acute complications in the general population, which 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) (Institute of Medicine 2007). 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 monograph.

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

Small for gestational age infants: The data are suggestive, but not definitive, of effects of chemotherapy for the treatment of cancer during pregnancy to impair fetal growth. The apparent rate of small for gestational age newborns following gestational exposure to chemotherapy was 8% (89/1118 liveborn infants); small for gestational age was identified as body weights that were <10th percentile of the normal population based on sex and gestational age at birth (Olsen *et al.* 2010). However, the apparent rate data on small for gestational age are challenging to compare to a common intrauterine growth curve because the data include variations in fetal growth rates due to the international nature of the literature (e.g., differences in geographical location and ethnicity) as well as temporal differences (e.g., the data were collected from reports published from 1950 to

2012) as well as for the lack of information on body weight provided by many studies (e.g., no body weight data or body weight and gestational age data were provided for 395 of 1118 conceptuses in the NTP monograph). Small for gestational infants was reported at rates comparable to the general population in several large case series of breast cancer patients treated with chemotherapy during pregnancy: 8% (Cardonick *et al.* 2010), 9% (Loibl *et al.* 2012), 4% (1/24 infants) (Berry *et al.* 1999) and 0 of 17 infants (Ring *et al.* 2005b). However, in one large prospective series, small for gestational age were reported more frequently in specific subgroups of patients treated with chemotherapy during pregnancy; specifically, of the 14 of 70 infants that were small for gestational age, 8 infants were born to mothers treated for hematological cancer (4 acute leukemia, 4 lymphoma) (Van Calsteren *et al.* 2010a). In contrast, another large case series without individual data reported no significant differences in body weight at birth between chemotherapy-exposed and control children (born to healthy mothers) matched for gestational age (Abdel-Hady el *et al.* 2012); the patients were treated for breast cancer (32%), lymphoma (16%) or leukemia (13%).

When observing individual agent data, several agents had high apparent rates of small for gestational age when compared to the 10th percentile for body weight by sex and gestational age. For example, the apparent rates for small for gestational age were higher for busulfan (28%; 8/29 liveborn infants) and docetaxel (19%; 4/21 liveborn infants). While these apparent rates are based on small sample sizes, reduced fetal growth was observed in developmental toxicity studies in animal administered these agents (see Sections **5.8** Busulfan and **5.15** Docetaxel). While it is possible that cancer chemotherapy during pregnancy may negatively affect fetal growth, more research on cancer subtypes and treatment regimens are needed to clarify this issue. As mentioned before, the increased risk of thrombosis observed with myeloproliferative neoplasias, including hematological cancers, has been reported to be associated with intrauterine growth restriction (Brenner *et al.* 2012).

Transient myelosuppression: Many antineoplastic chemotherapy drugs induce myelosuppression in patients directly administered these drugs (Perry and Mckinney 2008). The data are suggestive, but not definitive, that chemotherapy for the treatment of cancer may lead to transient myelosuppression in the newborn. Transient myelosuppression was reported for 46 of 1118 liveborn infants following gestational exposure to cancer chemotherapy; however, an apparent rate of transient myelosuppression was not calculated because it was not always clear whether a newborn's blood count had been evaluated. This myelosuppression generally resolved within the first 2 to 3 weeks of life, and 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). However, the data that were provided in the published reports were often insufficient to determine if complete blood counts of the newborn were conducted. The duration of time between cessation of treatment and birth was frequently not reported for the infants with transient myelosuppression. Furthermore, it is difficult to provide a point of reference to provide context for the transient myelosuppression findings because 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).

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) and all-*trans* retinoic acid (Roche 2008, Gziri *et al.* 2012). The evidence is inconclusive that chemotherapy for the treatment of cancer during

pregnancy that induces cardiotoxicity in treated patients also induces cardiotoxicity in fetuses and neonates exposed to the same agents in utero. Of a total of 1118 liveborn infants reviewed in the NTP monograph, only 10 infants were reported to have any symptoms of fetal or neonatal cardiotoxicity (e.g., arrhythmia, cardiomyopathy, tachycardia and heart failure) following gestational exposure to any cancer chemotherapy. An apparent rate was not calculated because it was not clear whether an assessment of fetal cardiac effects were routinely evaluated or consistently reported. The chemotherapy treatments used in the cases resulting in fetal/neonatal cardiotoxicity did not appear to be limited to one class of chemotherapeutic agents. Six singleton pregnancies were exposed to anthracyclines in polytherapy including: idarubicin (3 cases) (Achtari and Hohlfeld 2000, Siu *et al.* 2002, Niedermeier *et al.* 2005), idarubicin and mitoxtantrone (1 case) (Baumgartner *et al.* 2009), daunorubicin polytherapy (1 case) (Okun *et al.* 1979), and daunorubicin and mitoxantrone (Garcia *et al.* 1999). Three pregnancies were exposed to all-*trans* retinoic acid (Harrison *et al.* 1994, Leong *et al.* 2000, Takitani *et al.* 2005), including one singleton pregnancy exposed to idarubicin and all-trans retinoic acid (Siu *et al.* 2002). The remaining pregnancy was exposed to cyclophosphamide and cisplatin (King *et al.* 1991). 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 10 infants. For three of these infants (Okun *et al.* 1979, Garcia *et al.* 1999, Baumgartner *et al.* 2009), anemia was reported and it may have been the cause of the cardiotoxicity (Strauss 1986). Systematic testing and reporting of neonates for myelosuppression and anomalies of cardiac function are needed to better understand the effects of treatment with chemotherapy for cancer during pregnancy.

5. Is treatment with chemotherapy for cancer during pregnancy associated with adverse effects on infant growth and development at follow up evaluation?

   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. Of the studies reviewed in the NTP monograph, follow up data were available for 60% of the offspring gestationally exposed to chemotherapy for the treatment of cancer (670/1118 live born infants). Normal growth and development were reported for nearly all of the offspring with gestational exposure to chemotherapy. However, most of the children were not evaluated beyond the second year of life. The few studies that have conducted longer-term evaluations of the gestationally exposed offspring at ages ranging from 18 months to 20 years, have reported 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 continued follow-up evaluation (Amant *et al.* 2012). Thus, it is important to recognize that the data are limited and adverse effects may not be apparent until later in life (e.g., effects on reproduction and other reproductive function.)

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 reported for most chemotherapeutic regimens:** In most instances, the number of cases treated with an individual agent as monotherapy or in specific combination therapies (polytherapy) was small. Furthermore, differences in maternal disease, treatment regimen, doses, and timing of exposure complicate the interpretation of the pooled analysis of the NTP monograph. In addition, over 110 cancer chemotherapeutic agents are currently in use (Perry and Mckinney 2008); however, published data on use during pregnancy were only identified for 56 agents.
- **Small numbers conceptuses reported with specific types of major malformations:** The prevalence of the individual types of major malformations in the general population is infrequent (Correa *et al.* 2007). Given the limited number of conceptuses reported to be exposed to cancer chemotherapy, it is difficult to conduct a robust analysis for the effects of individual cancer chemotherapy exposure on the rate of occurrence of any specific malformation.
- **Reports with no information on the condition of the abortus or fetus:** Numerous reports of pregnancy outcomes involving induced abortions, spontaneous fetal deaths or stillbirths provide no information on the presence or absence of malformations in the conceptus. If the conceptus was carefully examined and its condition reported, it would provide additional information of value to analyses such are the present one.
- **Reports lacking information on individual cases:** Some larger case series reported data for the group as opposed to the individual case. Data for individual cases were often not reported for normal pregnancy outcomes (Mulvihill *et al.* 1987, Van Calsteren *et al.* 2010a). In contrast, individual data on timing of exposure and agents administered were provided for cases with malformed infants in these reports.
- **Lack of follow up examination and variable quality of the assessments:** The period of follow up examinations of offspring exposed in utero to cancer chemotherapy is very short in most cases (≤2 years). In addition, the quality and comprehensiveness of follow up examinations vary greatly among reports, and there is a lack of international standardized follow up assessments making it difficult to accurately compare data from different research groups around the world.
- **High rate of premature birth:** The high rate of preterm birth in infants with gestational exposure to cancer chemotherapy complicates the assessment of whether adverse effects observed at birth or in follow up examinations are due to the cancer chemotherapy or the preterm birth.
- **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. While the NTP monograph reviewed the pregnancy outcome data by individual chemotherapy agent, the appendix tables for each agent may also be mined to evaluate the pregnancy outcomes of specific treatment regimens. 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 (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 non-cancer diseases. For concerns regarding possible adverse developmental effects of drugs or environmental chemical exposures during pregnancy, the Organization of Teratogen Information Specialists (OTIS; www.mothertobaby.org) is a free and confidential counseling service that is available to the public.

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, Smith *et al.* 2003). 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 therapeutic modalities 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 known or suspected developmental toxicants. The current medical practice 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 structural malformations , but might lead to adverse effects on, for example, neurodevelopment or fertility, as well as pregnancy complications (Buekers and Lallas 1998, Loibl *et al.* 2006, Loibl 2007, Rizack *et al.* 2009, Azim *et al.* 2010a). 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 teratogenic 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 chemotherapeutic agents and they contribute information used to classify them in the US Food and Drug Administration (FDA) pregnancy categories. Such studies may not always be informative with regard to all human pregnancy outcomes; for example, the developmental toxicity studies in animals often administer the drug 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 (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 reports in order to provide physicians and their patients with a tool to help make clinical decisions. Of the over 110 cancer chemotherapeutic agents currently in use (Perry and Mckinney 2008), the NTP monograph included data on 56 agents for which pregnancy outcomes following gestational exposure were reported. 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[3] 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., abnormally low levels of amniotic fluid and spontaneous preterm birth)

4. Newborn weight and health (e.g., small for gestational size, 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. Information regarding the FDA pregnancy categories and the reported carcinogenic potential of each chemotherapeutic agent are listed in Appendix A Table 1. 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

[3] Major congenital malformations were identified using guidance from publications from the United States Center for Disease Control and Prevention (Rasmussen *et al.* 2003, Correa *et al.* 2007).

chemotherapy agents used to treat the tumor during pregnancy based on published literature. In addition, information regarding the Food and Drug Administration pregnancy categories and the reported carcinogenic potential of each chemotherapeutic agent are listed in Appendix A Table 1.

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 May 15, 2012. 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.

References Provided by Experts

In addition to other methods of identifying the relevant references, suggestions of relevant references were also received from technical experts and expert peer reviewers of the draft NTP monograph.

3.2 Criteria for Considering Studies for This Evaluation

3.2.1 Types of Studies

Studies Reporting Pregnancy Outcomes

Studies were considered relevant when they 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. A total of 1425 reports were identified from the literature search. From these reports and additional publications identified by hand searching and suggestions by the experts, 483 publications were identified as relevant. Of these publications, a total of 457 reports were ultimately included in the calculations of the apparent rates for different pregnancy outcomes in the NTP monograph, after excluding published abstracts and reports without data on individual pregnancy outcomes, and accounting for instances in which a specific case appeared in more than one publication (**Table 1**). The term conceptus is used to refer to a liveborn infant or an embryo or fetus from an induced abortion, spontaneous abortion, stillbirth or maternal/fetal death; this term is used in order to tally the data compiled in the NTP monograph. Identical twins would have originated from the same conceptus; however, the NTP monograph did not adjust the total number conceptuses for reported twin births; most reports of twin births did not specify if they were or were not monozygotic.

The majority of the studies with original data were case reports (i.e., the report of a single patient; 75%, 342/457 publications) and case series (20%, 90/457 publications); 56% of the pregnancy outcomes were reported in case reports (342/1276 conceptuses; 27%) and case series (371/1276 conceptuses; 29%) (**Table 1**). The NTP monograph categorized the publications reporting 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 with pregnancy outcomes associated with cancer chemotherapy use during pregnancy.

Study types	Number of studies	Number of conceptuses per study type
Case reports	342	357
Case series	90	371
Case series, retrospective	9	93
Cohort, retrospective	2	30
Survey, registry	1	158
Survey, retrospective	13	267
Total	457	1276

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, and also provided a summary table of the number of reported cases treated with each chemotherapeutic agent. In addition, the summary text was developed for each of the 33 cancer chemotherapy agents with greater than 10 cases, which 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 33 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 (Thomas and Andes 1982, Morton *et al.* 1995, Sotiropoulos and Adamidou 2004, Fogliatto and Brum 2005, Ibrahim *et al.* 2006, Cortes *et al.* 2008). Nine 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: (Janov *et al.* 1992, Kawamura *et al.* 1994, Germann *et al.* 2005, Ibrahim *et al.* 2006, Cortes *et al.* 2008, Abdel-Hady el *et al.* 2012, Aviles *et al.* 2012, Loibl *et al.* 2012), including two studies that were long-term follow up examinations of gestationally exposed offspring (Amant *et al.* 2012, Aviles *et al.* 2012). In addition, a retrospective cohort study by 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.* 1992b).

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 6 case reports (Baer 1991, Reynoso and Huerta 1994, Terada *et al.* 1997, Merimsky *et al.* 1999, Heartin *et al.* 2004, Choudhary *et al.* 2006) were subsequently reported in case series or retrospective surveys, 3 case series (Pizzuto *et al.* 1980, Aviles *et al.* 1990, Halaska *et al.* 2009, Peccatori *et al.* 2009) 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 twin pregnancy 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); thus, the twin pregnancy was counted using the case series, but did include the additional details of the follow up evaluation from the case report. Finally, four case reports (Herold *et al.* 2001, Kimby *et al.* 2004, Decker *et al.* 2006, Friedrichs *et al.* 2006) were tallied separately from a subsequent survey retrospective (Chakravarty *et al.* 2011); thus, these cases were not counted in the total cases tallied from the survey retrospective.

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. This patient base included: 1) women who were receiving chemotherapy treatment for cancer when they became pregnant and 2) women who were pregnant at the time of cancer diagnosis and received chemotherapy treatment. Pregnant women diagnosed with cancer were not included if they did not receive cancer chemotherapy during the pregnancy (e.g., due to deferral of treatment with chemotherapy until after pregnancy). Male cancer patients were not included in this review Similarly, the NTP monograph does not address the outcomes of pregnancies conceived after completion of chemotherapy for treatment of cancer.

3.2.5 Types of Interventions

Interventions Included

All cancer chemotherapeutic agents that were reported to be administered to cancer patients during pregnancy were included in the current review. 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 Section **3.3**). 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. A summary of the FDA pregnancy categories, International Agency for Research on Cancer carcinogenicity categories and the NTP's Report on Carcinogens cancer listings for these agents are provided in Appendix B Table 1.

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

Chemotherapeutic agent	Number of reported conceptuses	Location in the NTP monograph
5-Fluorouracil	179	Section 5.2, Appendix C Table 1
6-Mercaptopurine	86	Section 5.3, Appendix C Table 2
6-Thioguanine	53	Section 5.4, Appendix C Table 3
Actinomycin D	16	Section 5.5, Appendix C Table 4
All-*trans* retinoic acid	29	Section 5.6, Appendix C Table 5
Amsacrine	2	Appendix D Table 1
Behenoyl cytosine arabinoside	3	Appendix D Table 2
Bleomycin	97	Section 5.7, Appendix C Table 6
Busulfan	31	Section 5.8, Appendix C Table 7
Capecitabine	1	Appendix D Table 3
Carboplatin	17	Section 5.9, Appendix C Table 8
Carmustine	3	Appendix D Table 4
Chlorambucil	10	Appendix D Table 5
Cisplatin	105	Section 5.10, Appendix C Table 9
Cyclophosphamide	419	Section 5.11, Appendix C Table 10
Cytarabine	168	Section 5.12, Appendix C Table 11
Dacarbazine	58	Section 5.13, Appendix C Table 12
Dasatinib	3	Appendix D Table 6
Daunorubicin	108	Section 5.14, Appendix C Table 13
Docetaxel	21	Section 5.15, Appendix C Table 14
Doxorubicin	430	Section 5.16, Appendix C Table 15
Epirubicin	67	Section 5.17, Appendix C Table 16
Erlotinib	2	Appendix D Table 7
Etoposide	45	Section 5.18, Appendix C Table 17
Fludarabine	2	Appendix D Table 8
Gemcitabine	3	Appendix D Table 9
Gemtuzumab-oogamicin	1	Appendix D Table 10
Hydroxyurea	35	Section 5.19, Appendix C Table 18
Idarubicin	23	Section 5.20, Appendix C Table 19
Ifosfamide	11	Section 5.21, Appendix C Table 20
Imatinib	157	Section 5.22, Appendix C Table 21
Interferon alpha	43	Section 5.23, Appendix C Table 22
Irinotecan	2	Appendix D Table 11

Chemotherapeutic agent	Number of reported conceptuses	Location in the NTP monograph
Lapatinib	1	Appendix D Table 12
Lomustine	1	Appendix D Table 13
Melphalan	3	Appendix D Table 14
Methyl-GAG	3	Appendix D Table 15
Methotrexate	87	Section **5.24**, Appendix C Table 23
Mitoxantrone	17	Section **5.25**, Appendix C Table 24
Nilotinib	1	Appendix D Table 16
Nimustine	1	Appendix D Table 17
Nitrogen mustard	31	Section **5.26**, Appendix C Table 25
Oxaliplatin	5	Appendix D Table 18
Paclitaxel	38	Section **5.27**, Appendix C Table 26
Procarbazine	31	Section **5.28**, Appendix C Table 27
Rituximab	26	Section **5.29**, Appendix C Table 28
Streptozotocin	1	Appendix D Table 19
Tamoxifen	15	Section **5.30**, Appendix C Table 29
Teniposide	2	Appendix D Table 20
Trastuzumab	20	Section **5.31**, Appendix C Table 30
Triethylenemelamine	6	Appendix D Table 21
Trophosphamide	1	Appendix D Table 22
Vinblastine	85	Section **5.32**, Appendix C Table 31
Vincristine	228	Section **5.33**, Appendix C Table 32
Vindesine	1	Appendix D Table 23
Vinorelbine	15	Section **5.34**, Appendix C Table 33

Interventions Excluded

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

3.2.6 Types of Outcome Measures

To be included in the evaluation, studies had to present pregnancy outcomes following administration of cancer chemotherapy during pregnancy. 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 in the NTP monograph. Timing of gestation was based on a 40 week period of gestation determined by the beginning of the last menstrual period.

Primary Adverse Outcomes

- Major or minor congenital malformations in fetuses or newborns
- Spontaneous fetal death, spontaneous abortion (< 22 weeks gestation) and stillbirth (≥22 weeks gestation)
- Preterm birth
- Adverse effects on growth and development of the offspring

Secondary Adverse Outcomes

- Pregnancy complications, including but not limited to:
    - Intrauterine growth restriction (measurements of the fetus)
    - Abnormally low levels of amniotic fluid
- Adverse health issues in newborns
    - Small for gestational age
    - Transient myelosuppression
    - Cardiotoxicity

Spontaneous Fetal Death

Spontaneous fetal death was categorized as early spontaneous fetal death (referred to as spontaneous abortion) occurring at < 22 weeks of gestation and late spontaneous fetal death occurring at ≥22 weeks of gestation (referred to as stillbirth). Stillbirth was often reported as intrauterine fetal death or fetal demise in the individual reports (see Appendix C and Appendix D). Stillbirth is often identified as late fetal death (≥28 weeks of gestation) (Lawn *et al.* 2010); however, the NTP monograph identified stillbirth as including both early (≥22 to <28 weeks of gestation) and late spontaneous fetal death. Among the reports reviewed in the NTP monograph, stillbirth was often reported as intrauterine fetal death or fetal demise in the individual reports, and gestational age at death was not always provided (see Appendix C and Appendix D).

Terminations of pregnancy (also called induced abortions) were not included in the totals of spontaneous abortions or stillbirths. However, the NTP monograph did compile data on all pregnancies ending in termination of pregnancy in an effort to gather all available data on pregnancy complications and examination of the fetuses for malformations. Fetal deaths caused by death of the mother (called maternal/fetal deaths) were also reported separately from spontaneous abortions and stillbirths.

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 (Rasmussen *et al.* 2003, Correa *et al.* 2007). 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 transverse palmar crease, pectus excavatum or preauricular ear pits.

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 by experts at the CDC: 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).

Abnormally Low Levels of Amniotic Fluid

Levels of in amniotic fluid are determined by ultrasound examination and calculation of an amniotic fluid index (Shanks *et al.* 2011). Oligohydramnios refers to an abnormally small volume of amniotic fluid and is defined using several criteria including: 1) an amniotic fluid index less than the 95% (<5th percentile) for gestational age, 2) an amniotic fluid index of less than 5 cm, or amniotic fluid levels less than 300 mL or absence of single vertical amniotic fluid pocket of ≥2 cm (Norwitz *et al.* 2010). The amniotic fluid index of <5th percentile for gestational age is reported to be the most accurate or the two amniotic fluid index determination of oligohydramnios (Shanks *et al.* 2011). Anhydramnios is the complete absence of amniotic fluid. In the publications included in the NTP monograph, some researchers also reported progressive reductions in amniotic fluid following treatment with chemotherapy. Thus, an abnormally low level of amniotic fluid refers to pregnancies reporting a more general description of a reduction in amniotic fluid as well as those cases with anhydramnios and oligohydramnios.

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 ≤34 weeks of gestation and late preterm deliveries, which are births between 34 weeks to <37 weeks of gestation. 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 (~ 31 weeks of gestation or earlier), while births reported in the "9th month" of gestation or "at term" are considered term. Births reported in the "8th month" of gestation were considered to be late preterm deliveries (~35 weeks of gestation). Births that were reported as "near term" or ">8.5 months" 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.

Growth During Gestation

Intrauterine growth restriction refers to poor growth of a fetus in the womb during pregnancy, which can cause premature birth and has been associated with reduced viability of the fetus or the newborn (Mandruzzato *et al.* 2008). If an infant is born weighing less than 90% of newborns of a comparable age (<10th percentile), this is called small for gestational age.

The NTP monograph reported the apparent rate of reduced gestational growth at two developmental periods: 1) during in utero development – called intrauterine growth restriction, and 2) at birth – called small for gestational age.

- **Intrauterine growth restriction of the fetus**. This observation refers to poor growth of a fetus during pregnancy, which has been associated with premature birth and reduced viability of the fetus or the newborn (Mandruzzato *et al.* 2008). The draft NTP monograph compiled these observations as reported by the authors. All authors' reports of a cessation of intrauterine

growth or poor intrauterine growth of the fetus during pregnancy were included in the apparent rate of intrauterine growth restriction of the fetus.

- **Small for gestational age newborns**. This observation is made at birth and refers to a newborn whose body weight, length, or head circumference is less than 90% of newborns of comparable age and sex (<10th percentile) (Olsen *et al.* 2010). The NTP draft monograph identified a newborn as small for gestational age if it was <10th percentile based on sex, gestational age and body weight at birth. In cases lacking data on the sex of the infant, the data were compared to the intrauterine growth curves for female infants as a conservative measure since female infants tend to weigh less than male infants (Olsen *et al.* 2010). In addition, the draft NTP monograph also relied upon the author's reports to identify whether newborns were small for gestational age or had normal body weight. For example, small for gestational age was identified in one case study was identified by the authors' report of intrauterine growth arrest in an infant born at approximately 8 months of gestation with a birth weight of 1077 g (Diamond *et al.* 1960). In another example, normal body weight for gestational age were identified for infants in a case series based on the authors' report that none of the infants had a birth weight lower than the 10th percentile for gestational age (Ring *et al.* 2005b).

  Small for gestational age could not be determined for cases that lacked data on the body weight or gestational age at birth when normal body weight or small for gestational age was not reported by the authors. For example, small for gestational age could not be determined for a male infant with a birth weight of 2020 g and was reported as "full term" (Norhaya *et al.* 1994) or for a male infant with a birth weight of 2183 g and was estimated to be born between 8 and 9 months of gestation (Dugdale and Fort 1967).

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 possibly caused by preterm birth were also summarized in the text summary for each cancer chemotherapeutic agent.

Adverse Effects on Growth and Development of the Offspring

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 (monotherapy) or, more commonly, in combination with other cancer chemotherapeutic agents (polytherapy) (Appendix C and Appendix D). 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 at delivery, pregnancy outcomes, and follow up evaluations of the infant.

Time of exposure during pregnancy was primarily identified as: first trimester (beginning of last menstrual period (gestation week 1) through week 13), second trimester (14 to <28 weeks 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. The calculation of weeks of gestation is based on the number of weeks since the first day of the last menstrual period. Conception generally occurs in the second or third gestational week, since ovulation occurs between 11 and 21 days after the beginning of the last menstrual period. In contrast, developmental toxicity studies in laboratory animals define the day of conception as gestation day 0 or 1.

Route of delivery categories included: spontaneous vaginal birth (vaginal), induced vaginal birth (vaginal, induced), Cesarean-section (C-section) or not specified (NS). Spontaneous vaginal birth (vaginal) was assumed when publications stated that an infant was born or that the mother delivered a child with no additional information on the route of delivery; whereas, reports that did not mention the birth or the route of delivery were identified as not specified (NS). Pregnancy outcomes included pregnancy complications, sex, body weight, Apgar scores, 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. Bolded and bracketed statements were used to note items of information not provided in a publication, limitations noted in the report, conclusions that differ from those of the authors, and data conversions conducted by NTP 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 for gestational exposure to any chemotherapy regimen or to an individual agent (as monotherapy or in polytherapy) based on the total number of conceptuses, including liveborn infants as well as fetuses from termination of pregnancy (induced abortions), spontaneous fetal death (spontaneous abortions or stillbirths), and maternal/fetal deaths as per the outcome (described below) exposed. For spontaneous abortions, the denominator excluded termination of pregnancy and maternal/fetal death. For stillbirths, the denominator excluded termination of pregnancy, maternal/fetal death, and spontaneous abortion. For major malformations, the denominator included only liveborn infants and fetuses examined for birth defects from termination of pregnancy, spontaneous abortion, stillbirth, or maternal/fetal death. For all newborn health effects, the denominators included the total liveborn infants.

For major congenital malformations and spontaneous fetal death, data were analyzed by comparing the apparent rates of occurrence following exposure during the first trimester (i.e., exposures in the first trimester only as well as exposures in the first trimester and subsequent trimesters) 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. Infants were considered to be free of major congenital malformations if the report did not mention a congenital malformation or if it reported that

the infant was “normal”. The apparent rates of occurrence for other outcomes were reported simply for gestational exposure, i.e., exposure at any time during pregnancy, to chemotherapy for treatment of cancer; no analysis of trimester exposed was conducted for these outcomes. These apparent rates of occurrence may or may not reflect the actual rates of occurrence for this population.

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 apparent rates of occurrence for data for individual agents with greater numbers of exposed cases (e.g., cyclophosphamide, n=416 cases and 419 conceptuses and cytarabine, n=164 cases and 168 conceptuses).

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 effects; for example, a lack of examination of the aborted fetus following termination of pregnancy, (i.e., induced abortion), spontaneous fetal death, or maternal/fetal death, 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 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 cancers 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.

4.1 Breast Cancer and 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 November 15, 2012) (**Table 1**).

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

Table 3: Estimated new cases and deaths from breast cancer in the United States in 2013

	Female	Male
New Cases	232,340	2,240
Deaths	39,620	410
Source: *http://www.cancer.gov/cancertopics/types/breast* (accessed March 12, 2013)		

4.1.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of breast cancer among all women of reproductive age (15 to 44 years) in the United States was 40.0/100,000 (approximately 1/2,500) as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2012). These data represent the incidence of breast cancer collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.1.3 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. (2003), using California Cancer Registry records collected between 1991 and 1999, calculated the occurrence rate of breast cancer diagnosed during pregnancy to be 5.1/100,000 (approximately 1/20,000) 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 (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 rate of breast cancer in this study is approximately 1.3/100,000 live births or about 1/77,000, second in descending rank order following cancer of the cervix for this population.

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 23.6/100,000 pregnancies. Two-thirds of these cases were diagnosed postpartum, so approximately 7.9/100,000 or 1/13,000 was 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. (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 64/100,000 or about 1/1500 pregnancies. Ranges of rates 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.

4.1.4 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. (1992a), 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. (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 (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 (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. (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. (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. (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. (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. (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 effect 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. (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. (2009) 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. (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. (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. (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. (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 difference in overall survival.

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 rates of relapse and death were 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, Rodriguez *et al.* 2008, Moreira *et al.* 2010) 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.

4.1.5 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 2012f). 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. (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 taxanes during the second and third trimesters.

It is worth noting that the NCCN guidelines are not specific for pregnant patients, for whom treatment with methotrexate is generally avoided.

The chemotherapy agents used to treat breast cancer reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 4**.

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

Agent	Number of published reports*	Number of cases*	Location in NTP monograph
5-Fluorouracil	32	165	Appendix C Table 1
Carboplatin	1	1	Appendix C Table 8
Cyclophosphamide	45	275	Appendix C Table 10
Docetaxel	10	19	Appendix C Table 14
Doxorubicin	42	245	Appendix C Table 15
Epirubicin	16	58	Appendix C Table 16
Lapatinib	1	1	Appendix D Table 44
Methotrexate	12	25	Appendix C Table 23
Mitoxantrone	1	2	Appendix C Table 24
Paclitaxel	7	14	Appendix C Table 26
Tamoxifen	12	13	Appendix C Table 29
Trastuzumab	19	19	Appendix C Table 30
Vincristine	4	5	Appendix C Table 32
Vinorelbine	6	11	Appendix C Table 33

*Many published reports included data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.

4.2 Cervical Cancer and Pregnancy

4.2.1 Definition of Cervical Cancer:

The definition and estimated new cases and deaths are taken directly from the U.S. National Cancer Institute web site (*http://www.cancer.gov/cancertopics/types/cervical*: accessed November 15, 2012) (**Table 5**).

"**[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 2013

New cases	12,340
Deaths	4,030
http://www.cancer.gov/cancertopics/types/cervical (accessed March 12, 2013)	

4.2.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of cervical cancer among all women of reproductive age (15 to 44 years) in the United States was 8.0/100,000 as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2012). These data represent the incidence of cervical cancer collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.2.3 Occurrence Rate During Pregnancy:

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

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 3.6/100,000 (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 (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 11/100,000 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. (1982) reviewed the literature from 1960 to 1979 and reported that for carcinoma in situ, the rate was 130/100,000 or approximately 1/770 pregnancies and for invasive carcinomas the numbers were 45/100,000 or approximately 1/2205 pregnancies. Combining both in situ and invasive cancer types, the rate was 80.7/100,000 or approximately 1/1240 pregnancies based on 800 cases in 991,536 pregnancies. Duggan et al. (1993) report an rate of invasive cervical cancer diagnosed and/or treated during pregnancy of 12/100,000 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. (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 rate was 23/100,000 or 1/4348 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 3.6/100,000 (Smith *et al.* 2003) to 45/100,000 (Hacker *et al.* 1982).

4.2.4 Impact of Pregnancy on Prognosis:

There is general agreement in six papers published between 1990 and 2010 that pregnancy does not change the prognosis of cervical cancer.

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. The rather short period of follow-up limits the utility of this finding.

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 (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. (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. Mean length of follow-up was 13.6 years for pregnant patients and 14.8 years for controls.

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. The median length of follow-up was 10.8 years for the pregnant patients and 11.9 years for the non-pregnant controls.

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. (1996) conclude that literature supports the view that tumor characteristics and maternal survival are not adversely affected by pregnancy. 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. (2005) conclude that overall prognosis appears to be similar to the non-pregnant state.

4.2.5 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 guidelines list first-line combination therapies, possible first-line single agent therapies, and second-line therapies (NCCN Guidelines 2011).

The chemotherapy agents used to treat cervical cancer reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 6**.

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

Agent	Number of published reports*	Number of cases*	Location in the NTP monograph
5-Fluorouracil	1	1	Appendix C Table 1
Bleomycin	1	1	Appendix C Table 6
Carboplatin	1	1	Appendix C Table 8
Cisplatin	19	40	Appendix C Table 9
Cyclophosphamide	1	1	Appendix C Table 10
Paclitaxel	4	8	Appendix C Table 26
Vincristine	6	7	Appendix C Table 32
*Many published reports include data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.			

4.3 Hodgkin Lymphoma and 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 November 15, 2012) (**Table 7**).

"**[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. 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. Also called Hodgkin disease.

Table 7: Estimated new cases and deaths from Hodgkin lymphoma in the United States in 2013

New cases	9,290
Deaths	1,180
http://www.cancer.gov/cancertopics/types/hodgkin (accessed March 12, 2013)	

4.3.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of Hodgkin lymphoma among all women of reproductive age (15 to 44 years) in the United States was 3.4/100,000 as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2012). These data represent the incidence of Hodgkin lymphoma collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.3.3 Occurrence Rate During Pregnancy:

Two population-based studies addressed the rate of occurrence of pregnancy-associated Hodgkin lymphoma.

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 2.2/100,000 (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 (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 0.7/100,000 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.

4.3.4 Impact of Pregnancy on Prognosis:

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. (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. (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. (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.

4.3.5 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 2012c).

The chemotherapy agents used to treat Hodgkin lymphoma reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 8**.

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

Agent	Number of published reports*	Number of cases*	Location in NTP monograph
Bleomycin	13	49	Appendix C Table 6
Chlorambucil	3	4	Appendix D Table 38
Cisplatin	1	1	Appendix C Table 9
Cyclophosphamide	7	9	Appendix C Table 10
Cytarabine	1	1	Appendix C Table 11
Dacarbazine	12	45	Appendix C Table 12
Doxorubicin	14	52	Appendix C Table 13
Etoposide	2	2	Appendix C Table 17
Interferon alpha	1	1	Appendix C Table 22
Lomustine	1	1	Appendix D Table 45
Nitrogen Mustard	18	28	Appendix C Table 25
Procarbazine	16	28	Appendix C Table 27
Rituximab	1	1	Appendix C Table 28
Triethylenemelamine	3	3	Appendix D Table 52
Vinblastine	27	75	Appendix C Table 31
Vincristine	15	26	Appendix C Table 32

*Many published reports include data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.

4.4 Non-Hodgkin Lymphoma and 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 November 15, 2012) (**Table 9**).

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

Table 9: Estimated new cases and deaths from non-Hodgkin lymphoma in the United States in 2013

New cases	69,740
Deaths	19,020
http://www.cancer.gov/cancertopics/types/non-hodgkin (accessed March 12, 2013)	

The National Comprehensive Cancer Network lists 14 different tumor types under Non-Hodgkin Lymphoma (NCCN Guidelines 2012a):

- 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 (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 list presented above.

4.4.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of non-Hodgkin lymphoma among all women of reproductive age (15 to 44 years) in the United States was 4.3/100,000 as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2012). These data represent the incidence of non-Hodgkin lymphoma collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.4.3 Occurrence Rate During Pregnancy:

Two population-based studies addressed the rate of occurrence of pregnancy-associated Non-Hodgkin lymphoma.

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 0.7/100,000 (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 (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 0.2/100,000 live births or about 1/500,000. Lymphoma, not otherwise specified, was fourth in descending rank order following cancer of the cervix, breast, and ovary.

4.4.4 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. (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. (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.

4.4.5 Chemotherapy Agents Used to Treat Non-Hodgkin Lymphoma:

The National Comprehensive Cancer Network guidelines list therapies for the treatment of the 14 types of non-Hodgkin lymphoma noted above (NCCN Guidelines 2012a). The chemotherapy agents used to treat non-Hodgkin lymphoma reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 10**.

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

Agent	Number of published reports*	Number of cases*	Location in NTP monograph
6-Mercaptopurine	2	1	Appendix C Table 2
Bleomycin	10	21	Appendix C Table 6
Carmustine	1	1	Appendix D Table 37
Chlorambucil	3	3	Appendix D Table 38
Cisplatin	3	3	Appendix C Table 9
Cyclophosphamide	39	71	Appendix C Table 10
Cytarabine	7	13	Appendix C Table 11
Doxorubicin	30	55	Appendix C Table 15
Epirubicin	3	6	Appendix C Table 16
Etoposide	8	13	Appendix C Table 17
Ifosfamide	2	2	Appendix C Table 20
Methotrexate	6	11	Appendix C Table 23
Mitoxantrone	1	1	Appendix C Table 24
Procarbazine	2	2	Appendix C Table 27
Rituximab	11	25	Appendix C Table 28
Streptozotocin	1	1	Appendix D Table 50
Teniposide	2	2	Appendix D Table 51
Triethylenemelamine	1	1	Appendix D Table 52
Vincristine	37	69	Appendix C Table 32

*Many published reports include data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.

4.5 Leukemia and 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 November 15, 2012) (**Table 11**).

"**[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 2013

New Cases	48,610
Deaths	23,720
http://www.cancer.gov/cancertopics/types/leukemia (accessed March 12, 2013)	

4.5.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of leukemia among all women of reproductive age (15 to 44 years) in the United States was 3.0/100,000 as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2012). These data represent the incidence of leukemia collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.5.3 Occurrence Rate During Pregnancy:

Two population-based studies addressed the rate of occurrence of pregnancy-associated leukemia.

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 1.4/100,000 (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 cancer of the breast, cervix, thyroid, skin (melanoma), ovary, and Hodgkin lymphoma.

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 rate of leukemia in this study is approximately 0.4/100,000 live births or about 1/250,000, and was seventh in descending rank order following cancers of the cervix, breast, ovary, lymphoma, melanoma, and brain.

4.5.4 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 (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 (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 (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.

4.5.5 Chemotherapy Agents Used to Treat Leukemia:

The National Comprehensive Cancer Network presents guidelines for treating acute lymphoblastic leukemia (NCCN Guidelines 2012b), acute myeloid leukemia (NCCN Guidelines 2012d), and chronic myelogenous leukemia (NCCN Guidelines 2012d).

The chemotherapy agents used to treat leukemia reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 12**.

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

Agent	Number of published reports*	Number of cases*	Location in NTP monograph
6-Mercaptopurine	47	81	Appendix C Table 2
6-Thioguanine	35	50	Appendix C Table 3
All-trans retinoic acid	24	28	Appendix C Table 5
Amsacrine	1	1	Appendix D Table 34
Behenoyl cytosine arabinoside	3	3	Appendix D Table 35
Busulfan	23	30	Appendix C Table 7
Chlorambucil	2	2	Appendix D Table 38
Cyclophosphamide	17	26	Appendix C Table 10
Cytarabine	77	149	Appendix C Table 11
Dasatinib	3	3	Appendix D Table 39
Daunorubicin	57	105	Appendix C Table 13
Doxorubicin	17	41	Appendix C Table 15
Epirubicin	1	1	Appendix C Table 16
Etoposide	5	5	Appendix C Table 17
Fludarabine	2	2	Appendix D Table 41
Hydroxyurea	21	32	Appendix C Table 18
Idarubicin	16	22	Appendix C Table 19
Imatinib	22	152	Appendix C Table 21
Interferon alpha	20	34	Appendix C Table 22
Methotrexate	25	40	Appendix C Table 23
Methyl-GAG	4	4	Appendix D Table 46
Mitoxantrone	10	14	Appendix C Table 24
Nilotinib	1	1	Appendix D Table 47
Nitrogen mustard	1	1	Appendix C Table 25
Triethylenemelamine	1	1	Appendix D Table 52
Vincristine	48	91	Appendix C Table 32
Vindesine	1	1	Appendix D Table 53

*Many published reports include data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.

4.6 Ovarian Cancer and 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 November 15, 2012) (**Table 13**).

"**[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 2013

New cases	22,240
Deaths	14,030
http://www.cancer.gov/cancertopics/types/ovarian (accessed March 12, 2013)	

4.6.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of ovarian cancer among all women of reproductive age (15 to 44 years) in the United States was 4.1/100,000 as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (SEER 2012). These data represent the incidence of ovarian cancer collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.6.3 Occurrence Rate During Pregnancy:

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

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 2.4/100,000 (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. (2006) reported an occurrence rate of 1.8/100,000 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 4.2/100,000 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. (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 2.1/100,000 or about 1/48,000.

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 0.9/100,000 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 0.9/100,000 to 2.4/100,000, about a 2.7-fold range.

Other smaller published studies present varying rates of occurrence of ovarian cancer. Behtash et al. (2008) reported a rate of 8.3/100,000 deliveries at the Vali-Asr Hospital in Tehran, Iran between 1991 and 2002 based on 23 cases. Zhao et al. (2006), using records from the Peking Union Medical College Hospital, 1985 to 2003, reported a rate of 7.3/100,000 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. (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 11/100,000. Removing the two cases that were diagnosed postpartum, the number is 9/100,000 deliveries or about 1/11,000 for those diagnosed while pregnant or during delivery. 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 4.7/100,000 live births or approximately 1/21,000. 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 8/100,000 deliveries or 1/12,000. Ueda and Ueki (1996) 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 59/100,000 deliveries or about 1/1700. Finally, Munnell (1963) reported three ovarian cancers associated with pregnancy among 54,292 deliveries at the Columbia Presbyterian Medical Center in New York between 1947 and 1961. This gives an occurrence rate of 5.6/100,000 deliveries or about 1/18,000.

4.6.4 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. (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.

4.6.5 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 recommended chemotherapy agents for treating epithelial ovarian cancer, malignant germ cell tumors of the ovary, and recurrent germ cell tumors (NCCN Guidelines 2012e).

The chemotherapy agents used to treat ovarian cancer reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 14**.

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

Agent	Number of published reports*	Number of cases*	Location in NTP monograph
5-Fluorouracil	1	1	Appendix C Table 1
Actinomycin D	4	4	Appendix C Table 4
Bleomycin	13	18	Appendix C Table 6
Carboplatin	10	12	Appendix C Table 8
Cisplatin	34	43	Appendix C Table 9
Cyclophosphamide	14	14	Appendix C Table 10
Docetaxel	1	1	Appendix C Table 14
Doxorubicin	4	4	Appendix C Table 15
Etoposide	14	20	Appendix C Table 17
Irinotecan	1	1	Appendix D Table 43
Paclitaxel	9	12	Appendix C Table 26
Vinblastine	3	3	Appendix C Table 31
Vincristine	6	6	Appendix C Table 32
*Many published reports include data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.			

4.7 Melanoma and 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 November 15, 2012) (**Table 15**).

"**[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 2013

New cases	76,690
Deaths	9,480
http://www.cancer.gov/cancertopics/types/melanoma (accessed March 12, 2013)	

4.7.2 Occurrence Rate in Reproductive Age Women:

In 2009, the age-adjusted rate of melanoma among all women of reproductive age (15 to 44 years) in the United States was 10.0/100,000 as reported by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (2012). These data represent the incidence of melanoma collected from specific locations representing 28% of the United States population and were calculated using the SEER Cancer Query System (CanQues; *www.seer.cancer.gov/canques*). Rates were standardized using the United States population data from year 2000, included all races and were restricted to females between the ages of 15-44 years of age.

4.7.3 Occurrence Rate During Pregnancy:

Two population-based studies and several smaller studies addressed the rate of occurrence of pregnancy-associated melanoma.

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 3.1/100,000 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 (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 0.6/100,000 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 (1996), based on a retrospective analysis, stated that the rate was 14/100,000 pregnancies. Pavlidis (2002), based on a review of the literature (1970 to 1996), cited a figure of 260/100,000 deliveries. 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 of280/100,000. At the hospital in Tennessee, three cases were observed in 9400 deliveries over a 7-year period (1960 to 1967) for an occurrence of 30/100,000 deliveries.

These estimated occurrence rates range from 0.6/100,000 to 280/100,000. The substantial differences in the estimated rates 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. (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.

4.7.4 Impact of Pregnancy on Prognosis:

Early reports (Pack and Scharnagel 1951, Kjems and Krag 1993) 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 (Houghton *et al.* 1981, Colbourn *et al.* 1989, McManamny *et al.* 1989, MacKie *et al.* 1991, Travers *et al.* 1995, Lens *et al.* 2004, O'Meara *et al.* 2005).

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. (1985) had earlier reported similar results as 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. (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. (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. (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.

4.7.5 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). The NCCN Guidelines provide recommended chemotherapy agents for treating melanoma (Leachman *et al.* 2007, NCCN Guidelines 2013)

The chemotherapy agents used to treat melanoma reviewed in this monograph, the number of published reports for each agent, and the number of patients (cases) treated are shown in **Table 16**.

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

Agent	Number of published reports*	Number of cases*	Location in NTP monograph
Carmustine	2	2	Appendix D Table 37
Cisplatin	3	3	Appendix C Table 9
Dacarbazine	7	9	Appendix C Table 12
Interferon alpha	4	4	Appendix C Table 22
Nimustine	1	1	Appendix D Table 48
Tamoxifen	2	2	Appendix C Table 29
Vincristine	1	1	Appendix C Table 32
*Many published reports include data on multiple chemotherapy agents and many patients (cases) are treated with multiple chemotherapy agents; thus, the same report or case may appear in multiple agent tables.			

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

Of the 56 cancer chemotherapy agents used during pregnancy, the NTP monograph reviews the background information and developmental effects of 33 individual agents for which there were pregnancy outcomes reported for 10 or more cases (Sections 5.2 to 5.34)(Table 17). 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-signaling pathway components (also called targeted agents) (Table 17). It is important to note that some agents have multiple mechanisms of action.

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

Anti-metabolites • *5-Fluorouracil* • *6-Mercaptopurine* • *6-Thioguanine* • *Cytarabine* • *Hydroxyurea* • *Methotrexate* **DNA alkylating agents** • *Busulfan* • *Carboplatin* • *Cisplatin* • *Cyclophosphamide* • *Dacarbazine* • *Ifosfamide* • *Nitrogen mustard* • *Procarbazine*	**DNA intercalating agents** • *Actinomycin D* • *Daunorubicin* • *Doxorubicin* • *Epirubicin* • *Idarubicin* • *Mitoxantrone* **Microtubule function inhibitors** • *Docetaxel* • *Paclitaxel* • *Vinblastine* • *Vincristine* • *Vinorelbine*	**Topoisomerase II inhibitor** • *Etoposide* **Oxygen free radical generator** • *Bleomycin* **Targeted therapies** • *All-trans retinoic acid* • *Imatinib* • *Interferon alpha* • *Rituximab* • *Tamoxifen* • *Trastuzumab*
Note: Many of these agents have more than one mechanism of action		

5.1 Overall Analysis Based on Any Chemotherapy Exposure

5.1.1 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

The NTP monograph compiled data on a total of 1247 patients (also called cases) treated with chemotherapy for treatment of cancer during pregnancy. As previously mentioned, these patients were reported in 342 case reports (342 cases), 90 case series (363 cases), 9 retrospective case series (91 cases), 2 retrospective cohort studies (30 cases), 1 survey registry (156 cases), and 13 retrospective surveys (264 patients). Of the 7 frequently diagnosed cancers reviewed in the NTP monograph, the total number of cases treated per cancer type (% of total cases) was: leukemia, 492 cases (39%; 255 cases were acute leukemia, including 1 case of erythroleukemia); breast cancer, 369 cases (30%); Hodgkin lymphoma, 112 cases (9%); non-Hodgkin lymphoma, 88 (7%); ovarian cancer, 62 cases (5%), cervical cancer, 42 cases (3%); and melanoma, 12 cases (1%). Additional types of cancers receiving treatment with chemotherapy during pregnancy included: sarcoma (23 cases), choriocarcinoma (6 cases), adenoid cystic carcinoma (2 cases), multiple myeloma (2 cases), and cancers of the lung (10 cases), bowel/colon/colorectal/rectal (9 cases), pancreas (2 cases), central nervous sytem (1 case), kidney (Wilm tumor, 2 cases), tongue (1 case), urethra (1 case), and vagina (1 case). Also, there was one case each of the following cancer types: adenocarcinoma, myoblastoma, and neuroblastoma. Cancer type was not specified in 7 cases. The types of cancer that were treated with chemotherapy during pregnancy are also identified in the human gestational exposure section of each individual agent chapter (Sections **5.2** to **5.34**; Appendix C) and in the Appendix Table D for agents with 10 or fewer cases reported.

Of the 1247 cases, there were a total of 1261 pregnancies and 1276 conceptuses exposed to chemotherapy for treatment of cancer. Fifteen cases had two pregnancies each and 15 pregnancies yielded twin infants. Of the 1276 conceptuses, 397 conceptuses were exposed to chemotherapy during the first trimester, 851 conceptuses were exposed in the second and/or third trimester; timing of exposure was not specified for 28 conceptuses. Chemotherapy was administered as monotherapy to 320 cases (335 conceptuses) and as polytherapy to 807 cases (821 conceptuses). Data were insufficient to determine whether co-treatments were administered in 120 cases (120 conceptuses).

Termination of Pregnancy

Termination of pregnancy was reported for 79 singleton pregnancies (79 conceptuses) exposed to chemotherapy for the treatment of cancer. Sixty-eight pregnancies were terminated following first trimester exposure to chemotherapy and 11 pregnancies were terminated following second trimester exposure to chemotherapy.

Spontaneous Fetal Death

Spontaneous fetal death was reported in 73 singleton pregnancies (73 conceptuses) gestationally exposed to chemotherapy for treatment of cancer. Of these pregnancies, spontaneous abortion was reported for 48 pregnancies and 25 pregnancies ended in stillbirth. In addition, 6 singleton pregnancies ended due to maternal/fetal death. The apparent rate of spontaneous abortion was 13% (42/327 conceptuses, not including induced abortions or maternal/fetal deaths) following exposure to any cancer chemotherapy during the first trimester. The apparent rate of stillbirth following exposure to any cancer chemotherapy during the second and/or third trimester only was 2% (20/836 conceptuses, not including induced abortions, maternal/fetal deaths or spontaneous abortions).

Rates of Occurrence of Congenital Malformations

Major Malformations

Overall, the apparent rate of major malformations among all offspring exposed to cancer chemotherapy during pregnancy, regardless of the nature of the malformations or the gestational stage at exposure, was 5% (62/1156 conceptuses based on 1118 liveborn infants and examination of fetuses of 18 induced abortions, 4 spontaneous abortions, 14 stillbirths, and 2 maternal/fetal deaths). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Of the reports reviewed in the NTP monograph, the apparent rate of major malformations following to exposure to chemotherapy during the first trimester was 14% (41/303 conceptuses based on 281 liveborn infants and examination of the fetuses of 15 induced abortions, 2 spontaneous abortions, 4 stillbirths and 1 maternal/fetal death) compared to an apparent rate of major malformations of 3% (22/826 conceptuses based on 811 liveborn infants and examination of the fetuses of 3 induced abortions, 2 spontaneous abortions, 9 stillbirths, and 1 maternal/fetal deaths) following exposure during the second and/or third trimester only. Timing of exposure was not specified for 28 conceptuses, and none of these conceptuses were malformed.

However, some of the major congenital malformations included in this review of the literature were not likely to be associated with cancer chemotherapy use during pregnancy. Cancer chemotherapy exposures could not be associated with major malformations diagnosed prior to chemotherapy treatment (Sham 1996, Rouzi *et al.* 2009) or inherited conditions, e.g., familial polydactyly (Volkenandt *et al.* 1987) or hereditary spherocytosis (Cheung *et al.* 2009)). In addition, exposure to cancer chemotherapy in the second and/or third trimester only could not be associated with major malformations in structures or organs that are formed during the first trimester of pregnancy, including: agenesis (absence) of the right kidney and ureter (Boros and Reynolds 1977), Down syndrome (Roy *et al.* 1989, Hahn *et al.* 2006), gastroschisis (Cardonick *et al.* 2010), hypospadias (De Carolis *et al.* 2006), neurofibromatosis (spontaneous mutation) (Cardonick *et al.* 2010), pulmonary artery fistula (Cardonick *et al.* 2010), rectal atresia (Van Calsteren *et al.* 2010a), syndactyly of fingers or toes (Cardonick *et al.* 2010, Van Calsteren *et al.* 2010a), and ventricular septal defect (Niedermeier *et al.* 2005). In another singleton pregnancy, major malformations were clearly attributed to co-exposure to warfarin based on the constellation of malformations observed in the liveborn infant (Pye *et al.* 2008); thus, the cancer chemotherapy was not associated with major malformations in this infant. All subsequent calculations of the apparent rate of major malformations based on timing of exposure are adjusted to remove the malformations not likely caused by cancer chemotherapy during gestation. The reported major malformations observed in conceptuses that were possibly attributable to chemotherapy for treatment of cancer during pregnancy are identified in tables within each individual agent chapter (see Sections **5.2** to **5.34**). Thus, the apparent rate of major malformations possibly attributable to exposure to chemotherapy during the first trimester was 13% (40/303 conceptuses based on 281 liveborn infants and examination of the fetuses of 15 induced abortions, 2 spontaneous abortions, 4 stillbirths and 1 maternal/fetal death) compared to an apparent rate of major malformations of 1% (11/826 conceptuses based on 811 liveborn infants and examination of the fetuses of 3 induced abortions, 2 spontaneous abortions, 9 stillbirths, and 1 maternal/fetal deaths) following exposure during the second and/or third trimester only.

Minor Malformations

Minor malformations were reported in 25 liveborn infants and one induced abortus. The majority of these infants were exposed during the second and/or third trimester only (18 liveborn infants exposed in the second and/or third trimester only and 7 infants exposed during the first trimester). The minor

malformations reported included (1 infant per malformation unless stated otherwise): skeletal malformations (plagiocephaly (Cardonick *et al.* 2010), pectus excavatum, bilateral small protuberance on phalanx 5, and double cartilage rings in both ears (Van Calsteren *et al.* 2010a)); visceral malformations or anomalies (bilateral hydronephrosis with dilation of left proximal ureter (Garcia *et al.* 1999), bilateral ureteral reflux (Hahn *et al.* 2006), mild glandular hypospadias (Ghaemmaghami *et al.* 2009), inguinal hernia (Giannakopoulou *et al.* 2000)); cardiac defects (patent ductus arteriosus (Carradice *et al.* 2002), patent ductus arteriosus and small (<4 cm) secundum atrial septal defects (Siu *et al.* 2002) asymptomatic cardiac murmur (Li and Jaffe 1974), and minor ventricular septal defects (Peretz and Peretz 2003)). Other minor malformations or anomalies included: suspected holoprosencephaly (Cardonick *et al.* 2010), mild hydrocephalus (Potluri *et al.* 2006), microophthalmia (Li *et al.* 2007), adherence of iris to cornea (Reynoso *et al.* 1987), preauricular skin tags (Isaacs *et al.* 2001), patent mid-line perineal pit (Russell *et al.* 2007), and hemagiomas (4 infants) (Wells *et al.* 1968, Ring *et al.* 2005b, Cardonick *et al.* 2010, Van Calsteren *et al.* 2010a). The histological examination of an induced abortion observed a large cell in the testes that was reported to be a possible megakaryocyte (Jacobs *et al.* 1980). The reported minor malformations observed in conceptuses following treatment of cancer during pregnancy are identified in the individual agent chapter (see Sections **5.2** to **5.34**).

Pregnancy Complications and Newborn Health

The NTP also compiled information on pregnancy complications potentially associated with cancer chemotherapy use during pregnancy, specifically for: abnormally low levels of amniotic fluid, intrauterine growth restriction and spontaneous preterm birth. The apparent rate of abnormally low levels of amniotic fluid during pregnancy was 3% (33/1118 conceptuses based on liveborn infants) following gestational exposure to any cancer chemotherapy; this calculation included all cases reporting oligohydramnios, anhydramnios and any progressive reduction in amniotic fluid. Of note, the majority of cases reporting abnormally low levels of amniotic fluid were exposed to trastuzumab (42%; 14/33 liveborn infants, including one set of twins). Among the liveborn infants gestationally exposed to trastuzumab, the apparent rate of abnormally low levels of amniotic fluid was 74% (14/19 liveborn infants, including one set of twins). Intrauterine growth restriction (based on measurements of the fetus) was reported for 29 of 1118 liveborn infants (3%) as well as 1 singleton pregnancy ending in a stillbirth (Peterson *et al.* 2010). Other frequently occurring pregnancy complications among pregnancies yielding liveborn infants included: spontaneous preterm labor (63 pregnancies), preeclampsia (28 pregnancies, including two pregnancies with maternal hypertension) and premature rupture of membranes (17 pregnancies, including 3 pregnancies with spontaneous preterm labor).

Preterm birth (<37 weeks of gestation), via any route of delivery, was reported for approximately one-third of the infants gestationally-exposed to chemotherapy for treatment of cancer were born preterm (366/1119 liveborn infants). Specifically, early preterm birth (<34 weeks of gestation) was reported 176 infants (16%), late preterm delivery (34 to <36 weeks of gestation) was reported for 190 infants (17%) and 295 infants were reported to be born at term (26%). Data were insufficient to determine the timing of birth for the remaining 458 infants. The apparent rate of spontaneous vaginal preterm birth was only 9% (97/1118 liveborn infants), while the majority of the preterm infants were delivered via C-section (19%; 207/1118 liveborn infants). The remaining 6% of preterm infants (62/1118 liveborn infants) were delivered via vaginal induced deliveries. The data were insufficient to determine the route of delivery for 34 of the preterm infants. At birth, the apparent rate of small for gestational age newborns following gestational exposure to chemotherapy was 8% (90/1118 liveborn infants) as identified by body weights that were <10th percentile of the normal population based on sex and gestational age at birth

(Olsen *et al.* 2010). Normal body weight for gestational age was reported for 633 (57%) newborns and data were insufficient to determine small for gestational age for 395 (35%) newborns.

Transient myelosuppression was reported for 46 liveborn of 1118 liveborn infants following gestational exposure to cancer chemotherapy; however, an apparent rate of transient myelosuppression was not calculated because it was not always clear whether a newborn's blood count had been evaluated. This myelosuppression generally resolved within the first 2 to 3 weeks of life, and it resolved without treatment in the majority of cases. Myelosuppression was identified as reported as anemia, leukopenia, lymphopenia (lymphocytopenia), neutropenia, thrombocytopenia, granulocytopenia and bone marrow myelosuppression. There was one case of non-hemolytic anemia that was not included in the total liveborn infants with myelosuppression (Peres *et al.* 2001). Of a total of 1118 liveborn infants reviewed in the NTP monograph, only 10 infants were reported to have any symptoms of fetal or neonatal cardiotoxicity (e.g., arrhythmia, cardiomyopathy, tachycardia and heart failure) following gestational exposure to any cancer chemotherapy. An apparent rate was not calculated because it was not clear whether an assessment of fetal cardiac effects were routinely evaluated or consistently reported. Six singleton pregnancies were exposed to anthracyclines in polytherapy including: idarubicin (3 cases) (Achtari and Hohlfeld 2000, Siu *et al.* 2002, Niedermeier *et al.* 2005), idarubicin and mitoxtantrone (1 case) (Baumgartner *et al.* 2009), daunorubicin polytherapy (1 case) (Okun *et al.* 1979), and daunorubicin and mitoxantrone (1 case) (Garcia *et al.* 1999). Three pregnancies were exposed to all-trans retinoic acid (Harrison *et al.* 1994, Leong *et al.* 2000, Takitani *et al.* 2005), including one singleton pregnancy exposed to idarubicin and all-trans retinoic acid (Siu *et al.* 2002). The remaining pregnancy was exposed to cyclophosphamide and cisplatin (King *et al.* 1991). 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 10 infants. For three of these infants (Okun *et al.* 1979, Garcia *et al.* 1999, Baumgartner *et al.* 2009), anemia was reported and it may have been the cause of the cardiotoxicity (Strauss 1986). 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. Anemia may have contributed to fetal and neonatal cardiac malfunction in one liveborn infant gestationally exposed to cyclophosphamide and docetaxel in the first and second trimester (Massey Skatulla *et al.* 2012); other pregnancy complications included preeclampsia and the HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count).

Infant Death

Twenty-five of 1118 live born infants exposed to chemotherapy for treatment of cancer died; all, but one infant died within the first 4 months of life. Fifteen infants were born preterm, 2 infants were born at term; data were insufficient to determine the gestational age at delivery for 4 infants. Two preterm infants died of malformations observed prior to chemotherapy (Sham 1996, Rouzi *et al.* 2009). One infant born at gestation week 28 died of intercranial bleeding at age 10 days (Dilek *et al.* 2006). Respiratory distress was the cause of death for 5 preterm infants (Merskey and Rigal 1956, Rothberg *et al.* 1959, Dilek *et al.* 2006), including one infant with a small secundum atrial septal defect identified at autopsy (Thomas and Peckham 1976). Two newborns with hydrocephalus died within four hours of birth (Zemlickis *et al.* 1992b), including one infant with communicating hydrocephalus and several cardiac anomalies (Pye *et al.* 2008). Infections were the cause of death for 4 infants: one term infant died of an acute staphylococcus infection at 30 days (Ruiz Reyes and Tamayo Perez 1961), another term infant died of gastroenteritis at 90 days of age (Aviles *et al.* 1991), a preterm infant died of severe gastroenteritis at 3 months of age (Dilek *et al.* 2006), and a preterm infant died of septicemia at age 21 days (Aviles *et al.* 1991). Four infants who died had experienced oligo- or anhydramnios following

gestational exposure to trastuzumab. Of the trastuzumab-exposed infants, one preterm infant suffered from prematurity-related problem and died following decreasing kidney function at age 4 month (Weber-Schoendorfer and Schaefer 2008), a preterm infant died at age 21 weeks of multiple organ failure (Witzel *et al.* 2008), another preterm infant developed chronic renal failure at 21 weeks and died of respiratory arrest at 13 weeks (Beale *et al.* 2009), and a term newborn with severe pulmonary hypoplasia and atelectasis died at age day 1 (Warraich and Smith 2009). Four infants delivered early preterm died within their first 8 days of life with no etiology reported (Boland 1951, O'Leary and Bepko 1963, Giacalone *et al.* 1999, Meera *et al.* 2008). Another preterm newborn, which had experienced anhydramnios and intrauterine growth restriction, had anuria and died at age 7 (Fernandez *et al.* 1989). The remaining malformed infant died at 10 weeks following a respiratory infection, and autopsy revealed multiple internal malformations (Diamond *et al.* 1960). One infant died at 13 weeks due to a severe autoimmune disease (Cardonick *et al.* 2010).

Follow up Evaluations

Of the publications reviewed in the NTP monograph, follow up evaluations were reported for 670 of 1118 liveborn infants reviewed in the NTP monograph. The number of infants with follow up evaluation excludes the 21 infants who died (described above in Infant Death). Normal growth and development were reported for a majority of children gestationally exposed chemotherapy with reports of only 21 children with an adverse health effect at follow up examination (3%; 21 of 670 liveborn infants with follow up examination). Delays in growth were observed for 7 children ranging in age from 3 to 26 months (Doney *et al.* 1979, Gulati *et al.* 1986, Artlich *et al.* 1994, Garcia *et al.* 1999, Carradice *et al.* 2002, Cheung *et al.* 2009). Another infant 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). Mild to moderate hearing loss was observed in 3 children at ages ranging from 1 to 7 years (Raffles *et al.* 1989, Cardonick *et al.* 2010). Language and/or motor delays were observed in 4 children (Achtari and Hohlfeld 2000, Lam 2006), including one child with cranial malformations (Bawle *et al.* 1998). Three infants experienced developmental delays due to their major malformations, including Down syndrome (1 infant) and neurofibromatosis (1 infant) (Cardonick *et al.* 2010), bilateral ventriculomegaly and colpocephaly at birth (Paskulin *et al.* 2005). One twin had attention-deficit-hyperactivity disorder (Asperger syndrome), while the twin sibling was normal (Cardonick *et al.* 2010). Two offspring had disease-related issues, including one infant at age 9 months with normocytic anemia and a slightly palpable spleen. One infant at age 9 months had normocytic anemia and a slightly palpable spleen (McConnell and Bhoola 1973). The second child, born with Madelung syndrome, was the only instance of a child developing cancer following exposure to cancer chemotherapy; the mother was administered cyclophosphamide throughout the entire pregnancy, and his female twin did not have cancer and had normal growth and development (Zemlickis *et al.* 1993).

The age at follow up examination for most of these children with gestational exposure to chemotherapy was limited to the first few months or years of life. Based on the 438 offspring with individual data on age at follow up, the percentage of children with follow up examinations at ages ranging from birth to 2 years was 56% (246 children) based on published reports with individual biometric data). Fewer of the children gestationally exposed to cancer chemotherapy had follow examinations at later than 2 years of age (based on published reports with individual biometric data): 114 children (26%) at >2- 5 years of age, 59 children (13%) at >5-12 years of age, 16 children (4%) at >12-17 years of age, and 3 children (1%) at >17-22 years of age.

5.2 5-FLUOROURACIL

5.2.1 Mechanism of Action, Route of Administration, and Indications

Table 18: Pharmacology of 5-fluorouracil in adult humans

Molecular weight:	130.078
Protein binding:	**[Information not located]**
Metabolism:	Hepatic (90%); via a dehydrogenase enzyme; must be metabolized to be active
Half-life elimination:	Biphasic: Initial: 6-20 minutes; two metabolites, fluorodexouridine monophosphate and floxuridine triphosphate, have prolonged half-lives depending on the type of tissue
Distribution:	Vd: ~22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g., pleural effusions and ascitic fluid)
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours

Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum, CO_2, carbon dioxide, CSF, cerebral spinal fluid; NS, not specified; Vd, volume of distribution.

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 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. Additional information on the pharmacology of 5-fluorouracil is located in Table 18: Pharmacology of 5-fluorouracil in adult humans (**Table 18**).

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 intraperitoneally 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). In another study, 5-fluorouracil 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 (Boike *et al.* 1989). 5-fluorouracil was poorly eliminated in the rat fetus, which may explain the observed fetal toxicity at dosage levels lower than maternal toxicity (50 mg/kg versus 230 mg/kg, fetal versus maternal LD_{50}) (reviewed in Boike et al. (1989)). A third study 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 the publication (Van Calsteren *et al.* 2010b).

There are no published reports of breast milk transport of 5-fluorouracil in humans or in animal models.

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). Similar malformations have been observed in rats following intraperitoneal doses of 12 to 37 mg/kg bw/day 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. In contrast, administration of 5-fluorouracil at doses of 40 mg/kg bw/day to monkeys on gestation days 20 and 24, during organogenesis, did not induce malformations (Sandoz 2011). 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 bw/day 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/d in monkeys (Sandoz 2011).

In the peer-reviewed literature, intraperitoneal injections of 10 to 40 mg/kg bw/day 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). 5-Fluorouracil induced cleft palate and malformations of the skeletal system, e.g., leg, paw or tail malformations, in Wistar rat fetuses, when administered via intraperitoneal injections on gestation days 11 and 12 to the rat dam (Chaube *et al.* 1968).

5.2.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

5-Fluorouracil was administered to 178 female cancer patients (also called cases) during pregnancy from 18 case reports (18 cases), 12 case series (91 cases), 1 retrospective case series (7 cases), 2 retrospective cohort studies (6 cases), 5 retrospective survey studies (34 cases), and 1 registry survey (22 cases) (Appendix C Table 1). Among the 178 cases, 5-fluorouracil was used to treat breast cancer (165 cases), colorectal cancer (5 cases), colon cancer (1 case), and one case each of cancers of the cervix, ovary, bowel, rectum, and pancreas. Type of cancer was not specified for two cases.

5-Fluorouracil was administered during 178 pregnancies for a total of 179 exposed conceptuses, due to one twin pregnancy (Jeppesen and Osterlind 2011). 5-Fluorouracil was administered during the first trimester in 17 pregnancies (18 conceptuses due to one twin pregnancy). The drug was administered to 161 singleton pregnancies (161 conceptuses) in the second and/or third trimester only, including two case series that did not include individual data on timing of pregnancy (Hahn *et al.* 2006, Jameel and Jamil 2007). While individual data on the timing of exposure was not identified for 46 singleton pregnancies from two case series, it was assumed that these 46 pregnancies were likely treated in the second and third trimester because 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)). 5-Fluorouracil was administered as monotherapy to 6 cases (6 conceptuses) and as polytherapy to 172 cases (173 conceptuses).

Termination of Pregnancy

Three singleton pregnancies (3 conceptuses) were terminated by induced abortion following exposure to 5-fluorouracil, and all were exposed during the first trimester. Major malformations were observed at upon examination of two fetuses from induced abortions. Skeletal malformations and micrognathia were observed in a fetus from an induced abortion exposed to 5-fluorouracil in the first and second trimesters. The fetus was co-exposed to cyclophosphamide, epirubicin and radiation therapy in the first

trimester, followed by co-treatment with cyclophosphamide and methotrexate in the second trimester (Leyder *et al.* 2010). Examination 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 to 5-fluorouracil in the first and second trimesters beginning in the 11th week of gestation and was co-exposed to diagnostic X-rays in the first trimester (Stephens *et al.* 1980). A third induced abortion was performed following first trimester exposure to 5-fluorouracil and co-treatment with melphalan (Jochimsen *et al.* 1981); no examination of the fetus was reported.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 5 pregnancies, including 4 spontaneous abortions and one stillbirth. Spontaneous abortion was reported for 4 singleton pregnancies (4 conceptuses) exposed to 5-fluorouracil during the first trimester; no examination of the fetuses was reported. These four pregnancies were co-exposed to epirubicin and cyclophosphamide (Giacalone *et al.* 1999), melphalan (Jochimsen *et al.* 1981), or methotrexate (Zemlickis *et al.* 1992b, Ring *et al.* 2005b). One stillbirth of a normal fetus occurred at gestation week 25 following first trimester exposure and co-exposure to methotrexate (Peres *et al.* 2001).

Rate of Occurrence of Congenital Malformations

Major malformations

Table 19: Major malformations diagnosed at birth possibly attributable to in utero exposure to 5-fluorouracil

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Microcephaly, low set ears, hypertelorism, and a right palmar simian crease	31% (4/13)
	Flat nasal bridge, high arched palate, ventriculomegaly, colpocephaly, skeletal deformities of the hand (including syndactyly and hypoplasia of the digits), and a bicuspid aortic valve	
	Skeletal malformations of hands and feet, and micrognathia	
	Bilateral radial aplasia and absent digits on each hand, single umbilical artery, hypoplastic aorta, imperforate anus, common bladder and rectum, renal dysplasia, underdevelopment or absence of multiple organs	
2nd and/or 3rd only	Hemi-hypertrophy of the lower extremity	1% (2/161)
	Clubfoot	

[a] Data based on liveborn infants as well as examination of fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations occurred in 5 infants and 2 induced abortuses with gestational exposure to 5-fluorouracil (Table 19). Major malformations were reported for 2 liveborn infants and 2 fetuses from induced abortions exposed to 5-fluorouracil in the first trimester. One liveborn infant had hypertelorism, microcephaly, low set ears, and a right palmar simian crease following exposure to 5-fluorouracil and methotrexate from the first through third trimesters (gestation weeks 7.5 through 28.5) and radiotherapy in the second trimester (Bawle *et al.* 1998). Another liveborn infant had multiple skeletal deformities of the hand, flat nasal bridge, high arched palate, ventriculomegaly, colpocephaly, and a bicuspid aortic valve following exposure to 5-

fluorouracil, doxorubicin, and cyclophosphamide during the first and second trimesters (Paskulin *et al.* 2005). Major malformations were observed upon examination of two fetuses from induced abortions with first trimester exposure to 5-fluorouracil. Skeletal malformations and micrognathia were observed in one fetus from an induced abortion exposed to 5-fluorouracil in the first and second trimesters; the fetus was co-exposed to cyclophosphamide, epirubicin and radiation therapy in the first trimester, followed by co-treatment with cyclophosphamide and methotrexate in the second 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). Examination of a second induced abortus revealed 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 to 5-fluorouracil in the first and second trimesters beginning in the gestation week 11 and was co-exposed to diagnostic X-rays in the first trimester (Stephens *et al.* 1980). 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). Thus, the apparent rate of major malformations likely attributable to exposure to 5-fluorouracil in the first trimester was 31% (4/13 conceptuses based on 10 liveborn infants and examination of the fetuses of 2 induced abortions and 1 stillbirth).

Major malformations were observed in three infants exposed in the second and/or third trimester only. Hemi-hypertrophy of the lower extremity was observed in one infant following exposure to 5-fluorouracil monotherapy in the second and third trimester only (Cardonick *et al.* 2010). One case series reported one infant with clubfoot and another infant with Down syndrome following in utero exposure in the second and third trimesters only to 5-fluorouracil and co-treatments doxorubicin and cyclophosphamide (Hahn *et al.* 2006). However, Down syndrome was not caused by exposure to 5-fluorouracil in the second and third trimester. Thus, the apparent rate of major malformations likely attributable to exposure to 5-fluorouracil in the second and/or third trimester only was 2% (2/161 conceptuses based on 161 liveborn infants).

Minor Malformations

Minor malformations were reported in 5 liveborn infants gestationally-exposed to 5-fluorouracil. An inguinal hernia was diagnosed and repaired in an infant with exposure in the first and second trimesters to 5-fluorouracil and co-treated with cyclophosphamide (Giannakopoulou *et al.* 2000). One infant each had congenital bilateral ureteral reflux (Hahn *et al.* 2006) and doubled cartilage rings (Van Calsteren *et al.* 2010a) following second and third trimester exposure to 5-fluorouracil and co-exposure to doxorubicin and cyclophosphamide. A bilateral small protuberance on phalanx 5 was reported in an infant following second and third trimester exposure to 5-fluorouracil and co-treatment with epirubicin and cyclophosphamide (Van Calsteren *et al.* 2010a). Finally, one infant had a hemangioma on its abdomen, which the authors deemed was not due to chemotherapy (Ring *et al.* 2005b); the infant was exposed second and/or third trimester to 5-fluorouracil and co-treated with cyclophosphamide and methotrexate. **[It is possible that the infant with the hemangioma was, instead, treated with cyclophosphamide and co-treated with either doxorubicin or epirubicin; the authors did not report the treatments of individual patients.]**

Pregnancy Complications and Newborn Health

There were 171 liveborn infants with in utero exposure to 5-fluorouracil. 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.* 2005b). Reductions in amniotic fluid were reported in 2 pregnancies ranging from oligohydramnios (Cordoba *et al.* 2010) to a progressive reduction in amniotic fluid (Stephens *et al.* 1980). Preeclampsia was reported in two pregnancies (Berry *et al.* 1999, Kuerer *et al.* 2002), eclamptic seizures in one pregnancy (Muller *et al.* 1996), maternal hypertension in one pregnancy (Turchi and Villasis 1988), premature rupture of the membranes in one pregnancy (Jeppesen and Osterlind 2011), and spontaneous preterm labor occurred in 5 pregnancies (Berry *et al.* 1999, Giannakopoulou *et al.* 2000, Andreadis *et al.* 2004, Sharma *et al.* 2009).

Early preterm delivery (<34 weeks) was reported for 11 infants, late preterm delivery (34-36 weeks) was reported for 27 infants and 15 newborns were delivered at term. Data were insufficient to determine the gestational age at delivery for 117 infants. Of the 39 preterm infants, 6 infants were delivered via spontaneous vaginal birth, 2 infants were delivered via induced vaginal birth, and 24 infants were delivered via C-section (including 1 set of twins). Data were insufficient to determine the route of delivery for 6 preterm infants. Small for gestational age was reported for 11 infants and normal body weights were reported for 93 infants based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 67 infants.

Several health effects were observed in newborns. Breathing difficulties were observed in 23 infants, ranging from transient tachypnea to respiratory distress (Stadler and Knowles 1971, Berry *et al.* 1999, Giacalone *et al.* 1999, Giannakopoulou *et al.* 2000, Ginopoulos *et al.* 2004, Ring *et al.* 2005b, Hahn *et al.* 2006, Cardonick *et al.* 2010). Transient myelosuppression was reported in 5 infants, including: anemia (2 infants) (Cuvier *et al.* 1997, Giacalone *et al.* 1999), leukopenia (2 infants) (Berry *et al.* 1999, Giacalone *et al.* 1999), neutropenia and thrombocytopenia (1 infant) (Hahn *et al.* 2006). One infant with transient myelosuppression also had a subarachnoid hemorrhage (Hahn *et al.* 2009). Jaundice was reported in three infants, including one set of twins (Cardonick *et al.* 2010, Jeppesen and Osterlind 2011). One infant with breathing difficulties was also hypothyroid (Kanate *et al.* 2009).

Infant Deaths

One infant born at gestation week 31 died 8 days after birth; cause of death was not reported (Giacalone *et al.* 1999).

Follow Up Evaluations

Follow-up evaluations were available for 129 infants gestationally exposed to 5-fluorouracil, 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 178 pregnancies, including one twin pregnancy (179 conceptuses) (**Table 76**). Overall, the apparent rate of major malformations among all 5-fluorouracil-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 4% (7/174 conceptuses based on 171 liveborn infants and examination of the fetuses of 2 induced abortions and one stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in two liveborn infants and two fetuses terminated by induced abortion following exposure to 5-fluorouracil during the first trimester. There may be a pattern of craniofacial and/or skeletal malformations, usually involving the absence or fusion of the digits of the hand and/or foot, following first trimester exposure (Stephens *et al.* 1980, Bawle *et al.* 1998, Paskulin *et al.* 2005, Leyder *et al.* 2010). The major malformations observed following first trimester exposure to 5-fluorouracil in humans were similar to the types of malformations observed in mice and rats exposed during specific time periods within organogenesis. Thus, the apparent rate of major malformations following exposure to 5-fluorouracil during the first trimester was 5% (4/13 conceptuses based on 10 liveborn infants and examination of the fetuses of 2 induced abortions and one stillbirth). Major malformations were observed in 3 liveborn infants following second and/or third trimester only exposure to 5-fluorouracil. However, one major malformations (Down syndrome) was not likely caused by exposure to 5-fluorouracil in the second and/or third trimester only. Thus, the adjusted apparent rate of major malformations following exposure to 5-fluorouracil in the second and/or third trimester only was 1% (2/161 conceptuses based on 161 liveborn infants). In addition, exposure to 5-fluorouracil in the first trimester appeared to increase the rate of spontaneous abortion (**Table 76**). The apparent rate of spontaneous abortion following first trimester exposure to 5-fluorouracil was higher than the reported incidence in the general population (25% versus 13%) (Wilcox 2010).

5.3 6-MERCAPTOPURINE

5.3.1 Mechanism of Action, Route of Administration, and Indications

Table 20: Pharmacology of 6-mercaptopurine in adult humans	
Molecular weight:	151.181
Protein binding:	~19%
Metabolism:	Hepatic and in gastrointestinal mucosa; hepatically via xanthine oxidase and methylation via thiopurine methyltransferase (TPMT) to sulfate conjugates, 6-thiouric acid, and other inactive compounds; first-pass effect
Half-life elimination:	47 minutes
Distribution:	Vd > total body water; CNS penetration is poor
Time to peak, serum (C_{max}):	~2 hours
Excretion:	Urine (46% as 6-mercaptopurine and metabolites)

Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CNS, central nervous system; Vd,= volume of distribution.

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 and Mckinney 2008). 6-Mercaptopurine is administered orally. Additional information on the pharmacology of 6-mercaptopurine is located in **Table 20**.

6-Mercaptopurine is indicated for treatment of acute lymphocytic leukemia (Teva 2011a).

5.3.2 Evidence of Placental and Breast Milk Transport

Placental transfer has 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 gestation week 9, 14, and 15, 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 for other health conditions. Low concentrations of 6-mercaptopurine were reported in the breast milk of two patients receiving daily azathioprine to suppress immune function following kidney transplants (Coulam *et al.* 1982). Peak levels of the 6-mercaptopurine were 3.4 ng/mL after 2 hours and 4.5 ng/mL after 8 hours following an oral dose of 75 mg azathioprine in one patient (patient 1) and 18 ng/mL 2 hours after dosing in another patient (patient 2). 6-mercaptopurine was not detectable in multiple samples from

two patients collected at several time points within a 24-hour period after administrations (limit of detection at 5 ng/mL) (Moretti *et al.* 2006). In another study, 6-mercaptopurine was detected 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 (Sau *et al.* 2007). In contrast, 6-mercaptopurine was not detected in the blood of their neonates (Sau *et al.* 2007). Similarly, Gardiner et al. (2006) reported an 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 (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 0.8 mg/kg bw/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

Number of Cases, Publications, and Types of Cancer Treated

6-Mercaptopurine was administered to 83 female cancer patients (also called cases) during pregnancy identified from 24 case reports (24 cases), 14 case series (30 cases), 5 retrospective case series (23 cases), 1 retrospective cohort study (1 case), 1 registry survey (1 case), and 4 retrospective surveys (4 cases) (Appendix C Table 2). Among these 83 patients, 6-mercaptopurine was primarily used to treat acute leukemia, including: acute **[no classification given]** (3 cases); acute lymphocytic (33 cases); acute myelogenous leukemia (also called acute granulocytic leukemia) (31 cases), acute myelomonocytic leukemia (2 cases), acute promyelocytic leukemia (2 cases), and acute stem cell leukemia (1 case). It was also used to treat chronic myelogenous leukemia (also called chronic granulocytic leukemia; 7 cases), and non-Hodgkin lymphoma (1 case). The cancers of three additional patients treated with 6-mercaptopurine were listed only as leukemia (1 case), lymphocytic leukemia (probably sub-acute) (1 case), and not specified (1 case).

A total of 85 pregnancies and 86 conceptuses were exposed in utero to 6-mercaptopurine due to two patients having two pregnancies each (Diamond *et al.* 1960, Aviles and Niz 1988) and one patient giving birth to twins (Turchi and Villasis 1988). 6-Mercaptopurine was administered in the first trimester in 40

pregnancies and in the second and/or third trimester only in 41 pregnancies (42 conceptuses due to one twin pregnancy). Timing of exposure was not specified in 4 pregnancies. 6-Mercaptopurine was administered as monotherapy in 31 pregnancies, including 3 pregnancies with radiation therapy (Diamond *et al.* 1960, Loyd 1961, Lee *et al.* 1962) and one pregnancy treated with 6-mercaptopurine in the second month of gestation following exposure to nitrogen mustard during the first month of gestation (Hoover and Schumacher 1966). 6-Mercaptopurine was administered as polytherapy in 53 cases (54 conceptuses). Data were insufficient to determine whether the drug was administered as mono- or polytherapy in one case.

Termination of Pregnancy

One singleton pregnancy exposed to 6-mercaptopurine was terminated by induced abortion at 16 weeks gestation following exposure during the first trimester (Zuazu *et al.* 1991); no examination of the fetus was reported.

Spontaneous fetal death

Spontaneous fetal death occurred in 11 singleton pregnancies exposed in utero to 6-mercaptopurine, including 5 spontaneous abortions and 1 stillbirth following exposure during the first trimester. Spontaneous abortions ended 5 pregnancies exposed to 6-mercaptopurine in the first trimester. Authors reported normal fetuses from two of these spontaneous abortions following exposure to 6-mercaptopurine during the first trimester and co-exposed to nitrogen mustard (Hoover and Schumacher 1966), or during the first and second trimester and co-exposed to aminopterin and demecolcine (Smith *et al.* 1958). No examination of the fetuses was reported for the remaining three spontaneous abortions including: one pregnancy exposed in the first and second trimesters (Boggs *et al.* 1962), one pregnancy exposed in the first trimester (Zemlickis *et al.* 1992b), and one fetus exposed during the first trimester and co-exposed to methotrexate and vincristine (Bergstrom and Altman 1998). Polydactyly was reported in one stillborn fetus following exposure to 6-mercaptopurine and cyclophosphamide during the first through third trimesters (Mulvihill *et al.* 1987); this stillbirth occurred following premature detachment of the placenta.

Stillbirth was reported for one singleton pregnancy exposed to 6-mercaptopurine monotherapy during the second trimester (Greenlund *et al.* 2001); no examination of the fetus was reported. Another stillbirth occurred following exposure to 6-mercaptopurine monotherapy and timing of exposure not specified (Parekh *et al.* 1959); no examination of the fetus was reported.

Finally, three singleton pregnancies ended in maternal/fetal death following gestational exposure to 6-mercaptopurine. A normal fetus was reported from one maternal/fetal death occurring after exposure in the first and second trimesters to 6-mercaptopurine, cytarabine, daunorubicin, and vincristine (Feliu *et al.* 1988). Another normal fetus was reported from a maternal/fetal death occurring following second trimester exposure to 6-mercaptopurine monotherapy (Nicholson 1968). A third maternal/fetal death occurred following exposure to 6-mercaptopurine monotherapy in the first and second trimesters only (Nicholson 1968); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations following in utero exposure to 6-mercaptopurine were observed in 1 liveborn infant and 1 stillborn fetus (**Table 21**).

Table 21: Major malformations diagnosed at birth possibly attributable to in utero exposure to 6-mercaptopurine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Cleft palate, poorly developed external genitalia, bilateral microphthalmia and corneal opacities, poorly developed external genitalia, hypoplasia of the thyroid and ovaries, disseminated cytomegaly, and other abnormalities	6% (2/35)
	Polydactyly	
2nd and/or 3rd only	None	0% (0/41)
NS	None	0% (0/3)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths

The liveborn infant had 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., first trimester exposure, then to busulfan from first and third trimesters with the addition of 6-mercaptopurine again in the third 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). As mentioned above, polydactyly was reported in one stillborn fetus exposed in the first through third trimesters to 6-mercaptopurine and cyclophosphamide (Mulvihill *et al.* 1987). Thus, the apparent rate of major malformations following exposure to 6-mercaptopurine in the first trimester was 6% (2/35, including 31 liveborn infants and examination of the fetuses of 2 spontaneous abortions, 1 stillbirth, and 1 maternal/fetal death).

There were no major malformations following exposure to 6-mercaptopurine in the second and/or third trimester only (0/41 based on 40 liveborn infants and examination of the fetus for 1 maternal/fetal death).

Minor Malformations

Minor malformations were observed in one infant following gestational exposure to 6-mercaptopurine. An asymptomatic cardiac murmur was reported in one infant following exposure to 6-mercaptopurine in the first through third trimesters (Li and Jaffe 1974). In addition, cytogenetic analysis of the lymphocytes from a liveborn infant without malformations detected a normal karyotype but some chromosome breakage and a ring chromosome (Schleuning and Clemm 1987).

Pregnancy Complications and Newborn Health

There were several pregnancy complications 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 (1 pregnancy) (Coopland *et al.* 1969), premature separation of the placenta (2 pregnancies) (Mulvihill *et al.* 1987, Morishita *et al.* 1994), premature rupture of membranes (4 pregnancies) (Ravenna and Stein 1963, Doney *et al.* 1979, Okun *et al.* 1979, Gondo *et al.* 1990), and spontaneous preterm labor (13 pregnancies, including one case also reporting premature rupture of membranes) (Merskey and Rigal 1956, Rothberg *et al.* 1959, Diamond *et al.* 1960, Frenkel and Meyers

1960, Loyd 1961, Lee *et al.* 1962, Neu 1962, O'Leary and Bepko 1963, Nicholson 1968, McConnell and Bhoola 1973, Gondo *et al.* 1990, Hansen *et al.* 2001).

There were 74 liveborn infants gestationally exposed to 6-mercaptopurine. Early preterm delivery (<34 weeks) was reported for 13 infants, late preterm delivery (34 to<37 weeks) was reported for 20 infants and 27 infants were delivered at term (≥37 weeks). Data were insufficient to determine the gestational age at delivery for 14 infants. Of the preterm infants, 17 infants were delivered via spontaneous vaginal delivery, 3 infants were delivered via induced vaginal delivery, and 10 infants were delivered via C-section. Data were insufficient to determine the route of delivery for 3 infants. Small for gestational age was reported for 8 infants and 39 infants had normal body weights based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). The data reported were insufficient to determine small for gestational age in the remaining 27 infants.

Respiratory distress was reported for 4 preterm infants; three of these infants died shortly after birth (see Infant Deaths section below). Transient myelosuppression was reported in five infants, including anemia (McConnell and Bhoola 1973), bone marrow suppression (Okun *et al.* 1979), slight leukocytopenia (Khurshid and Saleem 1978), leukocytopenia and thrombocytopenia (Gondo *et al.* 1990), and pancytopenia (Pizzuto *et al.* 1980, Aviles and Niz 1988). The newborn with bone marrow suppression was also hydropic with marked abdominal distention and slight cardiomegaly (Okun *et al.* 1979); he was treated for congestive heart failure, which resolved successfully. 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 (1 infant) (Doney *et al.* 1979) and meconium aspiration syndrome (1 infant) (Hansen *et al.* 2001).

Infant Deaths

Seven infant deaths occurred in pregnancies exposed to 6-mercaptopurine. An infant with major malformations including cleft palate (reviewed above) died at age 10 weeks after developing grunting respiration and a cough at age 2 months (Diamond *et al.* 1960). 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, Rothberg *et al.* 1959, O'Leary and Bepko 1963); three of these infants had respiratory distress.

Follow Up Evaluations

Follow up examinations were available on 51 infants (including one set of twins) gestationally exposed to 6-mercaptopurine; examinations were conducted 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 had normocytic anemia with a slightly palpable spleen at age 9 months (McConnell and Bhoola 1973).

5.3.5 Summary of Pregnancy Outcomes for 6-mercaptopurine

In utero exposure to 6-mercaptopurine was documented for 85 pregnancies including one set of twins (86 conceptuses) (**Table 76**). Overall, the apparent rate of major malformations among all 6-mercaptopurine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 3% (2/79 conceptuses based on 74 liveborn infants and examination of the fetus for 2 spontaneous abortions, 1 stillbirth and 2 maternal/fetal deaths). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations possibly attributable to exposure to 6-mercaptopurine during the first trimester were

observed in 2 of 35 conceptuses (**Table 76**). One malformed infant had defects similar to malformations observed in developmental toxicity studies of rat fetuses exposed to 6-mercaptopurine during organogenesis: cleft palate and urogenital malformations (Diamond *et al.* 1960). This pregnancy was also co-exposed to busulfan and radiation therapy in the first trimester, which may also have contributed to the major malformations observed. Thus, the apparent rate of major malformations following exposure to 6-mercaptopurine in the first trimester was 6% (2/35 conceptuses based on 31 liveborn infants and examination of the fetuses of 2 spontaneous abortions, 1 stillbirth, and 1 maternal/fetal death). There were no major malformations following exposure to 6-mercaptopurine in the second and/or third trimester only (0/41 conceptuses based on 40 liveborn infants and examination of the fetus of 1 maternal/fetal death).

The apparent rate of major malformations following treatment of 6-mercaptopurine for cancer during the first trimester of pregnancy is similar to apparent rates of major malformations observed following exposure to azathioprine during pregnancy (reviewed in Polifka and Friedman 2002). Azathioprine is metabolized to the active metabolite 6-mercaptopurine, and the drug is used for the treatment of autoimmune diseases and immunosuppressive therapies for organ transplant recipients, which are not included in this monograph.

5.4 6-THIOGUANINE

5.4.1 Mechanism of Action, Route of Administration, and Indications

Table 22: Pharmacology of 6-Thioguanine in adult humans	
Molecular weight:	167.195
Protein binding:	**[Information not located]**
Metabolism:	Hepatic; rapidly and extensively via thiopurine methyltransferase (TPMT) to 2-amino-6-methylthioguanine (MTG; active) and inactive compounds
Half-life elimination:	Terminal: 5-9 hours
Distribution:	Does not reach therapeutic concentrations in the CSF
Time to peak, serum (C_{max}):	Within 8 hours; predominantly metabolite(s)
Excretion:	**[Information not located]**
Data from Brunton et al. (2011). Abbreviations: NS, not specified; CSF, cerebral spinal fluid, Cmax, time to reach maximal concentration in serum.	

6-Thioguanine is a purine analogue that belongs to a class of chemotherapy drugs known as anti-metabolites. It is a metabolite of azathiopurine and is structurally and functionally related to 6-mercaptopurine (GlaxoSmithKline 2013). 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. Additional information on the pharmacology of 6-thioguanine is located in **Table 22**.

6-Thioguanine is indicated for acute non-lymphoblastic leukemia (also called acute myelogenous leukemia). It has also been used in treating the chronic phase of chronic myelogeneous leukemia (GlaxoSmithKline 2013).

5.4.2 Evidence of Placental and Breast Milk Transport

Placental transfer is reported to occur following direct administration of 6-thioguanine in humans. 6-Thioguanine nucleotides were detected in the red blood cells of the umbilical cord blood at delivery following administration of 6-thioguanine 3 times per week for treatment of Crohn disease (de Boer *et al.* 2005). The levels of 6-thioguanine nucleotides in the umbilical cord blood were $1/12^{th}$ of the levels detected in maternal blood (41 versus 494 picomoles/$8x10^8$ red blood cells, respectively). At one month, the levels of 6-thioguanine in maternal blood were 442 picomoles/$8x10^8$ red blood cells and below the limit of detection in the infant (de Boer *et al.* 2005).

Breast milk transfer of 6-thioguanine in humans may be low or absent. 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 azathiopurine (Gardiner *et al.* 2006). These patients were administered the drug as immunosuppressive treatment for renal transplant rejection (2 patients) Crohn disease or autoimmune hepatitis (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 (GlaxoSmithKline 2013). 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 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 (i.e., organs of the chest and abdomen are arranged in a perfect mirror image of their normal position) (GlaxoSmithKline 2013).

In the published peer-reviewed literature, teratogenic effects or inhibited growth was observed following intravenous injection of pregnant rats treated with thioguanine at 10 mg/kg on gestation day 4 and 5 or 11 and 12 (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

Number of Cases, Publications, and Types of Cancer Treated

6-Thioguanine was administered to 50 female cancer patients (also called cases) during pregnancy identified from 20 case reports (20 cases), 10 case series (17 cases), 1 retrospective case series (1 case), 3 retrospective surveys (10 cases), and 1 retrospective cohort study (2 cases) (Appendix C Table 3). Among these 50 patients, 6-thioguanine was used to treat acute leukemia (type not specified, 1 case), acute myelogenous (also called acute granulocytic; 37 cases), acute myelomonocytic leukemia (2 cases), acute promyelocytic leukemia (4 cases), erythroleukemia (1 case), and acute lymphocytic leukemia (2 cases). It was also used to treat one patient with both acute myelogenous and acute lymphocytic leukemia and two cases of chronic myelogenous leukemia (also called chronic granulocytic).

A total of 53 singleton pregnancies (53 conceptuses) were exposed to 6-thioguanine due to three patients having two pregnancies each (Maurer *et al.* 1971, Schafer 1981, Plows 1982). 6-Thioguanine was administered during the first trimester in 9 pregnancies and in the second and/or third trimester only in 44 pregnancies. 6-Thioguanine was administered as polytherapy during all 53 pregnancies (53 conceptuses).

Termination of Pregnancy

Five singleton pregnancies were terminated by induced abortion. Examination of the fetus was reported for 1 of 4 fetuses with first trimester exposure. Post-mortem fetal evaluation of an induced abortion revealed a normal fetus following first trimester exposure and co-exposure to cytarabine in the first trimester, and vincristine and rubidomycin **[daunorubicin]** in the second trimester (Lilleyman *et al.* 1977). Normal chromosomes were detected in a second induced abortus following exposure to 6-thioguanine, and cytarabine during the first trimester (Maurer *et al.* 1971); no fetal data were provided. Examination of the fetus was not reported for the remaining two induced abortions following exposure during the first trimester to 6-thioguanine and cytarabine (Moreno *et al.* 1977) or to 6-thioguanine, daunorubicin, cytarabine and hydroxyurea (Zemlickis *et al.* 1992b).

Examination of the fetus was reported for 2 of 2 induced abortions with exposure in the second trimester only. Examination of the fetus revealed a normal fetus of an induced abortion following second trimester exposure to 6-thioguanine, hydroxyurea, daunorubicin, cytarabine, vincristine (Doney *et al.* 1979); the fetus had a slightly enlarged spleen. A normal fetus was reported following exposure in the second trimester and co-exposed to cytarabine (Maurer *et al.* 1971); chromosome analysis of this fetus revealed chromosomal mosaicism, including two normal male spreads, two spreads with trisomy C and one very abnormal chromosome.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 6 singleton pregnancies (6 conceptuses), including 2 spontaneous abortion and 4 stillbirths. No examination of the fetus was reported for the spontaneous abortion which occurred 20 days following first trimester exposure to 6-thioguanine and co-treatments daunorubicin, cytarabine and vincristine (Zuazu *et al.* 1991). No malformation was reported in a fetus from a second spontaneous abortion that occurred at gestation week 20 after second trimester exposure to 6-thioguanine, daunorubicin and cytarabine (Volkenandt *et al.* 1987). No congenital malformations were observed any of the 4 stillbirths occurring following second trimester exposure to 6-thioguanine and co-exposure to: cytarabine (Plows 1982), cytarabine and daunorubicin (O'Donnell *et al.* 1979), or cytarabine and doxorubicin (Zuazu *et al.* 1991, Zemlickis *et al.* 1992b). One of the normal stillborn fetuses had bruising and petechiae (broken capillaries under the skin) over multiple areas (Zemlickis *et al.* 1992b). In another case, the stillbirth occurred at 30 weeks of gestation following severe preeclampsia and toxemia at 29 weeks of gestation (O'Donnell *et al.* 1979),

Rate of Occurrence of Congenital Malformations

Major malformations

Table 23: Major malformations diagnosed at birth possibly attributable to in utero exposure to 6-thioguanine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Choanal stenosis; mild hypotelorism; severe brachycephaly; hypoplasia of the anterior cranial base, supra orbital structures, and naso-and orpharynx; premature closure of both coronal sutures and the metopic suture; bilateral 4 finger hands with hypoplastic thumbs; bilateral absent radii; small ostium secundum-type atrial septal defect.	33% (2/6)
	Distal limb defects: absence of medial 2 digits of both feet, absence of the distal phalanges of both thumbs, and remnant of right thumb was very hypoplastic	
2nd and/or 3rd only	None	0% (0/44)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations following in utero exposure to 6-thioguanine were observed in 4 liveborn infants. Major malformations occurred in two infants exposed during the first 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 following exposure to cytarabine and daunorubicin at the beginning of the first trimester until gestation week 5(Artlich *et al.* 1994). The infant's skeletal malformations included: choanal stenosis, braciocephaly, hypoplasia of several cranial structures and premature closure of cranial sutures as well as bilateral 4-fingered hands with hypoplastic thumbs and bilateral absent radii. Another infant had distal limb defects following exposure to 6-thioguanine and co-treatment with cytarabine during the entire pregnancy (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. Thus, the apparent rate of major malformations following exposure to 6-thioguanine in the first trimester was 33% (2/6 based on 4 liveborn infants and examinations of the fetuses of 2 induced abortuses) (**Table 23**).

Major malformations were observed in two infants with exposure to 6-thioguanine in the second and/or third 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 second and third trimester to 6-thioguanine and co-exposed to cytarabine and daunorubicin (Roy *et al.* 1989). Neither of the incidence of polydactyly or Down syndrome were considered possibly attributable to exposure to 6-thioguanine in the second and/or third trimesters. Thus, the apparent rate of major malformations following exposure in the second and/or third trimester was 0% (0/44 based on 37 liveborn infants and examinations of the fetus of 5 stillbirths and 2 induced abortions).

Minor Malformations

Minor malformations were observed in one liveborn infant. Congenital adherence of the iris to the cornea, a minor malformation, was diagnosed in an infant at age 2 years (Reynoso *et al.* 1987). Although not a minor malformation, chromosomal mosaicism was observed in an induced abortus with second trimester exposure to 6-thioguanine and cytarabine (Maurer *et al.* 1971).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications 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).One pregnancy each experienced polyhydramnios (Artlich *et al.* 1994) and fetal distress (Veneri *et al.* 1996). Preeclampsia was treated and resolved in one case yielding a liveborn infant (Bartsch *et al.* 1988). In a second case, severe preeclampsia and toxemia preceded a stillbirth (O'Donnell *et al.* 1979). Two pregnancies had preterm spontaneous rupture of membranes (Volkenandt *et al.* 1987, Udink ten Cate *et al.* 2009) and five pregnancies had spontaneous preterm labor (Doney *et al.* 1979, Taylor and Blom 1980, Tobias and Bloom 1980, Reynoso *et al.* 1987).

There were 41 liveborn infants gestationally exposed to 6-thioguanine. Early preterm delivery (<34 weeks) was reported for 11 infants, late preterm delivery (34-36 weeks) was reported for 9 infants and 18 infants were delivered at term. Data were insufficient to determine the timing of delivery for 3 infants. Of the 20 preterm infants, 9 infants were born via spontaneous vaginal delivery, 3 infants were born via induced vaginal delivery, and 6 infants were delivered via C-section; data were insufficient to determine the route of delivery for the remaining 2 infants. Small for gestational age was determined for 6 infants and 27 infants were of normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age in the remaining 8 infants.

Respiratory distress was reported for 4 infants (Bartsch *et al.* 1988, Artlich *et al.* 1994, Requena *et al.* 1995), including a preterm infant with a mild meningeal hemorrhage (Veneri *et al.* 1996). One premature infant had electrolyte abnormalities and hypoglycemia , which resolved after 7 months (Doney *et al.* 1979). Three infants had transient myelosuppression, including thrombocytopenia (Taylor and Blom 1980, Reynoso *et al.* 1987) and thrombocytopenia with leukopenia and neutropenia (Udink ten Cate *et al.* 2009). Jaundice was reported for two newborns (Au-Yong *et al.* 1972), including one infant with thrombocytopenia (Taylor and Blom 1980). Low hemoglobin was reported in one infant (Gulati *et al.* 1986).

Infant Deaths

No infant deaths occurred following gestational exposure to 6-thioguanine.

Follow Up Evaluations

Follow up evaluations were reported for 33 children gestationally exposed to 6-thioguanine; evaluations occurred 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; however, 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 53 singleton pregnancies (53 conceptuses)(**Table 76**). Overall, the apparent rate of major malformations among all 6-thioguanine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 8% (4/50 conceptuses based on 41 liveborn infants and examination of the fetuses of 4 induced abortions and 5 stillbirths). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in two infants with exposure to 6-thioguanine during the first trimester exposure. One infant had multiple cranial and distal limb defects and a small ostium secundum-type atrial septal defect (Artlich *et al.* 1994). The second infant had distal limb defects in both his feet and hands (Schafer 1981). The skeletal malformations of the cranium and distal limbs were consistent with effects of 6-thioguanine in developmental toxicity studies in rats. Thus, the apparent rate of major malformations attributable to exposure to 6-thioguanine during the first trimester was 33% (2/6 conceptuses). The major malformations observed in 2 infants with exposure to 6-thioguanine in the second and/or third trimester only was not likely due to exposure outside of the period of organogenesis (e.g., polydactyly and Down syndrome). Thus, the adjusted apparent rate of major malformations following exposure to 6-thioguanine in the second and/or third trimester was 0% (0/44 conceptuses based on 37 liveborn infants and examination of the fetus of 2 induced abortions and 5 stillbirths).

In addition, the apparent rate of stillbirths following 6-thioguanine exposure in the second and/or third trimester only resulted in a higher apparent rate of stillbirths (12%) than the frequency of stillbirths in the general population of the US (12% versus 0.3-0.6% (range) (MacDorman 2005) (**Table 76**). This increase in the apparent rate of stillbirth may be due to gestational exposure to 6-thioguanine or to the polytherapy regimen. It has also been hypothesized that acute leukemia during pregnancy may increase the risk of spontaneous fetal loss (Brenner *et al.* 2012).

5.5 ACTINOMYCIN D

5.5.1 Mechanism of Action, Route of Administration, and Indications

Table 24: Pharmacology of actinomycin D in adult humans	
Molecular weight:	1255.4294
Protein binding:	**[Information not located]**
Metabolism:	Minimal
Half-life elimination:	~36 hours
Distribution:	Does not penetrate blood-brain barrier
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	~30% in urine and feces within 1week
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum	

Actinomycin D is a cytotoxic antibiotic produced by Streptomyces parvullus. It elicits cytotoxic effects by binding DNA and inhibiting RNA synthesis (Lundbeck Inc 2009). Actinomycin D is administered intravenously. Additional information on the pharmacology of actinomycin D is located in **Table 24**.

Actinomycin D is indicated for Wilms tumor (kidney), childhood rhabdomyosarcoma, Ewing sarcoma and metastatic, nonseminomatous testicular cancer (Lundbeck Inc 2009). It is also used as palliative treatment for locally recurrent and locoregional solid malignancies (Lundbeck Inc 2009).

5.5.2 Evidence of Placental and Breast Milk Transport

Placental and breast milk transport of actinomycin D in humans is not known. In laboratory animal studies, actinomycin D was detected in mammalian embryos by radioautograph **[presumably following maternal exposure in the rat]** (reviewed in 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 2009). Administration of 25 to 100 µg/kg bw of actinomycin D on gestation day 10 in the rat induced various degrees of craniorachischisis, defects of the nervous system and branchial arch malformations, while actinomycin D administered after gestation day 10 did not induce embryonic defects (reviewed in Shepard and Lemire 2004). Actinomycin D was teratogenic to hamster embryos when administered in doses of 200 or 300 µg/kg bw prior to implantation (Elis and DiPaolo 1970). The most common malformations reported were omphalocele, micrognathia or agnathia, microcephaly, exencephaly, hydrocephalus, spina bifida, and several malformations of the extremities, such as amelia and phocomelia, usually involving the forelimbs. Actinomycin D was also teratogenic in avian embryos. 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.

5.5.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Actinomycin D was administered to 15 cancer patients (also called cases) during pregnancy identified from 14 case reports (14 cases) and 1 registry survey (1 case) (Appendix C Table 4). Among these 15 patients, actinomycin D was used to treat the following cancers: ovarian cancer (4 cases), Ewing sarcoma (2 cases), rhabdomyosarcoma (4 cases), Wilms tumor (kidney; 2 cases), and choriocarcinoma of ovary (1 case),the uterus (1 case) and vagina (1 case).

A total of 15 pregnancies were exposed to actinomycin D (16 conceptuses due to one twin pregnancy (Freedman *et al.* 1962)). Actinomycin D was administered only in the second and/or third trimesters to all reported pregnancies (16 conceptuses); no pregnancies were exposed to the drug during the first trimester. Actinomycin D was administered as polytherapy in all 15 pregnancies (16 conceptuses).

Termination of Pregnancy

No terminations of pregnancy were reported.

Spontaneous Fetal Death

No spontaneous abortions or stillbirths were reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

No major malformations were reported.

Minor Malformations

No minor malformations were reported.

Pregnancy Complications and Newborn Health

Pregnancy complications were reported for some pregnancies exposed to actinomycin D. Spontaneous preterm labor was reported for 4 singleton pregnancies (Weed *et al.* 1979, Kim and Park 1989, Martin *et al.* 1997, Brudie *et al.* 2011). Another pregnancy reported complications of anhydramnios and intrauterine growth restriction at four weeks after chemotherapy administration (Fernandez *et al.* 1989). Placenta previa was reported in 1 singleton pregnancy (Cardonick *et al.* 2010).

There were a total of 16 liveborn infants gestationally exposed to actinomycin D. Early preterm delivery (<34 weeks) was reported for 7 infants, late preterm delivery (34 to <37 weeks) was reported for 3 infants and 4 infants were delivered at term. Data were insufficient to determine the gestational age at delivery for 2 infants. Of the preterm infants, 3 infants were born via spontaneous vaginal delivery, 1 infant was born via induced vaginal delivery, and 6 infants were born via C-section. Small for gestational age was determined for 1 infant and 13 infants had normal body weight based on sex, gestational age, and body weight at birth. Data were insufficient to determine small for gestational age for 2 infants.

Infant health issues included two infants with respiratory distress (Corapcioglu *et al.* 2004), including one infant who also required intravenous calcium (Haerr and Pratt 1985). Another newborn was treated for transitory focal seizures and a urinary tract infection (Hutchison *et al.* 1968).

Infant Deaths

One infant died following gestational exposure to actinomycin D (Fernandez *et al.* 1989). This infant was exposed in the second trimester to actinomycin D, 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; she had experienced anhydramnios and intrauterine growth restriction. Autopsy revealed cerebral hemorrhaging attributed to prematurity, but no renal abnormalities (Fernandez *et al.* 1989).

Follow Up Evaluations

Follow-up evaluations were reported for 10 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 Outcomes for actinomycin D

Exposure to actinomycin D is documented for 15 pregnancies and 16 conceptuses, including one twin pregnancy (**Table 78**). Overall, the apparent rate of major malformations among all actinomycin D-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 0% (0/16 conceptuses based on 16 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Actinomycin D was administered in the second and/or third trimester only in all 15 pregnancies. Thus, the apparent rate of major malformations following gestational exposure to actinomycin D in the second and/or third trimester only was 0% (0/16 conceptuses based on 16 liveborn infants).

5.6 ALL-*TRANS* RETINOIC ACID

5.6.1 Mechanism of Action, Route of Administration, and Indications

Table 25: Pharmacology of all-*trans* retinoic acid in adult humans	
Molecular weight:	300.439
Protein binding:	>95%, predominantly to albumin
Metabolism:	Hepatic via CYP; primary metabolite: 4-oxo-all-*trans*-retinoic acid; displays autometabolism
Half-life elimination:	Terminal: Parent drug: 0.5-2 hours
Distribution:	**[Information not located]**
Time to peak, serum (C_{max}):	1-2 hours
Excretion:	Urine (63%); feces (30%)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum.	

All-*trans* retinoic acid (ATRA, tretinoin) is a chemical related to retinol (vitamin A). Vitamin A plays an important role in normal embryogenesis. Thus, increases or reductions in the level of this vitamin raise concerns for adverse effects (Sulik 2010). All-*trans* retinoic acid is an antineoplastic agent, which acts to induce cytodifferentiation and decrease proliferation of cancer cells. In the treatment of acute promyelocytic leukemia (APL), all-*trans* retinoic acid induces the highly proliferative immature white blood cells to differentiate into functional cells, which helps to alleviate the disease (Roche 2008). All-*trans* retinoic acid is administered orally. Additional information on the pharmacology of all-*trans* retinoic acid is located in **Table 25**.

All-trans retinoic acid is indicated for acute promyelocytic leukemia (APL). All-trans retinoic acid is also administered for non-cancerous health conditions, such as severe cystic acne; the drug is administered as topical ointment (Ortho Dermatologics 2013).

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. All-*trans* retinoic acid was reported to have 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. (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, causing fetal resorptions and a decrease in live fetuses in all animals studied (Roche 2008). 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). On a mg/m^2 basis, these doses are, respectively, approximately 1/20, ¼, and ½ of the human dose. Likewise, it caused fetal resorptions and decreases in the numbers of live fetuses in these same species.

The peer-reviewed literature reported many examples of the embryolethal and teratogenic effects of all-*trans* retinoic acid. For example, embryolethality was increased in a dose-related manner following 5 mg (22%), 10 mg (50%) and 20 mg (100%)/ kg bw/day 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). 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 bw/day on gestation days 10-24 (Hendrickx and Hummler 1992). No malformations were reported at 5 mg/kg bw/day; however, one fetus out of seven exhibited intrauterine growth retardation (Hendrickx and Hummler 1992). All-*trans* retinoic acid (10 mg/kg bw/day) 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 gingiva, cleft palate or abnormalities of the shape of the skull. The most common musculoskeletal malformations reported in pigtail monkey were missing postaxial phalanges of the foot and hand, and abnormal curvature of the spine (kyphosis and scoliosis)(Fantel *et al.* 1977). Some other malformations observed in pigtail monkey fetuses gestationally exposed to all-*trans* retinoic acid were muscular-joint contractures, syndactylies, transposition of great vessels of the heart, and other abnormalities (e.g., anal atresia).

In addition, all-*trans* retinoic acid and other retinoids have been studied extensively in laboratory rodents for their adverse neurobehavioral effects following exposure during gestation. Retinoids are reported to cause behavioral dysfunctions as well as malformations of the central nervous system. Adams recently reviewed the neurobehavioral teratology of retinoids (Adams 2010).

5.6.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

All-*trans* retinoic acid was administered to 28 cancer patients (also called cases) during pregnancy (29 conceptuses, including one set of twins) identified from 18 case reports (18 cases), 5 case series (8 cases), and 1 retrospective survey (3 cases) (Appendix C Table 5). In these patients, the drug was used to treat acute promyelocytic leukemia (24 cases) and acute myelogenous leukemia (5 cases).

A total of 28 pregnancies were exposed to all-*trans* retinoic acid (29 conceptuses, including one set of twins (Stentoft *et al.* 1994)). All-*trans* retinoic acid was administered in the first trimester in 5 pregnancies (5 conceptuses) and in the second and/or third trimester only in 23 pregnancies (24 conceptuses due to a twin pregnancy). All-trans retinoic acid was administered as monotherapy in 15 pregnancies (16 conceptuses due to one set of twins) and as polytherapy in 13 pregnancies (13 conceptuses).

Termination of Pregnancy

Two induced abortions was performed following first trimester exposure to all-trans retinoic acid and co-exposure to daunorubicin and cytarabine (Chelghoum *et al.* 2005); no examination of the fetus was reported.

Spontaneous Fetal Death

One spontaneous abortion occurred following exposure in the first trimester to all-trans retinoic acid, daunorubicin and cytarabine (Chelghoum *et al.* 2005); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were reported in two infants gestationally-exposed to all-*trans* retinoic acid. One infant was diagnosed in utero with Potter syndrome (bilateral renal agenesis and oligohydramnios) prior to the administration of all-*trans* retinoic acid in the third trimester (Sham 1996); this infant died 30 minutes after birth. This major malformation (Potter syndrome) was not attributable to the chemotherapy because it was diagnosed prior to treatment. Thus, the apparent rate of malformations following exposure to all-*trans* retinoic acid in the first trimester was 0% (0/2 conceptuses based on 2 liveborn infants).

No major malformations were observed following exposure to all-*trans* retinoic acid in the second and/or third trimester only. Thus, the apparent rate of malformations following exposure to all-*trans* retinoic acid in the second and/or third trimester was 4% (0/24 conceptuses based on 24 liveborn infants).

Minor Malformations

Minor malformations were observed in 3 infants with gestational exposure to all-*trans* retinoic acid. Patent ductus arteriosus was reported for all 3 preterm infants gestationally-exposed to all-*trans* retinoic acid. One infant born in gestation week 36 weeks, had a small patent ductus arteriosus accompanied by two small secundum atrial septal defects (Siu *et al.* 2002). The two small atrial secundum defects were considered minor in this infant because they measured only 2.5 mm diameter (each) at age 1.5 years and they did not significantly impact blood flow in the heart. The remaining two infants with patent ductus arteriosus were born prior to 34 weeks of gestation: one infant was exposed to all-*trans* retinoic acid and idarubicin in the second and third trimesters (Carradice *et al.* 2002) and the remaining infant was exposed in the third trimester to all-*trans* retinoic acid monotherapy (Takitani *et al.* 2005). Patent ductus arteriosus and patent ovale foramen are commonly observed in premature infants (Institute of Medicine 2007). In all three cases, this condition resolved with further growth of the infant, and , in one case, treatment with indomethacin (Carradice *et al.* 2002).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications were reported with in utero exposure to all-*trans* retinoic acid. Other pregnancy complications included: preeclampsia (1 pregnancy) (Siu *et al.* 2002), premature rupture of membranes (1 pregnancy) (Carradice *et al.* 2002) and spontaneous preterm labor (4 pregnancies) (Sham 1996, Incerpi *et al.* 1997, Consoli *et al.* 2004, Dilek *et al.* 2006). Fetal ascites, oligohydramnios, as well as intrauterine growth restriction due to placental insufficiency, occurred in one pregnancy (Carradice *et al.* 2002). Intrauterine growth restriction was reported in a second infant (Terada *et al.* 1997, Takitani *et al.* 2005). As mentioned previously, one pregnancy had oligohydramnios associated with bilateral renal agenesis diagnosed prior to treatment with all-*trans* retinoic acid (Sham 1996). Fetal distress occurred in one pregnancy (Nakamura *et al.* 1995). Fetal arrhythmia occurred in two fetuses (Leong *et al.* 2000), including one fetus that also had abnormal systolic motion of the mitral valve (Terada *et al.* 1997, Takitani *et al.* 2005).

There were 26 liveborn infants with in utero exposure to all-*trans* retinoic acid. Early preterm delivery (<34 weeks) was reported for 15 infants, late preterm delivery (34 to <37 weeks) was reported for 8 infants, and three infants were delivered at term. Of the 12 preterm infants, 7 infants were delivered via spontaneous vaginal birth (including 1 set of twins), 2 infants were delivered via induced vaginal birth, and 13 infants were delivered via C-section; data was insufficient to determine the route of delivery for one preterm infant. Twenty-three infants had normal body weight based on data reported for sex, gestational age and body weight at birth of each infant, and the data were insufficient to identify small for gestational age in the remaining 3 infants.

Health issues were reported for several of the preterm infants. Respiratory distress was reported for 12 infants. Another infant with breathing difficulties suffered from pulmonary hypoplasia and bilateral pneumothorax (Carradice *et al.* 2002). Jaundice was reported in 5 infants, including one preterm infant with small bilateral subependymal hemorrhages (Incerpi *et al.* 1997).

Health issues related to cardiac function occurred in three infants gestationally exposed to all-*trans* retinoic acid. 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 (Terada *et al.* 1997, Takitani *et al.* 2005); the symptoms disappeared after one day. Moderate dilation of the right atrium and right ventricle was reported in an infant with a small patent ductus arteriosus and two small secundum atrial septal defects (Siu *et al.* 2002). At age 1.5 months, this infant had normal growth and no signs of congestive heart failure (i.e., the right atrial and right ventricular dilation had resolved). In addition, the ductus arteriosus closed, and, although there remained persistence of the small secundum atrial septal defects, they did not significantly impact blood flow through the heart (Siu *et al.* 2002).

Infant Deaths

Two infant deaths occurred in pregnancies exposed to all-*trans* retinoic acid. One premature infant died 30 minutes after birth; this infant had been diagnosed with Potter syndrome prior to the administration of all-*trans* retinoic acid in the third trimester (Sham 1996). A second neonate died on day 1 after developing respiratory distress (Dilek *et al.* 2006); this early preterm infant had normal hematological values and was exposed in the second and third trimesters and co-exposed to daunorubicin and cytarabine.

Follow Up Evaluations

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). An infant diagnosed with two small secundum atrial septal defect at birth had normal growth and no signs of congestive heart failure at age 1.5 months (Siu *et al.* 2002); while the small secundum atrial septal defects persisted, they did not significantly impact blood flow through the heart (Siu *et al.* 2002).

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 (**Table 81**). Overall, the apparent rate of major malformations among all all-*trans* retinoic acid-exposed offspring, regardless of the nature of the malformations or the gestational

stage at exposure, was 8% (2/26 conceptuses based on 26 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). None of the infants had major malformations attributable to gestational exposure to all-trans retinoic acid. Thus, the apparent rate of major malformations was 0% following exposure during the first trimester (2 conceptuses based on 2 liveborn infants) and in the second and/or third trimester (24 conceptuses based on 24 liveborn infants). Abnormal cardiac function was reported for 3 infants with in utero exposure to all-trans retinoic acid; all three infants were exposed in the second and third trimesters. Specifically, arrhythmia was reported for two newborns (Harrison *et al.* 1994, Terada *et al.* 1997, Takitani *et al.* 2005), and one infant experienced dilation of the right atrium and ventricle. Further investigation of possible effects of all-*trans* retinoic acid on heart development and function are needed.

A similar drug, 13-*cis* retinoic acid, is administered as an oral capsule for the treatment of severe cystic acne (Roche 2011). Systemic use of 13-*cis* retinoic acid during the first 10 weeks of gestation has been reported to induce spontaneous abortion as well as fetal abnormalities in humans (Lammer *et al.* 1985, Rizzo *et al.* 1991). The major malformations reported following oral exposure to 13-*cis* retinoic acid for the treatment of cystic acne include: craniofacial malformations (e.g., microtia or anotia, cleft palate, and micrognathia), thymic, (e.g., hypoplasia or absence of the thymus), cardiac, (e.g., conotruncal or aortic arch defects), and central nervous structures (e.g., hydrocephalus and microcephalus) as well as limb reduction and other skeletal defects (Lammer *et al.* 1985, Rizzo *et al.* 1991). The malformation data reported for systemic exposure to 13-*cis* retinoic acid during gestation in humans for treatment of cystic acne corroborate with developmental toxicity studies of all-*trans* retinoic acid in rodents and monkeys. Thus, the absence of such effects in pregnancy outcomes following first trimester exposure to all-*trans* retinoic acid reviewed in the draft NTP monograph may be due to the very small sample size (2 liveborn infants) and the timing of exposure during the first trimester.

There is evidence that prenatal exposure to all-*trans* retinoic acid can impact neurodevelopment and function in animal studies (reviewed in Adams 2010); however, effects on human neurodevelopment and function are not well-understood.

5.7 BLEOMYCIN

5.7.1 Mechanism of Action, Route of Administration, and Indications

Table 26: Pharmacology of bleomycin in adult humans	
Molecular weight:	1415.56
Protein binding:	1%
Metabolism:	Via several tissues including hepatic, GI tract, skin, pulmonary, renal, and serum
Half-life elimination:	Biphasic (renal function dependent): Normal renal function: Initial: 1.3 hours; Terminal: 9 hours End-stage renal disease: Initial: 2 hours; Terminal: 30 hours
Distribution:	Vd: 22 L/m^2; highest concentrations in skin, kidney, lung, heart tissues; lowest in testes and GI tract; does not cross blood-brain barrier
Time to peak, serum (C_{max}):	IM: Within 30 minutes
Excretion:	Urine (50% to 70% as active drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum, GI, gastrointestinal; IM, intramuscular; Vd, volume of distribution	

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 administered via injection either intramuscularly, intravenously or subcutaneously. Additional information on the pharmacology of bleomycin is located in **Table 26**.

Bleomycin is indicated for Hodgkin and non-Hodgkin lymphomas, squamous cell carcinomas, testicular cancer, and malignant pleural effusion (Bristol-Myers Squibb 2010a).

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 2010a).

5.7.3 Laboratory Animal Developmental Toxicity

Bleomycin is reported to induce teratogenic effects in rats, but not in rabbits (Bristol-Myers Squibb 2010a). In rats, administration of intraperitoneal doses of 1.5 mg/kg bw/day (~1.6 times the recommended human dose on a unit/m^2 basis) on gestation days 6 to 15 caused skeletal malformations, shortened the brachiocephalic artery as well as the hydroureter in the fetuses. Bleomycin was not teratogenic in rabbits, but induced abortions at intravenous doses of 1.2 mg/kg bw/day (~2.4 times the recommended human dose on a unit/m^2 basis) given on gestation days 6 to 18.

Teratogenic effects of bleomycin are also described in the peer-reviewed literature. 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 (reviewed in Shepard and Lemire 2004).

5.7.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Bleomycin was administered to 94 female cancer patients (also called cases) during pregnancy identified from 24 case reports (24 cases), 8 case series (20 cases), 1 retrospective case series (22 cases), 1 retrospective cohort study (1 case), 2 retrospective surveys (4 cases), and 1 registry survey (23 cases) (Appendix C Table 6). Among these patients, bleomycin was used to treat Hodgkin lymphoma (49 cases), non-Hodgkin lymphoma (20 cases), Burkitt lymphoma (1 case), ovarian cancer (18 cases) and one case each of Ewing sarcoma, Kaposi sarcoma, adenocarcinoma (primary cancer not identified), and cervical cancer. Cancer type was not specified in two cases.

There were a total of 95 pregnancies with 97 conceptuses exposed to bleomycin due to one patient having two pregnancies (Dilek *et al.* 2006) and two sets of twins (Nantel *et al.* 1990, Cardonick *et al.* 2010). Bleomycin was administered during the first trimester in 15 singleton pregnancies (15 conceptuses). The drug was administered in the second and/or third trimester only in 80 pregnancies (82 conceptuses due to two sets of twins), including two singleton pregnancies for which individual timing of exposure was not provided but were likely exposed in the second and/or third trimester only (Jameel and Jamil 2007). It was assumed that these cases were likely exposed in the second and/or third trimester only since the reported age of initiation of chemotherapy ranged from 11-34 weeks (median 23 weeks (Hahn *et al.* 2006)) or 12-33 weeks (mean = 24 weeks (Jameel and Jamil 2007)). Bleomycin was administered as polytherapy to all 94 cases (95 pregnancies and 97 conceptuses).

Termination of Pregnancy

Two singleton pregnancies were terminated by induced abortion. 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 first trimester to bleomycin, nitrogen mustard, vincristine, procarbazine, doxorubicin, vinblastine, and dacarbazine. No examination of the fetus was reported for a second induced abortus exposed in the second trimester to bleomycin polytherapy (D'Incalci *et al.* 1983).

Spontaneous Fetal Death

One spontaneous fetal loss occurred following gestational exposure to bleomycin. One stillbirth occurred following second and third trimester exposure to bleomycin, doxorubicin, vinblastine, and dacarbazine (Dilek *et al.* 2006); no fetal examination data were reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were reported in 5 liveborn infants exposed in utero to bleomycin, including one infant exposed during the first trimester. One infant had 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 exposed during the first trimester to bleomycin, doxorubicin, vinblastine and dacarbazine. Thus, the apparent rate of major malformations following exposure to bleomycin during the first trimester was 7% (1/15 conceptuses based on 14 liveborn infants and examination of the fetus for one induced abortion) (**Table 27**).

Major malformations occurred in 4 liveborn infants exposed to bleomycin in the second and/or third trimester only. Syndactyly of the 4th and 5th fingers was reported in one infant with second and third trimester exposure to bleomycin, doxorubicin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Another infant had bilateral syndactyly of digits II and III following exposure in the second and third trimesters to bleomycin, doxorubicin, vinblastine as well as dacarbazine, nitrogen mustard, vincristine and procarbazine (Van Calsteren *et al.* 2010a). Profound ventriculomegaly and cerebral atrophy were observed in an infant with exposure in the second trimester to bleomycin, etoposide and cisplatin (Elit *et al.* 1999); mild to moderate ventriculomegaly occurred prenatally three weeks following exposure in the 2nd trimester.

Table 27: Major malformations diagnosed at birth possibly attributable to in utero exposure to bleomycin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses)
During 1st	Floating thumb malformation on the left hand (i.e. partial agenesis of a metacarpal and hypoplasia of two phalanges)	7% (1/15)
2nd and/or 3rd only	Cerebral atrophy and ventriculomegaly	1% (1/80)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Another infant had a spontaneous mutation for neurofibromatosis and genetic hearing loss (his parents were carriers) (Cardonick *et al.* 2010); this infant was exposed during the second and third trimesters to bleomycin, cisplatin and etoposide. The syndactylies and the spontaneous mutation for neurofibromatosis were not likely caused by exposure to bleomycin in the second or third trimesters. These types of skeletal malformations are induced during the period of organogenesis in the first trimester and the spontaneous mutation for neurofibromatosis would have occurred in a parental germ cell prior to conception. Thus, the adjusted apparent rate of major malformations following exposure to bleomycin in the second and/or third trimester only was 1% (1/80 conceptuses based on 80 liveborn infants).

Minor Malformations

Minor malformations were observed in three infants following in utero exposure to bleomycin. One newborn had plagiocephaly following second and third trimester exposure to bleomycin, doxorubicin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Pectus excavatum was observed in another infant with exposure in the second and third trimesters (Van Calsteren *et al.* 2010a); this infant was exposed to bleomycin, doxorubicin, vinblastine, dacarbazine, nitrogen mustard, vincristine and procarbazine. Mild glandular hypospadias (considered a first degree hypospadias) was reported in an infant exposed during the second trimester to bleomycin, etoposide and cisplatin (Ghaemmaghami *et al.* 2009).

Pregnancy Complications and Newborn Health

Pregnancy complications occurred following exposure to bleomycin in utero. Inhibition of fetal growth was reported in six singleton pregnancies, reported as intrauterine growth restriction (2 pregnancies) (Motegi *et al.* 2007, Ghaemmaghami *et al.* 2009, Benjapibal *et al.* 2010), fetal growth retardation (1 pregnancy) (Lambert *et al.* 1991), and small for gestational age (2 pregnancies) (Han *et al.* 2005, Fadilah *et al.* 2006). Oligohydramnios or a reduction in amniotic fluid occurred in two singleton pregnancies (Motegi *et al.* 2007, Ghaemmaghami *et al.* 2009), which also suffered from inhibited fetal growth. Other pregnancy complications included: pregnancy-induced hypertension (1 case) (Motegi *et al.* 2007) and preeclampsia (4 cases) (Lambert *et al.* 1991, Horbelt *et al.* 1994, Anselmo *et al.* 1999, Benjapibal *et al.*

2010). Premature rupture of membranes occurred in one singleton pregnancy (Ghaemmaghami and Hasanzadeh 2006). Spontaneous preterm labor was reported in 3 pregnancies, including one twin pregnancy (Raffles *et al.* 1989, Nantel *et al.* 1990, Moore and Taslimi 1991), and one singleton pregnancy experienced transient spontaneous preterm labor (Ortega 1977). Fetal distress occurred in one case (Lambert *et al.* 1991).

A total of 94 liveborn infants were gestationally exposed to bleomycin. Early preterm delivery (<34 weeks) was reported for 11 infants, late preterm delivery (34 to <37 weeks) was reported for 16 infants, and 37 infants were delivered at term. Gestational age at delivery was not specified for 30 infants. Of the preterm infants, 9 infants were born via spontaneous vaginal delivery, and 18 infants were born via C-section. Small for gestational age was determined for 12 infants and 65 infants had normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 17 infants.

A few health effects were observed in infants exposed to bleomycin in utero. Respiratory difficulties were reported in 5 newborns, including transient tachypnea (Malone *et al.* 1986) , respiratory distress (Haerr and Pratt 1985, Malhotra and Sood 2000), respiratory distress and apnea (Elit *et al.* 1999), and severe respiratory distress and pneumothorax (Raffles *et al.* 1989). Hypoglycemia was reported for three infants (Cardonick *et al.* 2010), 2 infants had jaundice (Rawlinson *et al.* 1984, Lambert *et al.* 1991), and another newborn was treated with intravenous calcium (Haerr and Pratt 1985). Transient myelosuppression occurred in two infants, including anemia (1 infant) (Horbelt *et al.* 1994) and leukopenia with neutropenia, anemia and thrombocytopenia (Raffles *et al.* 1989); one infant with leukopenia also experienced hair loss at day 10 (Raffles *et al.* 1989).

Infant Deaths

No infant deaths were reported following gestational exposure to bleomycin.

Follow Up Evaluations

Of the 76 infants with follow-up evaluations, normal development was reported for 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 95 pregnancies, including two twin pregnancies, for a total of 97 conceptuses (**Table 80**). Overall, the apparent rate of major malformations among all bleomycin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 5% (5/95 conceptuses based on 94 liveborn infants and examination of the fetus of 1 induced abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Of the 15 pregnancies exposed to bleomycin during the first trimester, only one newborn had a major malformation (i.e., partial agenesis of a metacarpal and hypoplasia of two phalanges) (Dilek *et al.* 2006). Bleomycin is reported to induce skeletal malformations of the limbs when administered during organogenesis in developmental toxicity studies of rats. Thus, the apparent rate of major malformations following exposure to bleomycin during the first trimester

was 7% (1/15 conceptuses). Major malformations were observed in four newborns exposed to bleomycin in the second and/or third trimester only. However, only one malformation was likely caused by bleomycin polytherapy: ventriculomegaly and cerebral atrophy in a newborn (Elit *et al.* 1999); mild ventriculomegaly was first observed prenatally following one week following initiation of chemotherapy. Thus, the adjusted apparent rate of major malformations following exposure to bleomycin in the second and/or third trimester only was 1% (1/80 conceptuses based on 80 liveborn infants).

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 (Wiebe and Sipila 1994)), and it is thought to induce cytotoxicity via DNA damage (PDL BioPharma 2007). Busulfan can be administered by intravenous injection (PDL BioPharma 2007) or orally (GlaxoSmithKline 2003). Additional information on the pharmacology of busulfan is located in **Table 28**.

Table 28: Pharmacology of busulfan in adult humans

Molecular weight:	246.303
Protein binding:	32% to plasma proteins and 47% to red blood cells
Metabolism:	Extensively hepatic: glutathione conjugation followed by oxidation
Half-life elimination:	2-3 hours
Distribution:	Vd: ~1L/kg; levels in CSF equal to levels in plasma
Time to peak, serum (C_{max}):	Oral: ~1 hour; IV: within 5 minutes
Excretion:	Urine: 25% to 60% predominantly as metabolites, <2% as unchanged drug

Data from Brunton et al. (2011). Abbreviations: CSF, cerebral spinal fluid; IV, intravenous, Vd, volume of distribution.

Busulfan is indicated for chronic myelogenous leukemia (also called chronic myeloid, myelocytic, or granulocytic leukemia) (PDL BioPharma 2007).

5.8.2 Evidence of Placental and Breast Milk Transport

Placental transport and breast milk transfer of busulfan in humans is unknown.

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 as per manufacturer's product information (PDL BioPharma 2007). In particular, intraperitoneal injections of busulfan at 10 mg/kg bw/d 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 bw 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 bw to pregnant WKAH/Hkm rats on gestation days 10, 10.5 or 11 (Kato *et al.* 1990). Germ cell dysgenesis has been reported following in utero exposure to similar doses of busulfan in both rats (Heller and Jones 1964) and mice (Jansz and Pomerantz 1985).

Busulfan is also teratogenic in birds. Injections of busulfan into incubating eggs impaired hatchability in Japanese quail at doses of 210 and 420 µg (Hallett and Wentworth 1991). The surviving quail offspring in the 420 µg busulfan dose group 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 of doses ranging from 1 to 500 µg busulfan injected into the egg (Aige-Gil and Simkiss 1991).

5.8.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Busulfan was administered to 31 female cancer patients (also called cases) during pregnancy identified from 15 case reports (15 cases), 5 case series (8 cases), 1 retrospective case series (3 cases), 2 retrospective cohort studies (2 cases), and 1 retrospective survey (1 case)(Appendix C Table 7). Among these patients, busulfan was used to treat two types of leukemia: chronic myelogenous (also called chronic granulocytic; 30 cases) and acute granulocytic (n=1 case).

Of these 31 cases, a total of 31 singleton pregnancies (31 conceptuses) were exposed to busulfan due to one case having two pregnancies while taking the drug (Lee *et al.* 1962). Busulfan was administered during the first trimester only or in the first and subsequent trimesters in 21 pregnancies (21 conceptuses). Busulfan was administered in the second and/or 3rd trimester only in 6 pregnancies (6 conceptuses) and timing of exposure was not specified for 5 pregnancies. Busulfan was generally administered as monotherapy to these patients: 23 pregnancies (23 conceptuses) exposed to busulfan only and 9 pregnancies (9 conceptuses) exposed to busulfan in combination with 6-mercaptopurine or 6-mercaptopurine and radiation therapy.

Termination of Pregnancy

Two singleton pregnancies (2 conceptuses) were terminated following busulfan exposure in the first trimester. Histological analysis of the first induced abortus at gestation week 6 revealed myeloschisis (cleft spinal cord) (Abramovici *et al.* 1978); the pregnancy had been exposed during the first trimester to busulfan monotherapy. No fetal data were reported for the other induced abortion performed at gestation week 16 (Zuazu *et al.* 1991); the fetus had been exposed to busulfan and 6-mercaptopurine in the first trimester from gestation week 6 to 10.

Spontaneous Fetal Death

One spontaneous fetal death occurred following gestational exposure to busulfan. 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 first trimester]** (Lee *et al.* 1962); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 3 liveborn infants and 1 induced abortus following gestational exposure to busulfan. Two of the liveborn infants and one induced abortus with major malformations were exposed during the first trimester. One newborn had cleft palate, bilateral microphthalmia (abnormal smallness of the eye) and bilateral corneal opacities as well as poorly differentiated genitalia (Diamond *et al.* 1960); this infant was exposed in the first, second and third trimesters to busulfan and was co-treated with radiation therapy prior to conception, and exposed to 6-mercaptopurine in the first and third 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); the authors attributed the cytomegaly to 6-mercaptopurine exposure in the first trimester. Another infant required surgery at age 2 months to remedy pyloric stenosis (Earll and May 1965); this infant had been exposed to busulfan monotherapy during the first through third trimesters. As previously mentioned, myeloschisis (cleft spinal cord) was observed in an induced abortus following

exposure to busulfan monotherapy during the first trimester (Abramovici *et al.* 1978). Thus, the apparent rate of major malformations following exposure to busulfan during the first trimester was 16% (3/19 conceptuses based on 18 liveborn infants and examination of the fetus of 1 induced abortion) (**Table 29**).

Table 29: Major malformations observed at birth possibly attributable to in utero exposure to busulfan

Trimester exposed	Major malformations observed[a]	Apparent rate (affected/total conceptuses[a])
During 1st	Myeloschisis (cleft spinal cord)	16% (3/19)
	Cleft palate, microphthalmia (small eyes), poorly differentiated genitalia	
	Pyloric stenosis	
2nd and/or 3rd only	None	0% (0/6)
NS	None	0% (0/5)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations were observed in one liveborn infant exposed to busulfan monotherapy in the second and/or third trimester only. Congenital absence of the right kidney and right ureter accompanied by hydronephrosis of the left kidney and dilation of the left ureter were observed in an infant exposed in the second and third trimester to busulfan monotherapy beginning on gestation week 20 (Boros and Reynolds 1977). However, it is unlikely that the malformation was induced by busulfan because the exposure began after the development of kidney architecture (gestation week 5 to 15) (Larsen 1997). Thus, the adjusted apparent rate of major malformations following exposure to busulfan in the second and/or third trimester only was 0% (0/6 conceptuses based on 5 liveborn infants). In addition, there were no major malformations reported in the 5 infants for which timing of exposure to busulfan was not specified.

Minor Malformations

No minor malformations were reported following in utero exposure to busulfan.

Pregnancy Complications and Newborn Health

There were relatively few pregnancy complications reported for pregnancies exposed to busulfan during cancer treatment. Spontaneous preterm labor was reported in four pregnancies (Lee *et al.* 1962, Nicholson 1968, Zuazu *et al.* 1991, Ozumba and Obi 1992). There were no reports of intrauterine growth restriction of the fetus during pregnancy.

There were 29 liveborn infants with gestational exposure to busulfan. Early preterm delivery (<34 weeks) was reported for 1 infant, late preterm delivery (34 to <37 weeks) was reported for 5 infants, and 17 infants were delivered at term (≥37 weeks); the data were insufficient to identify age at birth for the remaining 6 infants. Three of the preterm infants were delivered via spontaneous vaginal birth and 1 infant via C-section; route of delivery was not specified for 2 preterm infants. Eight newborns were small for gestational age, and 8 infants had normal body weight based upon data reported on sex, birth weight and gestational age at birth of each infant (Olsen *et al.* 2010), including one infant with intrauterine growth arrest as reported by the authors (Diamond *et al.* 1960). The data reported were insufficient to identify small for gestational age in the remaining 13 infants. A "premature appearance" was reported for a normal infant, who was delivered at term (White 1962).

Infant Deaths

Death was reported for two infants. One malformed premature infant died at 10 weeks of age after developing "grunting respiration and a cough" at 2 months of age (Diamond *et al.* 1960). A second neonate, died at age 30 days due to an acute staphylococcus infection (Ruiz Reyes and Tamayo Perez 1961); **[this infant was born at approximately 37 weeks of gestation]**.

Follow Up Evaluations

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 was reported for 32 singleton pregnancies (**Table 77**). Overall, the raw apparent rate of major malformations among all busulfan-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 13% (4/30 conceptuses based on 29 liveborn infants and examination of the fetus of 1 induced abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major congenital malformations were reported in 2 liveborn infants and one induced abortion following first trimester exposure to busulfan. One malformed infant had defects similar to malformations observed in developmental toxicity studies of rat fetuses exposed to busulfan during organogenesis: cleft palate and microphthalmia (Diamond *et al.* 1960). This pregnancy was also co-exposed to 6-mercaptopurine, which may also have contributed to the major malformations observed (e.g., cleft palate and urogenital malformations. Thus, the apparent rate of major malformations following exposure to busulfan during the first trimester was 16% (3/19 conceptuses based on 18 liveborn infants and examination of the fetus of 1 induced abortion). One major malformation was observed in a liveborn infant with exposure to busulfan in the second and third trimesters only: congenital absence of the right kidney and ureter; however, it was not likely that exposure to busulfan beginning at gestation week 20 would have induced this malformation. Thus, the adjusted apparent rate of major malformations following exposure to busulfan in the second and/or third trimester only was 0% (0/6 conceptuses based on 6 liveborn infants).

Busulfan also appeared to cause fetal growth retardation with 25% of newborns observed to be small for gestational age based on data on sex, gestational age at birth and birth weight (**Table 77**).

5.9 CARBOPLATIN

5.9.1 Mechanism of Action, Route of Administration, and Indications

Table 30: Pharmacology of carboplatin in adult humans	
Molecular weight:	373.2666
Protein binding:	Carboplatin: 0%; platinum (from carboplatin): irreversibly binds to plasma proteins
Metabolism:	Minimally hepatic to aquated and hydroxylated compounds
Half-life elimination:	Clcr >60 mL/minute: Carboplatin: 2.6-5.9 hours (based on a dose of 300-500 mg/m2); Platinum (from carboplatin): ≥5 days
Distribution:	Vd: 16 L (based on a dose of 300-500 mg/m^2); into liver, kidney, skin, and tumor tissue
Time to peak, serum (C_{max}):	Not specified
Excretion:	Urine (~70% as carboplatin within 24 hours; 3% to 5% as platinum within 1-4 days)
Data from Brunton et al. (2011). Abbreviations: Clcr, creatinine clearance; Cmax, time to reach maximal concentration in serum; CNS, central nervous system; Vd, volume of distribution.	

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 is not cell cycle specific (Bedford 2004). Carboplatin is administered intravenously on a body surface area (mg/m^2) basis. Additional information on the pharmacology of carboplatin is located in **Table 30**.

Carboplatin is indicated for ovarian cancer (Bedford 2004).

5.9.2 Evidence of Placental and Breast Milk Transport

There is evidence that carboplatin and similar platinum-derivatives (e.g., cisplatin) can cross the placenta in humans. Platinum DNA adducts were detected in maternal blood and placental tissue of a patient administered cisplatin and cyclophosphamide during the second and third trimester and subsequently treated with carboplatin and cyclophosphamide in the third trimester of pregnancy (Henderson *et al.* 1993). In another study, platinum DNA adducts were detected in both maternal blood at gestation week 30 and in cord blood at delivery (at gestation week 37) of a cancer patient treated with carboplatin (400 mg/m^2 every 4 weeks); the first dose was administered at gestation week 22 and the last dose was administered nine weeks prior to delivery **[~gestation week 26]** (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 7 pregnant baboons at a median gestational age of 129 days (Van Calsteren *et al.* 2010c). In studies of mice, total platinum was reported to easily cross 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 (Van Calsteren *et al.* 2010d).

Breast milk transfer of carboplatin in humans is not known. Finally, the possibility of maternal transfer of carboplatin to the infant via breastfeeding is not known.

5.9.3 Laboratory Animal Developmental Toxicity

Carboplatin induced embryolethal and teratogenic effects in rat fetuses when administered during the early period of organogenesis. 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 bw/day on gestation days 6 to 9 versus controls (Kai *et al.* 1989), while there was no significant difference between carboplatin-treated groups and controls dosed on gestation days 7 to 10. The congenital malformations produced by carboplatin included: gastroschisis, dilation of cerebral ventricles, cleft sternum, fused ribs, and malformed thoracic vertebra. Delayed ossification was observed in rat fetuses treated during both administration periods (gestation days 6-9 or 7-10), which the authors suggested may be caused by fetal growth retardation (Kai *et al.* 1989). As reviewed in Shepard et al. (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 bw/day on gestation days 7 to 17.

5.9.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Carboplatin was administered to 17 pregnant cancer patients (also called cases) identified from 12 case reports (12 cases), 1 case series (1 case), and 1 registry survey (4 cases) (Appendix C Table 8). Among these patients, carboplatin was used to treat cancers of the ovary (12 cases), lung (2 cases), breast (1 case), central nervous system (1 case), and cervix (1 case). A total of 17 singleton pregnancies (17 conceptuses) were exposed to carboplatin.

Carboplatin was administered in the second and/or third trimester only in all 17 singleton pregnancies (17 conceptuses); it was not administered during the first trimester in any case. Carboplatin was administered as monotherapy in 6 cases and as polytherapy in 11 cases.

Termination of Pregnancy

No terminations of pregnancy were reported.

Spontaneous Fetal Death

A spontaneous abortion of a fetus with gastroschisis occurred at gestation week 19 in one patient (Cardonick *et al.* 2010); this fetus had been exposed in the second trimester only.

Rate of Occurrence of Congenital Malformations

Major Malformations

There was only one major malformation reported following gestational 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 to carboplatin in the second trimester only. This malformation was not likely attributable to carboplatin due to timing of development of the malformation (during early organogenesis) and the timing of exposure to carboplatin. Specifically, the abdominal wall is well-developed by gestation weeks 10-12 (Sadler and

Feldkamp 2008). Thus, the adjusted apparent rate of major malformations following gestational exposure to carboplatin in the second and/or third trimester only was 0% (0/17 conceptuses based on 16 liveborn infants and examination of the fetus of 1 spontaneous abortion). There were no conceptuses exposed to carboplatin during the first trimester.

Minor Malformations

No minor malformations were reported with gestational exposure to carboplatin.

Pregnancy Complications and Newborn Health

Relatively few pregnancy complications were reported in pregnancies exposed to carboplatin. Anhydramnios and intrauterine growth restriction was observed in one singleton pregnancy that was treated with carboplatin, docetaxel and trastuzumab in the second and third trimesters (Gottschalk *et al.* 2011). Spontaneous preterm labor occurred in one singleton pregnancy (Azim *et al.* 2009b). Gestational diabetes and preeclampsia were observed in another singleton pregnancy at gestation weeks 30 and 34 (Henderson *et al.* 1993).

There were 16 liveborn infants born following gestational exposure to carboplatin. Early preterm delivery (<34 weeks) was reported for 6 infants, late preterm delivery (34-36 weeks) was reported for 6 infants, and 1 infant was delivered at term (≥37 weeks). Data were insufficient to determine the age of delivery for 3 infants. Of the preterm infants, 1 infant was delivered via spontaneous vaginal birth and 11 infants were delivered via C-section. Two newborns were reported as small for gestational age (Cardonick *et al.* 2010) and 13 infants had normal body weight at birth as per sex, gestational age and body weight at birth. Data were insufficient to determine small for gestational age for 1 infant.

Infant health effects included anemia, which was reported for two newborns (Hubalek *et al.* 2007, Gurumurthy *et al.* 2009). Both of these newborns, who were born preterm, had either minor respiratory distress (Hubalek *et al.* 2007) or breathing difficulties requiring surfactant treatment followed by placement 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 (Gurumurthy *et al.* 2009).

Infant Deaths

No infant deaths were reported with gestational exposure to carboplatin.

Follow Up Evaluations

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) (**Table 77**). Overall, the raw apparent rate of major malformations among all carboplatin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 6% (1/17 conceptuses based on 16 liveborn infants and examination of the fetus of 1 spontaneous abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). None of the infants were exposed in the first trimester. Gastroschisis

was reported in a fetus from a spontaneous abortion at gestation week 19 following second trimester exposure to carboplatin (Cardonick *et al.* 2010). While gastroschisis has also been reported in developmental toxicity studies of mice exposed to carboplatin on gestation days 6 and 9 (Kai *et al.* 1989), it was not likely due to carboplatin exposure in the second trimester because the abdominal wall is well developed by gestation week 12. Thus, the adjusted rate of major malformations following exposure to carboplatin during second and/or third trimester only was 0% (0/17 conceptuses based on 16 liveborn infants and examination of the fetus of 1 spontaneous abortion).

5.10 CISPLATIN

5.10.1 Mechanism of Action, Route of Administration, and Indications

Table 31: Pharmacology of cisplatin in adult humans

Molecular weight:	302.0632
Protein binding:	>90%
Metabolism:	Nonenzymatic; inactivated (in both cell and bloodstream) by sulfhydryl groups; covalently binds to glutathione and thiosulfate
Half-life elimination:	Initial: 20-30 minutes; Beta: 60 minutes; Terminal: ~24 hours; Secondary half-life: 44-73 hours
Distribution:	Vd (steady state in plasma): 11-12 L/m^2; high concentrations in tissues of kidney, liver, intestine, and testes, but poor penetration of CNS
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Urine (>90%); feces (minimal)

Data from Brunton et al. (2011) and Bristol-Myers Squibb **(2010b)**. Abbreviations: C_{max}, time to reach maximal concentration in serum; CNS, central nervous system, Vd, volume of distribution.

Cisplatin, an inorganic compound, is a *cis*-isomer of diammine dichloroplatinum. Cisplatin is a DNA-alkylating agent, and it also induces interstrand and intrastrand crosslinks in DNA, which inhibits the growth of cancer cells. Its action is not cell-cycle specific. Cisplatin is administered by intravenous injection (Bristol-Myers Squibb 2010b) or intraperitoneal injection (Markman 2009) on a body surface area (mg/m^2) basis. Additional information on the pharmacology of cisplatin is located in **Table 31**.

Cisplatin is indicated for the treatment of metastatic testicular tumors, metastatic ovarian tumors, and advanced bladder cancer (Bristol-Myers Squibb 2010b). 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

Placental transport of cisplatin in humans has been documented. In a twin pregnancy, levels of cisplatin in the amniotic fluid were observed to be 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 third trimester (Marnitz *et al.* 2009). At birth at gestation week 32, cisplatin levels in the umbilical cord bloods of the twin infants were 57.1 and 61.2 µg/L, which was approximately one-third of the amniotic fluid levels (data not provided). Nearly equivalent levels of cisplatin were detected in maternal blood and umbilical cord blood at birth in 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. Another case report reported cisplatin levels of 40 µg/mL **[40 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, cisplatin was detected in the maternal serum, amniotic fluid and umbilical cord artery serum at birth for 7 patients (Marnitz *et al.* 2010). 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. In addition to serum level evaluations, platinum DNA adducts were detected in maternal blood and placental tissue of a patient administered cisplatin and cyclophosphamide during the second and third trimester, followed

by carboplatin and cyclophosphamide during the third 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. Cisplatin 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).

Breast milk transport of cisplatin in humans has been documented. Two studies report platinum in breast milk. 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 third daily dose of cisplatin at 30 mg/m^2 intravenously with co-treatments etoposide and bleomycin, following a C-section at gestation week 33. In another study, levels of platinum in breast milk were, at minimum, one-tenth of plasma levels throughout the 18 hours of sampling of a patient administered cisplatin at 60 mg/m^2 (or 100 mg total dose) and cyclophosphamide intravenously per cycle (Ben-Baruch *et al.* 1992). For example, platinum levels were approximately 0.25 versus 2.8 ng/mL **[0.25 versus 2.8 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. (1985) reported that levels of platinum were undetectable in breast milk versus detection of a maximum value of 2.99 µg/mL **[2.99 mg/L]** in plasma 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. (1983) report that the embryonic LD_{50}s were 1.0 to 2.9 mg cisplatin/kg bw/d in the rat and 5.2 mg cisplatin/kg bw/d in the mouse during the period of organogenesis; theses doses are below the estimated human dose of 6 mg/kg bw/day. Other studies also reported dose-dependent increases in fetal resorptions during organogenesis, but not after organogenesis, in the mouse (Kopf-Maier *et al.* 1985), rat (Muranaka *et al.* 1995) as well as the rabbit. High 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 doses comparable to those inducing fetal mortality (Lazar *et al.* 1979, Kopf-Maier *et al.* 1985, Muranaka *et al.* 1995). While 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 in utero exposure to cisplatin 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 (1988) suggested that 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 and Merker 1983, Kopf-Maier *et al.* 1985). Köpf-Maier et al. (1983, 1985) 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

Number of Cases, Publications, Types of Cancer Treated

Cisplatin was administered to 103 female cancer patients (also called cases) during pregnancy identified from 48 case reports (48 cases), 13 case series (43 cases), 2 retrospective cohort studies (3 cases), 1 retrospective survey (1 case), and 1 registry survey (8 cases) (Appendix C Table 9). Among these 103 patients, cisplatin was used to treat cancers of the ovary (43 cases), cervix (40 cases), lung (6 cases), pancreas (1 case), tongue (1 case) and urethra (1 case) as well as melanoma (3 cases). In addition, cisplatin was used to treat Hodgkin lymphoma (1 case), non-Hodgkin lymphoma (2 cases), diffuse lymphoblastic lymphoma (1 case), adenocarcinoma of the liver (primary tumor not identified; 1 case), adenoid cystic carcinoma (2 cases), and neuroblastoma (1 case).

A total of 103 pregnancies (105 conceptuses) were exposed to cisplatin, including two twin pregnancies (Cardonick *et al.* 2010, Marnitz *et al.* 2010). Cisplatin was administered during the first trimester in 5 cases (5 conceptuses) and the second and/or third trimester only in 98 cases (100 conceptuses due to two sets of twins). Cisplatin was administered as monotherapy in 33 cases (34 conceptuses due to 1 set of twins) and as polytherapy in 71 cases (72 conceptuses due to one set of twins).

Termination of Pregnancy

One pregnancy was terminated by induced abortion at gestation week 13 following exposure to cisplatin monotherapy in the first trimester beginning on gestation week 10 (Jacobs *et al.* 1980). 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).

Spontaneous Fetal Death

Spontaneous fetal death occurred in two singleton pregnancies. One spontaneous abortion occurred at gestation week 22 following second trimester exposure to cisplatin monotherapy (Gambino *et al.* 2011); no examination of the fetus was reported. Stillbirth of a normal fetus occurred at gestation week 26 following exposure during the second trimester to cisplatin and etoposide (Peres *et al.* 2001).

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 4 liveborn infants gestationally exposed to cisplatin. One major malformations was observed in a liveborn infant exposed during the first trimester. This newborn had blepharophimosis, microcephaly, and hydrocephalus following exposure to cisplatin, doxorubicin and cyclophosphamide beginning in gestation week 5 through gestation week 10. Blepharophimosis is characterized by bilateral ptosis (drooping eyelids) with reduced lid size, a flat nasal bridge with a small orbital rim. Thus, the apparent rate of major malformations following exposure during the first

trimester was 1% (1/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 induced abortion) (Table 32).

Table 32: Major malformations diagnosed at birth possibly attributable to in utero exposure to cisplatin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Blepharophimosis, microcephaly, and hydrocephalus	1% (1/5)
2nd and/or 3rd only	Ventriculomegaly and cerebral atrophy	1% (1/98)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths.

Major malformations were reported in 4 liveborn infants exposed in utero to cisplatin in the second and/or third trimester only. Ventriculomegaly and cerebral atrophy were observed in one newborn who had been diagnosed with ventriculomegaly at gestation week 26 and 5 days, one week after initiation of chemotherapy in the second trimester (Elit *et al.* 1999); this pregnancy was exposed to cisplatin, etoposide and bleomycin (Elit *et al.* 1999). A second liveborn infant exposed to cisplatin and docetaxel in the second and third trimester suffered from ventriculomegaly, which was diagnosed prior to chemotherapy and appeared to worsen during chemotherapy exposure (Rouzi *et al.* 2009); this infant died at age 5 days after from congenital malformations detected prior to chemotherapy exposure. Hereditary spherocytosis was diagnosed at one year of age in an infant gestationally exposed during the second trimester to cisplatin and paclitaxel (Cheung *et al.* 2009). 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 second and third trimester to cisplatin, etoposide, and bleomycin. Of these major malformations, the occurrence of ventriculomegaly diagnosed prior to chemotherapy (Rouzi *et al.* 2009), hereditary spherocytosis (Cheung *et al.* 2009), and the spontaneous neurofibromatosis mutation (Cardonick *et al.* 2010) were not caused by exposure to cisplatin in the second or second and third trimesters. Thus, the adjusted apparent rate of major malformations following exposure to cisplatin in the second and/or third trimester was 1% (1/99 conceptuses based on 98 liveborn infants and examination of the fetus of 1 stillbirth).

Minor Malformations

Two liveborn infants had minor malformations following gestational exposure to cisplatin and one terminated fetus had a histological anomaly. One infant was diagnosed with microphthalmia with severe hypermetropia at age 1 year (Li *et al.* 2007); this infant was exposed in the first and second trimesters to cisplatin, carmustine, dacarbazine, and tamoxifen. A second infant had mild glandular hypospadias, considered first degree hypospadias, following exposure in the third trimester to cisplatin, etoposide, and bleomycin (Ghaemmaghami *et al.* 2009). Histological examination of the fetus terminated by induced abortion revealed a large giant cell in the testes, possibly a megakaryocyte (Jacobs *et al.* 1980); all other organs were normal.

Pregnancy Complications and Newborn Health

A variety of pregnancy complications were observed following in utero exposure to cisplatin. Intrauterine growth restriction was observed in 8 fetuses resulting in liveborn infants (Arango *et al.* 1994, Han *et al.* 2005, Gottschalk *et al.* 2009, Benjapibal *et al.* 2010) (Tseng and ChangChien 2004), including 3 fetuses with reductions in amniotic fluid levels (Buller *et al.* 1992, Motegi *et al.* 2007, Ghaemmaghami *et al.* 2009). Polyhydramnios was reported in one singleton pregnancy (Bayhan *et al.* 1999). Preeclampsia occurred in 3 pregnancies (Henderson *et al.* 1993, Horbelt *et al.* 1994, Benhaim *et*

al. 2008) and pregnancy-induced hypertension was reported in one pregnancy (Raghunath and Shashi 2006). Premature rupture of the membranes occurred in 5 pregnancies (Bayhan *et al.* 1999, Ghaemmaghami and Hasanzadeh 2006) (Gambino *et al.* 2011), including two cases that also had spontaneous preterm labor (King *et al.* 1991, Huang *et al.* 2004). Spontaneous preterm labor occurred in four additional pregnancies (Raffles *et al.* 1989, Kim *et al.* 1996), including two pregnancies in which it resolved with treatment (Karam *et al.* 2007, Li *et al.* 2011). 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).

There were a total of 102 liveborn infants gestationally exposed to cisplatin. Early preterm birth (<34 weeks) was observed for 34 infants, late preterm delivery (34 weeks to <37 weeks) was reported for 30 infants and 17 infants were delivered at term. Data were insufficient to determine the gestational age at delivery for 21 infants. Of the preterm deliveries, 4 infants were delivered via spontaneous vaginal delivery, 1 infant was delivered via induced vaginal delivery, and 54 infants were delivered via C-section. Data were insufficient to determine the route of delivery for 5 infants. Small for gestational age was determined for 13 newborns (Abellar *et al.* 2009, Cardonick *et al.* 2010) (Buller *et al.* 1992, Arango *et al.* 1994, Caluwaerts *et al.* 2006, Benjapibal *et al.* 2010) (Han *et al.* 2005, Ghaemmaghami *et al.* 2009, Gottschalk *et al.* 2009) (Tseng and ChangChien 2004, Raghunath and Shashi 2006, Motegi *et al.* 2007, Kim *et al.* 2008), and 61 newborns had normal body weight based on sex, gestational age, and body weight at birth. Data were insufficient to determine small for gestational age in 28 infants.

A variety of health effects were observed in liveborn infants gestationally exposed to cisplatin. Respiratory difficulties were reported in 13 newborns (Malone *et al.* 1986, King *et al.* 1991, Bayhan *et al.* 1999, Elit *et al.* 1999, Malhotra and Sood 2000, Bader *et al.* 2007a, Robova *et al.* 2007, Garcia-Gonzalez *et al.* 2008, Boyd *et al.* 2009, Marnitz *et al.* 2010, Rabaiotti *et al.* 2010, Fruscio *et al.* 2012). Transient myelosuppression was reported in 7 infants, including anemia (Raffles *et al.* 1989, Horbelt *et al.* 1994, Peres *et al.* 2001, Robova *et al.* 2007, Rabaiotti *et al.* 2010, Gambino *et al.* 2011), profound leukopenia with neutropenia by day 3 and alopecia at 10 days of age (Raffles *et al.* 1989), and decreased white blood cells and platelets at 10 days of age (Janne *et al.* 2001). Other transient newborn health effects included: hypoglycemia (1 infant) (Boyd *et al.* 2009), a mild elevation in creatinine(2 infants)(Caluwaerts *et al.* 2006, Karam *et al.* 2007), and jaundice (3 infants) (Peres *et al.* 2001, Tseng and ChangChien 2004, Cheung *et al.* 2009). Tachycardia was observed in one newborn (King *et al.* 1991). One infant had an intraventricular hemorrhage, and was discharged from the hospital healthy after 40 days (Fruscio *et al.* 2012). The placentas of three normal liveborn infants had abnormalities, including malignant melanoma (DiPaola *et al.* 1997), areas of infarction (Cardonick *et al.* 2010) and foci of villous edema (Buller *et al.* 1992).

Infant Deaths

One infant death occurred following gestational exposure to cisplatin. An infant with second trimester exposure to cisplatin polytherapy died 5 days after birth from congenital malformations detected prior to chemotherapy exposure (Rouzi *et al.* 2009).

Follow Up Evaluations

Follow up evaluations 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 Asperger 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 103 pregnancies with 105 conceptuses, including two sets of twins (**Table 77**). Overall, the apparent rate of major malformations among all cisplatin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 5% (5/104 conceptuses based on 102 liveborn infants and examination of the fetuses of 1 induced abortion and 1 stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in one infant with exposure to cisplatin polytherapy during the first trimester during the period of organogenesis (Kim *et al.* 1996). Thus, the apparent rate of major malformations following exposure to cisplatin during the first trimester was 20% (1/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 induced abortion). Ventriculomegaly and cerebral atrophy were observed in an infant with second trimester exposure to cisplatin polytherapy (Elit *et al.* 1999). The remaining three major malformations were not caused by cisplatin exposure in the second and/or third trimester only: ventriculomegaly with other congenital malformations that were observed prior to treatment with cisplatin (1 infant) (Rouzi *et al.* 2009), spontaneous mutation for neurofibromatosis and genetic hearing loss (both parents were carriers) (1 infant) (Cardonick *et al.* 2010), and hereditary spherocytosis (1 infant) (Cheung *et al.* 2009). Thus the apparent rate of major malformations possibly attributable to exposure to cisplatin in the second and/or third trimester only was 1% (1/98 conceptuses based on 97 liveborn infants and examination of the fetus of 1 stillbirth). There were no major malformations reported in conceptuses exposed to cisplatin during the first trimester (0/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 induced abortion).

Microphthalmia, a minor malformation, was reported in one infant exposed to cisplatin polytherapy in the first and second trimester (Li *et al.* 2007). Developmental toxicity studies in rats and chickens have also observed microphthalmia and anophthalmia following exposure to cisplatin during the period of organogenesis. Finally, gestational exposure to cisplatin may have caused a higher rate of small for gestational age newborns (13%; 13 of 100 liveborn infants). Fetal growth restriction was frequently reported in developmental toxicity studies of laboratory animals exposed to cisplatin, regardless of timing of exposure during pregnancy (**Table 77**).

5.11 CYCLOPHOSPHAMIDE

5.11.1 Mechanism of Action, Route of Administration, and Indications

Table 33: Pharmacology of cyclophosphamide in adult humans	
Molecular weight:	261.0875
Protein binding:	10% to 60%
Metabolism:	Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard
Half-life elimination:	3-12 hours
Distribution:	Vd: 0.48-0.71 L/kg; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)
Time to peak, serum (C_{max}):	Oral: ~1 hour; IV ~ 1 hour; metabolites: 2-3 hours
Excretion:	Urine (<30% as unchanged drug, 85% to 90% as metabolites)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CSF, cerebral spinal fluid; IV, intravenous; Vd, volume of distribution.	

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 DNA to inhibit the growth of rapidly dividing cancer cells. Cyclophosphamide may be administered orally or by intravenous injection. Additional information on the pharmacology of cyclophosphamide is located in **Table 33**.

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).

5.11.2 Evidence of Placental and Breast Milk Transport

Placental transport of cyclophosphamide may occur in humans. In a case report, amniotic fluid levels of cyclophosphamide were approximately 25% (2.1 µg/mL) of the drug concentration in maternal plasma at one hour post-administration of the last IV dose of 400 mg/m^2 prior to C-section delivery of the infant (D'Incalci *et al.* 1982). Transplacental transfer of cyclophosphamide has also been documented in baboons. 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.* 2010b). At 24 hours post-treatment, cyclophosphamide and the metabolite were undetectable in fetal and maternal plasma. Cyclophosphamide was also detected in the amniotic fluid and the cerebral spinal fluid of the fetus and mother in the baboon studies; 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 (Van Calsteren *et al.* 2010b).

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 lactation beginning at postnatal day 20 (Durodola 1979); she had also been treated with cyclophosphamide during pregnancy. The infant's leukocyte and platelet counts were rapidly depressed over 3 daily doses of cyclophosphamide to the mother with leukocyte and platelet counts falling from pretreatment values of 4,800/mm^3 and 270,000/mm^3 to 3,200/mm^3 and 47,000/mm^3, respectively (Durodola 1979). The mother died at postnatal day 23 (the day of the 3rd dose) and no follow-up data were available for the infant. Transient neutropenia occurred 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 (Amato and Niblett 1977). 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. (1968) administered cyclophosphamide by intraperitoneal injection at 7 to 10 mg/kg bw to pregnant Wistar rats on gestation day 11 or 12 and reported skeletal malformations in their fetuses including retarded or clubbed legs, ectrodactyly, polydactyly, syndactyly, brachydactyly of the paws, absent or malformed (short or kinky) tails, and encephalocele or exencephaly. A single intraperitoneal injection of cyclophosphamide at 20 mg/kg bw to pregnant Swiss Webster mice on gestation 9 through 14 resulted in an increased number of resorptions and a variety of gross and skeletal teratogenic effects in the mouse fetuses (Gibson and Becker 1968). The skeletal malformations included cleft palate, exencephaly, kinky tail, polydactyly, syndactyly, ectrodactyly, adactyly, fusion of the long bones, curvature of the long bones, and missing ribs and the soft tissue malformations included open eyes, aphakia, microphakia, hydronephrosis, and hydrocephalus. In contrast, an increase in resorptions and inhibited growth but no gross malformations were induced by doses of 5 and 10 mg/kg bw (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 bw 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).

In the primate, cyclophosphamide is both embryotoxic and teratogenic. Administration of cyclophosphamide (10 mg/kg bw) to pregnant Rhesus monkeys on gestation days 27 and 29 resulted in cleft lip and/or cleft palate, and exophthalmos in 6 of 10 offspring. In addition, one offspring had a kinky tail and another had partially fused eyelids and skeletal anomalies, including fused ribs, missing ulna, missing several carpal bones and ectrosyndactyly of the left hand. Administration of cyclophosphamide (10 mg/kg bw) 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 bw) or for a long duration (10 days of gestation) (McClure *et al.* 1979).

5.11.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Cyclophosphamide was administered to 416 female cancer patients (also called cases) during pregnancy identified from 90 case reports (90 cases), 17 case series (100 cases), 4 retrospective case series (33 cases), 10 retrospective surveys (74 cases), 2 retrospective cohort studies (8 cases) and 1 registry survey (111 cases) (Appendix C Table 10). Among these patients, cyclophosphamide was used to treat breast cancer (275 cases), ovarian cancer (14 cases), uterine choriocarcinoma (1 case), sarcoma (1 case), Ewing sarcoma (3 cases), rhabdosarcoma (3 cases), soft tissue sarcoma (2 cases), undifferentiated sarcoma (1 case), adenoid cystic carcinoma (2 cases), granulocytic sarcoma (breast; 1 case), cervix (small cell carcinoma; 1 case) and vaginal neuroendocrine carcinoma (1 case). Cyclophosphamide was also used to treat hematological cancers including acute lymphocytic leukemia (23 cases), acute myeloid leukemia (3 cases), multiple myeloma (1 case), Hodgkin lymphoma (9 cases), non-Hodgkin lymphoma (55 cases), Burkitt lymphoma (10 cases), large B-cell lymphoma (2 case), B-cell lymphoma (2 case), T-cell leukemia/lymphoma (1 case), and subcutaneous panniculitis-like T-cell lymphoma (1 case). In addition, cancer type was not specified in 4 cases.

A total of 416 pregnancies and 419 conceptuses were exposed to cyclophosphamide due to three sets of twins (Reynoso *et al.* 1987, Nantel *et al.* 1990, Lycette *et al.* 2006). Cyclophosphamide was administered during the first trimester in 48 cases (49 conceptuses due to one set of twins (Reynoso *et al.* 1987)). The drug was administered in the second and/or third trimester only in 368 cases (370 conceptuses due to two sets of twins (Nantel *et al.* 1990, Lycette *et al.* 2006)), including 47 singleton pregnancies from two studies that did not specify individual timing of exposure during gestation but were likely exposed during the second and/or third trimester (Hahn *et al.* 2006, Jameel and Jamil 2007). 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). Cyclophosphamide was most commonly administered as polytherapy (413 cases; 415 conceptuses due to two sets of twins). Only 6 cases (7 conceptuses due to one set of twins) were treated with cyclophosphamide as monotherapy.

Termination of Pregnancy

Nine singleton pregnancies were medically terminated following exposure to cyclophosphamide, including 7 singleton pregnancies with exposure during the first trimester. Skeletal malformations were observed in the fetal autopsies of two induced abortions following exposure to cyclophosphamide in the first and second trimesters. One fetus had syndactyly of the first and second 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 following exposure to cyclophosphamide, 5-fluorouracil, and epirubicin and radiation therapy in the first trimester and then exposure to cyclophosphamide, 5-fluorouracil and methotrexate in the second trimester (Leyder *et al.* 2010). A 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); the fetus was co-exposed to radiation therapy in the first trimester. No examination of the fetus was reported for the remaining 5 induced abortions performed in the first trimester (Zuazu *et al.* 1991, Chelghoum *et al.* 2005).

Two singleton pregnancies with exposure to cyclophosphamide during the second and/or third trimester only were terminated by induced abortion. Examination revealed a normal fetus from an induced abortion following second trimester exposure to cyclophosphamide and intrathecal methotrexate

(Armitage *et al.* 1977). No examination of the fetus was reported for an induced abortion following second trimester exposure (Zemlickis *et al.* 1992b).

Spontaneous Fetal Death

Spontaneous fetal death was reported for 10 singleton pregnancies exposed to cyclophosphamide, including 4 spontaneous abortions and 2 stillbirths following exposure in the first trimester. No fetal data were reported for any of the spontaneous abortions which occurred following exposure to cyclophosphamide in the first trimester in combination with 5-fluorouracil and epirubicin (Giacalone *et al.* 1999) or 5-fluorouracil and methotrexate (Zemlickis *et al.* 1992b), or exposure during the first trimester to cyclophosphamide in combination with 5-fluorouracil and methotrexate (Ring *et al.* 2005b) or vincristine (Zuazu *et al.* 1991). Polydactyly was observed in one stillborn exposed during the first trimester to cyclophosphamide and 6-mercaptopurine (Mulvihill *et al.* 1987); this pregnancy was complicated by premature detachment of the placenta (placenta abruptio). The stillbirth of a normal fetus occurred at gestation week 25 after first trimester exposure to cyclophosphamide, 5-fluorouracil and methotrexate (Peres *et al.* 2001).

Stillbirth occurred in 4 singleton pregnancies with second and/or third trimester only exposure to cyclophosphamide. A normal fetus at was reported for a stillborn exposed during the second and third trimesters to cyclophosphamide, doxorubicin, vincristine, and rituximab (Cardonick *et al.* 2010). No examination of the fetus was reported for another pregnancy ending in stillbirth following exposure in the second trimester to cyclophosphamide, vincristine, doxorubicin, ifosfamide, etoposide, cytarabine, and rituximab (Peterson *et al.* 2010); this fetus experienced oligohydramnios and intrauterine fetal growth restriction prior to death. Finally, no examination of the fetus was reported for the remaining two stillbirths exposed during the second trimester to: cyclophosphamide and epirubicin (Giacalone *et al.* 1999) or cyclophosphamide, vincristine, doxorubicin, and dacarbazine (Jameel and Jamil 2007).

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 9 liveborn infants, 2 induced abortuses and 1 stillborn fetus, including 4 liveborn infants, 2 induced abortuses and 1 stillborn fetus with exposure during the first trimester. Skeletal malformations were reported in one infant exposed to cyclophosphamide monotherapy during the first, second and third trimesters (Greenberg and Tanaka 1964); the skeletal malformations included 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. 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 first and second trimester exposure to cyclophosphamide, doxorubicin and cobalt therapy (Murray *et al.* 1984). Skeletal malformations were reported for another infant who was exposed during the first and second trimesters to cyclophosphamide, doxorubicin and 5-fluorouracil (Paskulin *et al.* 2005); the malformations included microencephaly, bilateral ventriculomegaly and colpocephaly, a flat nasal bridge and high arched palate, and multiple skeletal malformations of the hands (i.e., bilateral syndactyly of the 1st and 2nd fingers, and a cleft between the 2nd and 3rd). 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 first, second and third trimesters to cyclophosphamide monotherapy (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). As mentioned above, major malformations of the digits were reported in two induced abortuses (Toledo *et al.* 1971, Leyder *et al.* 2010) and one stillborn fetus (Mulvihill *et al.* 1987). Thus, the apparent rate of major malformations following exposure to cyclophosphamide during the first trimester was 15% (7/39 conceptuses based on 35 liveborn infants and examination of the fetuses of 2 stillbirths and 2 induced abortions) (**Table 34**).

Table 34: Major malformations diagnosed at birth possibly attributable to in utero exposure to cyclophosphamide

Trimester exposed	Major malformations reported	Apparent rate (affected/total conceptuses[a])
During 1st	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	
	Imperforate anus and rectovaginal fistula	
	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	
	Madelung deformity of the right arm, esophageal atresia, anomalous inferior vena cava, undescended testes and an extra pair of collecting systems for the kidneys	
	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	
	Missing phalanges in both feet and had only a single left coronary artery	
	Polydactyly	18% (7/39)
2nd and/or 3rd only	Pyloric stenosis	
	Clubfoot (2 infants)	1% (3/367)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Major malformations were observed in 5 liveborn infants exposed to cyclophosphamide in the second and/or third trimester only. Pyloric stenosis was reported in 1 infant following second and third trimester exposure to cyclophosphamide and doxorubicin, then docetaxel (Cardonick *et al.* 2010). A small main pulmonary fistula was observed in an infant following second and third trimester exposure to cyclophosphamide and doxorubicin (Cardonick *et al.* 2010). Clubfoot was reported in an infant following second and third trimester exposure to cyclophosphamide and epirubicin (Cardonick *et al.* 2010); this infant also had a hemangioma on the left eye, which is considered a minor malformation. Down syndrome was reported in one infant and clubfoot in another infant following second and/or third trimester exposure to cyclophosphamide, 5-fluorouracil and doxorubicin (Hahn *et al.* 2006). Of these malformations, the incidence of Down syndrome and the pulmonary fistula were not likely caused by exposure to cyclophosphamide following conception or organogenesis, respectively. Thus, the adjusted apparent rate of major malformations following exposure to cyclophosphamide in the second and/or third trimester only was 1% (3/367

conceptuses based on 365 liveborn infants and examination of the fetuses of 1 induced abortion and 1 stillbirth).

Minor Malformations

Minor malformations were reported in 8 liveborn infants exposed to cyclophosphamide in the second and/or third trimester only. Bilateral ureteral reflux was reported in an infant exposed in the second and/or third trimester to cyclophosphamide, 5-fluorouracil and doxorubicin (Hahn *et al.* 2006). A retrospective survey reported 3 infants with minor malformations following second and third trimester exposure to cyclophosphamide polytherapy: hip subluxation in an infant exposed to cyclophosphamide and doxorubicin; bilateral protuberance on phalanx 5 in an infant exposed to cyclophosphamide, 5-fluorouracil and epirubicin; and double cartilage rings in both ears in an infant exposed to cyclophosphamide, 5-fluorouracil, doxorubicin and radiation therapy (Van Calsteren *et al.* 2010a). Hemangiomas were reported in 3 infants exposed to cyclophosphamide polytherapy in the second and/or third trimester only, including second and third trimester exposure to cyclophosphamide, vincristine, methotrexate, daunorubicin, asparaginase, and 6-mercaptopurine (Van Calsteren *et al.* 2010a); second and third trimester exposure to cyclophosphamide and epirubicin (Cardonick *et al.* 2010); and exposure in the second and/or third trimester to cyclophosphamide, 5-fluorouracil, and methotrexate with either doxorubicin or epirubicin (individual treatment data not provided) (Ring *et al.* 2005b).

Two infants had minor malformations that subsided over time. Suspected holoprosencephaly was diagnosed in a newborn exposed during the second and third trimesters to cyclophosphamide, 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 second trimester, and treated with docetaxel beginning at gestation week 26 and into the third trimester (Potluri *et al.* 2006). This case of mild hydrocephalus regressed spontaneously over several months.

Pregnancy Complications and Newborn Health

A variety of pregnancy complications occurred following in utero exposure to cyclophosphamide. Polyhydramnios was observed in one pregnancy (Bayhan *et al.* 1999). A reduction in amniotic fluid levels was reported in 5 singleton pregnancies yielding liveborn infants (Hansen *et al.* 2001, Meyer-Wittkopf *et al.* 2001, Cordoba *et al.* 2010, Shieh and Mehta 2011), including one singleton pregnancy with placental insufficiency accompanied by oligohydramnios and intrauterine growth retardation (Massey Skatulla *et al.* 2012). In addition, a reduction in amniotic fluid and intrauterine growth retardation was reported in one singleton pregnancy that ended in stillbirth (Peterson 2008). Intrauterine growth retardation was observed in three additional pregnancies (Lambert *et al.* 1991, Cordoba *et al.* 2010), including one case where intrauterine growth restriction was due to placental insufficiency (Ring *et al.* 2005b). Additional fetal health issues included fetal distress (1 fetus) (Ali *et al.* 2009a), an abnormal cardiotocogram and low biophysical profile score occurred in another (Mavrommatis *et al.* 1998), and a pathological fetal heart rate, reverse flow in the umbilical artery, fetal centralization and negative A wave in the venous duct (Massey Skatulla *et al.* 2012). Spontaneous preterm labor was reported in 20 cases (Andreadis *et al.* 2004) (Weed *et al.* 1979, Webb 1980, Berrebi *et al.* 1983, Meador *et al.* 1987, Reynoso *et al.* 1987, Kim and Park 1989, Nantel *et al.* 1990, King *et al.* 1991, Moore and Taslimi 1991, Martin *et al.* 1997, Berry *et al.* 1999, Giannakopoulou *et al.* 2000, Hansen *et al.* 2001, Huang *et al.* 2004, Ring *et al.* 2005b, Decker *et al.* 2006, Sharma *et al.* 2009, Brudie *et al.* 2011), and four cases had transient spontaneous preterm labor (Ortega 1977, Durodola 1979, Meyer-

Wittkopf *et al.* 2001, Lycette *et al.* 2006). Preeclampsia occurred in 7 cases (Lambert *et al.* 1991, Henderson *et al.* 1993, Berry *et al.* 1999, Kuerer *et al.* 2002, Gonzalez-Angulo *et al.* 2004, Chakravarty *et al.* 2011), including one case with preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) (Massey Skatulla *et al.* 2012). One case each had maternal hypotension (Turchi and Villasis 1988),gestational diabetes (Henderson *et al.* 1993), and eclamptic seizures (Muller *et al.* 1996). Spontaneous preterm rupture of membranes occurred in 9 cases (Okun *et al.* 1979, Webb 1980, Meador *et al.* 1987, King *et al.* 1991, Bayhan *et al.* 1999, Ginopoulos *et al.* 2004, Huang *et al.* 2004, Ali *et al.* 2009a, Udink ten Cate *et al.* 2009). Other pregnancy complications included: placenta previa (1 case) (Cardonick *et al.* 2010).

There were a total of 400 liveborn infants gestationally exposed to cyclophosphamide. Early preterm delivery (<34 weeks) was reported for 37 infants, late preterm delivery (34 to <37 weeks) was reported for 56 infants, and 74 infants were delivered at term. Data were insufficient to determine the gestational age at delivery for 233 infants. Of the preterm infants, 27 infants were born via spontaneous vaginal delivery, 9 infants were born via induced vaginal delivery, and 47 infants were born via C-section. Data were insufficient to determine the route of delivery for 10 preterm infants. Small for gestational age was reported for 28 newborns and 263 infants had normal body weight based on sex, gestational age, and body weight at birth. Data were insufficient to determine small for gestational age for 109 infants.

Respiratory difficulties were reported for 37 infants reported as respiratory distress (17 infants) (Berrebi *et al.* 1983, Haerr and Pratt 1985, King *et al.* 1991, Mavrommatis *et al.* 1998, Berry *et al.* 1999, Giacalone *et al.* 1999, Achtari and Hohlfeld 2000, Giannakopoulou *et al.* 2000, Ginopoulos *et al.* 2004, Kerr 2005, Ring *et al.* 2005b, Lam 2006, Ali *et al.* 2009a, Cordeiro *et al.* 2009, Cardonick *et al.* 2010), transient tachypnea (7 infants) (Berry *et al.* 1999, Cardonick *et al.* 2010)), breathing difficulties (13 infants) (Bayhan *et al.* 1999, Ginopoulos *et al.* 2004, Hahn *et al.* 2006), and requiring resuscitation (1 infant) (Massey Skatulla *et al.* 2012). Meconium aspiration was diagnosed in 2 infants (Cardonick *et al.* 2010) with one infant requiring oxygen therapy (Hansen *et al.* 2001). One infant had hypocapnia with hypotonia (Cardonick *et al.* 2010). A total of 19 newborns were diagnosed with transient myelosuppression reported as: anemia (5 infants) (Aviles and Niz 1988, Zuazu *et al.* 1991, Udink ten Cate *et al.* 2009, Cardonick *et al.* 2010), anemia, leukopenia, neutropenia and thrombocytopenia (1 infant) (Udink ten Cate *et al.* 2009), leukopenia (4 infants) (Khurshid and Saleem 1978, Berry *et al.* 1999, Garcia *et al.* 1999, Giacalone *et al.* 1999, Udink ten Cate *et al.* 2009, Cardonick *et al.* 2010), an absence or decrease of B-cells (4 infants) (Decker *et al.* 2006, Friedrichs *et al.* 2006, Chakravarty *et al.* 2011), neutropenia (1 infant) (Giacalone *et al.* 1999, Hahn *et al.* 2006, Udink ten Cate *et al.* 2009, Cardonick *et al.* 2010), neutropenia and thrombocytopenia (1 infant) (Hahn *et al.* 2006), thrombocytopenia (2 infants) (Hahn *et al.* 2006, Udink ten Cate *et al.* 2009, Cardonick *et al.* 2010, Massey Skatulla *et al.* 2012), and severe bone marrow hypoplasia (1 infant) (Okun *et al.* 1979). Hyperbilirubinemia (also called jaundice) was reported for 12 infants (Dreicer and Love 1991, Lambert *et al.* 1991, Hansen *et al.* 2001, Kerr 2005, Cardonick *et al.* 2010). One infant had tachycardia (King *et al.* 1991), and two newborns were treated for acute cardiac failure (Achtari and Hohlfeld 2000), including one infant who also had slight cardiomegaly, an enlarged spleen, a petechial rash and was hydropic (Okun *et al.* 1979). The other infant treated for acute cardiac failure had a ventricular hemorrhage and was treated for necrotizing enterocolitis (Achtari and Hohlfeld 2000). Another infant had a subarachnoid hemorrhage (Hahn *et al.* 2006). 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 *et al.* 1999).

Infant Deaths

Three Infant deaths occurred following gestational exposure to cyclophosphamide. One newborn died at age 8 days and the examination of the fetus 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).

Follow Up Evaluations

Follow up evaluations were available for 284 infants at ages ranging from 6 weeks to 22 years, including 4 children for which age at follow up was not specified (Khurshid and Saleem 1978, Murray *et al.* 1984, Ohara and Teramoto 2000, Huang *et al.* 2004). 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 (Lam 2006, Cardonick *et al.* 2010), 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 (crossed-eyes) at age 9 and was healthy at age 22 years (Zemlickis *et al.* 1993). Another child, who had hypocapnia as a newborn, was diagnosed with periventricular leukomalacia at age 2 months and had developmental delay (Cardonick *et al.* 2010). Speech delay was diagnosed in two other children (Cardonick *et al.* 2010). Other health problems included otitis media (3 children), mild hearing loss with recurrent otitis media (1 child), reactive airway disease (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

Exposure to cyclophosphamide was documented for 416 pregnancies for a total of 419 conceptuses, including three sets of twins (**Table 77**). Overall, the apparent rate of major malformations among all cyclophosphamide-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 3% (13/405 conceptuses based on 400 liveborn infants and examination of the fetuses of 3 stillbirths and 3 induced abortions). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Of the 47 pregnancies (48 conceptuses due to 1 set of twins) exposed to cyclophosphamide during the first trimester, major malformations were observed in four liveborn infants, 2 induced abortuses and 1 stillborn fetus. Skeletal malformations were common to 6 singleton pregnancies exposed during the first trimester, including: the absence or hypoplasia of bones in the hands or feet (3 liveborn infants, 1 induced abortus) (Greenberg and Tanaka 1964, Toledo *et al.* 1971, Reynoso *et al.* 1987, Paskulin *et al.* 2005, Leyder *et al.* 2010), syndactyly of the digits in the hand (1 liveborn infant and 1 induced abortus) (Paskulin *et al.* 2005, Leyder *et al.* 2010), cranial malformations (2 liveborn infants) (Greenberg and Tanaka 1964, Paskulin *et al.* 2005), and polydactyly (1 stillbirth) (Mulvihill *et al.* 1987). Comparable patterns of skeletal

and other malformations have been observed in infants of women administered cyclophosphamide during the first trimester for treatment of autoimmune conditions leading to the hypothesis of a cyclophosphamide syndrome of malformations following exposure during organogenesis (Vaux *et al.* 2003). Furthermore, similar skeletal malformations have been observed in developmental toxicity studies in laboratory animals exposed to cyclophosphamide during the period of organogenesis. The apparent rate of major malformations following first trimester exposure to cyclophosphamide was 18% (7/39 conceptuses). In contrast, the adjusted apparent rate of major malformations following exposure to cyclophosphamide in the second and/or third trimester only was 1% (3/367 conceptuses based on 364 liveborn infants and examination of the fetuses of 1 induced abortion and 1 stillbirth).

5.12 CYTARABINE (Cytosine arabinoside)

5.12.1 Mechanism of Action, Route of Administration, and Indications

Table 35: Pharmacology of cytarabine in adult humans

Molecular weight:	243.218
Protein binding:	**[Information not located]**
Metabolism:	Primarily hepatic; metabolized by deoxycytidine kinase and other nucleotide kinases to aracytidine triphosphate (active); about 86% to 96% of dose is metabolized to inactive uracil arabinoside (ARA-U); intrathecal administration results in little conversion to ARA-U due to the low levels of deaminase in the CSF
Half-life elimination:	IV: Initial: 7-20 minutes; Terminal: 1-3 hours; IT: 2-6 hours
Distribution:	Vd: Total body water; widely and rapidly since it enters the cells readily; crosses blood-brain barrier with CSF levels of 40% to 50% of plasma level
Time to peak, serum (C_{max}):	SC: 20-60 minutes
Excretion:	Urine (~80%; 90% as metabolite ARA-U) within 24 hours

Data from Brunton et al. (2011). Abbreviations: CSF, cerebral spinal fluid; Cmax, time to reach maximal concentration in serum; IT, intrathecal; IV, intravenous; SC, subcutaneous; Vd, volume of distribution.

Cytarabine is in the group of antineoplastic agents known as antimetabolites. It 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 injection. Additional information on the pharmacology of cytarabine (parent compound) is located in **Table 35**.

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 2008a).

5.12.2 Evidence of Placental and Breast Milk Transport

Placental transport of cytarabine in humans is not known. However, cytarabine was reported to cross the placenta in mice (Van Calsteren *et al.* 2010d). Pregnant dams were administered 100 mg/kg cytarabine by injection in the tail vein and, 90 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.

There are no published reports of breast milk transfer of cytarabine in humans or laboratory animals.

5.12.3 Laboratory Animal Developmental Toxicity

According to the manufacturer product label, cytarabine is teratogenic in mice, inducing cleft palate, phocomelia, deformed appendages, and skeletal abnormalities at doses ≥2 mg/kg/day administered intraperitoneally during organogenesis (about 0.2 times the recommended human dose on mg/m^2 basis) (SkyePharma 2003). In rats, cytarabine induced deformed appendages when 20 mg/kg was administered as a single intraperitoneally dose on day 12 of gestation (about 4 times the recommended human dose on mg/m^2 basis). In rats administered single intraperitoneal doses of 50 mg/kg (about 10 times the recommended human dose on mg/m^2 basis) on day 14 of gestation, reduced prenatal and

postnatal brain size and permanent impairment of learning ability were observed. When administered to mice during the period of organogenesis, embryotoxicity was characterized by decreased fetal weight at 0.5 mg/kg/day (about 0.05 times the recommended human dose on mg/m^2 basis), and increased early and late resorptions. Decreased live litter sizes at 8 mg/kg/day were observed (approximately equal to the recommended human dose on mg/m^2 basis) (SkyePharma 2003).

In other studies, cytarabine has been shown to induce teratogenic effects in mice, rats, and chicks, including skeletal defects, cleft palate, cerebellar hypoplasia, microcytic renal changes, and retinal dysplasia. Percy et al. (1975) reports that treatment of pregnant ICR Swiss mice and Sprague-Dawley rats by subcutaneous injection of 12.5, 25 or 50 mg/kg bw/day cytosine arabinoside on 3 consecutive days, beginning GD 16 in mice and GD 18 in rats, resulted in segmental cerebellar hypoplasia and focal microcyctic renal cortical dysplasia in both rats and mice as well as retinal dysplasia in rats exposed to 50 mg/kg bw/day cytosine arabinoside. As reviewed in Shepard et al. (2004), rats administered oral doses of cytarabine on days 7-17 with doses up to 10 mg/kg bw and found fetal toxicity and digital defects. No effects were observed at the 1.6 mg/kg bw dose. Also summarized in Shepard et al. (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 bw on gestation days 7-12 in the mouse and 15-60 mg **[/kg bw]** 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 bw 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 bw 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 bw/day resulted in decreased fetal body weight at 8 mg/kg bw/day and increased cleft palate, renoureteral agenesis or hypoplasia and poly- or oligodactyly at 2 mg/kg bw/day dose (Ortega *et al.* 1991). Intraperitoneal treatment of Wistar rats with cytarabine at 50 mg/kg bw 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). Various skeletal changes of the forepaw and hindpaw occurred in the offspring of pregnant Jcl:ICR mice treated with a single intraperitoneal dose of 5 mg cytarabine/kg bw 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).

In other laboratory animal studies, a single intraperitoneal injection of a dose range of cytarabine (20-800 mg/kg) administered to pregnant Wistar rats 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). Development of the chick embryo was inhibited by an injection of 0.025 mg cytarabine/egg on Day 4 of incubation (Karnofsky and Lacon 1966). 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. Chick 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

Number of Cases, Publications, and Types of Cancer Treated

Cytarabine was administered to 164 female cancer patients (also called cases) during pregnancy identified from 50 case reports (50 cases), 19 case series (47 cases), 6 retrospective case series (30 cases), 5 retrospective surveys (28 cases), 2 retrospective cohort studies (6 cases) and 1 registry survey (3 cases) (Appendix C Table 11). Among these patients, cytarabine was primarily used to treat acute myelogenous leukemia (also called acute granulocytic leukemia; 99 cases) as well as acute promyelocytic leukemia (11 cases), erythroleukemia (1 case), acute lymphocytic leukemia (16 cases), acute myelogenous/acute lymphocytic leukemia (1 case) and acute leukemia (type not specified; 14 cases). In addition, cytarabine was used to treat chronic myelogenous leukemia (also called chronic granulocytic leukemia; 4 cases), Hodgkin lymphoma (1 case), non-Hodgkin lymphoma (10 cases), Burkitt lymphoma (3 cases), and granulocytic sarcoma of the breast (1 case).

A total of 164 singleton pregnancies (168 conceptuses) were exposed to cytarabine due to 4 patients having two pregnancies each (Schafer 1981, Plows 1982, Aviles and Niz 1988, Maurer *et al.* 2009). Cytarabine was administered during the first trimester in 34 pregnancies (34 conceptuses), and in the second and/or third trimester only in 121 pregnancies (125 conceptuses). The timing of exposure was not specified for 13 pregnancies (13 conceptuses). Cytarabine was predominantly administered as polytherapy (161 cases; 165 singleton pregnancies), and was administered as monotherapy to 3 cases (3 singleton pregnancies).

Termination of Pregnancy

A total of 17 pregnancies exposed to cytarabine were terminated by induced abortion, including 10 pregnancies exposed to cytarabine during the first trimester. Examination revealed a normal fetus from an induced abortion following first and second trimester exposure to cytarabine and co-exposure to daunorubicin, vincristine and 6-thioguanine (Lilleyman *et al.* 1977). No examination of the fetus was available for an induced abortus with normal chromosomes following exposure to cytarabine and 6-thioguanine during the first trimester (Maurer *et al.* 1971). No examination of the fetus was reported for the remaining 8 induced abortions following first trimester exposure to cytarabine polytherapy (Moreno *et al.* 1977, Fassas *et al.* 1984, Zemlickis *et al.* 1992b, Chelghoum *et al.* 2005).

Seven pregnancies exposed to cytarabine in the second and/or third trimester only were terminated by induced abortion. Examination revealed a normal fetus with an enlarged spleen in an induced abortus exposed in the second trimester to cytarabine and co-treatments daunorubicin, vincristine, 6-thioguanine and hydroxyurea (Doney *et al.* 1979). A normal fetus with abnormal chromosomes (i.e., a mosaicism of Trisomy group C) were observed in the induced abortus exposed in the second trimester to cytarabine and co-treatment 6-thioguanine (Maurer *et al.* 1971). No fetal data were provided for the remaining 5 induced abortions (Chelghoum *et al.* 2005).

Spontaneous Fetal Death

Spontaneous fetal death occurred in 20 singleton pregnancies exposed to cytarabine, including 4 spontaneous abortions occurring following first trimester exposure. No examination of the fetus was reported for these 4 spontaneous abortions which followed first trimester exposure to cytarabine and co-treatment with: daunorubicin only (1 pregnancy) (Zuazu *et al.* 1991), daunorubicin and all-trans retinoic acid (1 pregnancy) or daunorubicin and mitoxantrone (1 pregnancy) (Chelghoum *et al.* 2005) or vincristine and 6-thioguanine (1 pregnancy) (Zuazu *et al.* 1991).

Spontaneous fetal death occurred in 13 singleton pregnancies exposed to cytarabine in the second and/or third trimester only, including 3 spontaneous abortions. Examination of one spontaneous abortus revealed a normal fetus following second trimester exposure to cytarabine, daunorubicin and 6-thioguanine (Volkenandt *et al.* 1987). No examination of the fetus was reported for the remaining 2 spontaneous abortions, which were exposed in the second trimester to: cytarabine, vincristine and doxorubicin (Awidi *et al.* 1983), and cytarabine and daunorubicin (Greenlund *et al.* 2001).

Nine singleton pregnancies ended in stillbirth following exposure to cytarabine and all were exposed in the second and/or third trimester only. Normal fetuses were reported from 6 stillbirths that occurred following exposure to cytarabine polytherapy including: second trimester exposure to cytarabine and daunorubicin (Ali *et al.* 2003); second trimester exposure to cytarabine and 6-thioguanine (Plows 1982); second and third trimester exposure to cytarabine, daunorubicin and 6-thioguanine (O'Donnell *et al.* 1979); second and third trimester exposure to cytarabine, daunorubicin, mitoxantrone, and idarubicin (Reynoso and Huerta 1994), third trimester exposure to cytarabine, daunorubicin, 6-thioguanine and vincristine (Zuazu *et al.* 1991); and second trimester exposure to cytarabine, doxorubicin, and 6-thioguanine (Zemlickis *et al.* 1992b). Bruising and petechia was observed in multiple areas of one fetus that was normal at examination (Zemlickis *et al.* 1992b), and severe preeclampsia and toxemia preceded the stillbirth of another normal fetus (O'Donnell *et al.* 1979). An additional normal fetus at stillbirth was reported following exposure to cytarabine and idarubicin (Peres *et al.* 2001); timing of exposure was not specified. No examination of the fetus was reported for the remaining 4 stillbirths following exposure: in the second trimester to cytarabine and daunorubicin (Ali *et al.* 2003), in the second trimester to cytarabine, vincristine, daunorubicin, asparaginase, and methotrexate (intrathecal) (Molkenboer *et al.* 2005), and in the second and third trimesters to cytarabine, idarubicin and fludarabine (Paşa *et al.* 2009). The fourth stillbirth without examination of the fetus was preceded by oligohydramnios and early intrauterine growth restriction following second trimester exposure to cytarabine, cyclophosphamide, doxorubicin, ifosfamide, etoposide, vincristine, and rituximab (Peterson *et al.* 2010).

In addition, maternal deaths during pregnancy lead to fetal death in two singleton pregnancies. Maternal death at 23 weeks gestation revealed a normal fetus following exposure in the first and second trimesters to cytarabine, daunorubicin, vincristine, and 6-mercaptopurine (Feliu *et al.* 1988). A second maternal and fetal death occurred at approximately gestation week 24 following second trimester exposure to cytarabine, daunorubicin and vincristine (Greenlund *et al.* 2001); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 8 liveborn infants gestationally exposed to cytarabine. Major malformations were observed in 4 singleton pregnancies exposed during the first trimester. 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 first trimester to cytarabine, daunorubicin, and 6-thioguanine. 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 (Artlich *et al.* 1994). Atrial septal defect and bilateral loss of the radius and 5^{th} digit were reported following exposure during the first trimester to cytarabine, vincristine and doxorubicin (Ebert *et al.* 1997). Distal limb defects were reported in another infant following exposure during the entire pregnancy to cytarabine and 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). Major malformations were observed in a fourth infant following exposure during the first trimester to cytarabine monotherapy (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). Thus, the adjusted apparent rate of major malformations following exposure to cytarabine during the first trimester was 19% (4/21 conceptuses based on 19 liveborn infants and examination of the fetuses of 1 induced abortion and 1 maternal/fetal death) (**Table 36**).

Table 36: Major malformations diagnosed at birth possibly attributable to in utero exposure to cytarabine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Choanal stenosis; mild hypotelorism; severe brachycephaly; hypoplasia of the anterior cranial base, supra orbital structures, and naso-and orpharynx; premature closure of both coronal sutures and the metopic suture; bilateral 4 finger hands with hypoplastic thumbs; bilateral absent radii; small ostium secundum-type atrial septal defect.	19% (4/21)
	Distal limb defects: absence of medial 2 digits of both feet, absence of the distal phalanges of both thumbs, and remnant of right thumb was very hypoplastic	
	Atrial septal defect and bilateral loss of the radius and 5th digit	
	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	
2nd and/or 3rd only	None	0% (0/109)
NS[b]	None	0% (0/13)

[a] Data based on liveborn infants and examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths.
[b] NS, timing of exposure not specified.

Major malformations were observed in 4 infants following exposure to cytarabine in the second and/or third trimester only. Hypospadias was reported in a newborn exposed in the third trimester to cytarabine and daunorubicin (De Carolis *et al.* 2006). 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 second trimester to cytarabine and idarubicin. Down syndrome was diagnosed in a newborn exposed the in the second and third trimesters to cytarabine and daunorubicin (Roy *et al.* 1989). Polydactyly was reported in an infant exposed in the third trimester to cytarabine, daunorubicin and 6-thioguanine (Volkenandt *et al.* 1987); the infant had a family history of polydactyly. The malformations observed in these infants were not likely caused by exposure to cytarabine in the second and/or third trimesters due to the developmental stage at which these birth defects arise (generally in the period of organogenesis) and, in the case of polydactyly, the family history of polydactyly. Thus, the adjusted apparent rate of major malformations following second and/or third trimester exposure to cytarabine was 0% (0/109 conceptuses based on 100 liveborn infants and examination of the fetus of 2 induced abortions, 1

spontaneous abortion and 6 stillbirths). In addition, no major malformations were observed in the 12 liveborn infant and 1 stillbirth for which timing of exposure to cytarabine was not specified 0% (0/13 conceptuses).

Minor Malformations

Minor malformations were observed in two liveborn infants, and chromosome abnormalities were reported for one liveborn infant and one induced abortus, following gestational exposure to cytarabine. Congenital adherence of the iris to the cornea was diagnosed in a 2-year old infant, who had been exposed in the third trimester to cytarabine 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 second and third trimesters to cytarabine, daunorubicin and mitoxantrone. One additional health anomaly was observed: chromosomal breakage and a ring chromosome in an otherwise normal infant (Schleuning and Clemm 1987). As mentioned above, one induced abortus had chromosome abnormalities (Trisomy C group mosaicism) following second trimester exposure to cytarabine and 6-thioguanine (Maurer *et al.* 1971).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications and infant health effects were reported following gestational exposure to cytarabine. Polyhydramnios occurred in one singleton pregnancy (Artlich *et al.* 1994). Oligohydramnios occurred in three singleton pregnancies yielding liveborn infants (Garcia *et al.* 1999, Hansen *et al.* 2001, Peres *et al.* 2001, Matsuo *et al.* 2004, Peterson *et al.* 2010), including one pregnancy that also experienced reduction in amniotic fluid (Scherf and Price 1996). Eight pregnancies reported inhibited fetal growth following chemotherapy administration, including intrauterine fetal growth restriction (D'Emilio *et al.* 1989, Hsu *et al.* 1995, Claahsen *et al.* 1998, Garcia *et al.* 1999, Peres *et al.* 2001, Baumgartner *et al.* 2009, 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. (1994) and Scherf et al. (1996) appear to be the same case, but are considered as two separate case reports in this evaluation.]** Fetal cardiac effects were observed in 3 singleton pregnancies, including: cardiomyopathy (Baumgartner *et al.* 2009), fetal tachycardia (Garcia *et al.* 1999), and mild systolic dysfunction in both ventricles, mild dilation of the right ventricle and a mildly smaller left ventricle (Niedermeier *et al.* 2005). Transient cerebral ventriculomegaly occurred in one fetus experiencing cardiomyopathy (Baumgartner *et al.* 2009). In addition, fetal distress was reported in 4 pregnancies (Hsu *et al.* 1995, Veneri *et al.* 1996, Claahsen *et al.* 1998, Yucebilgin *et al.* 2004). Other pregnancy complications included: transient preeclampsia (treated and resolved, 1 case) (Bartsch *et al.* 1988), premature rupture of membranes (2 cases) (Volkenandt *et al.* 1987, Udink ten Cate *et al.* 2009), and spontaneous preterm labor (9 cases) (Doney *et al.* 1979, Taylor and Blom 1980, Tobias and Bloom 1980, Fassas *et al.* 1984, Reynoso *et al.* 1987, Hansen *et al.* 2001, Yucebilgin *et al.* 2004). Labor was induced in one case because the patient was seriously ill (Roy *et al.* 1989). In addition, severe preeclampsia and toxemia preceded the stillbirth of a normal fetus (O'Donnell *et al.* 1979).

There were 131 liveborn infants gestationally exposed to cytarabine. Early preterm delivery (<34 weeks) was reported for 28 infants, late preterm delivery (34 to <37 weeks) was reported for 26 infants, and 49 pregnancies were delivered at term. Data were insufficient to determine the timing of delivery of 28 infants. Of the 54 preterm infants, 17 infants were delivered via spontaneous vaginal delivery, 6 infants were delivered via induced vaginal, 26 infants delivered via C-section; data were insufficient to determine the route of delivery for the remaining 5 infants. Small for gestational age was determined for 17 newborns and 77 infants had normal body weight based on sex, gestational age and body weight

at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 37 newborns.

Breathing difficulties occurred in 14 newborns (Bartsch *et al.* 1988, Murray *et al.* 1994, Requena *et al.* 1995, Scherf and Price 1996, Veneri *et al.* 1996, Garcia *et al.* 1999, Delgado-Lamas and Garces-Ruiz 2000, De Carolis *et al.* 2006, Dilek *et al.* 2006, Lam 2006, Baumgartner *et al.* 2009), 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). Transient myelosuppression was reported in 14 newborns (Doney *et al.* 1979, Taylor and Blom 1980, de Souza *et al.* 1982, Murray *et al.* 1984, Reynoso *et al.* 1987, Aviles and Niz 1988, Hsu *et al.* 1995, Scherf and Price 1996, Peres *et al.* 2001, Matsuo *et al.* 2004, Baumgartner *et al.* 2009, Biener *et al.* 2009, Udink ten Cate *et al.* 2009). Jaundice was observed in 5 infants (Au-Yong *et al.* 1972, Dara *et al.* 1981, Hansen *et al.* 2001, Peres *et al.* 2001). One infant had polycythemia (Dara *et al.* 1981), another had low hemoglobin (Gulati *et al.* 1986). One infant suffered from meconium aspiration (Hansen *et al.* 2001), and the amniotic fluid was meconium-stained in 2 infants (Claahsen *et al.* 1998, Yucebilgin *et al.* 2004). Other health effects observed in newborns included: a moderate meningeal hemorrhage (Veneri *et al.* 1996), hyponatremia and hypoglycemia (1 infant) (Garcia *et al.* 1999), elevated creatinine and transient hepatopathy (1 infant) (Matsuo *et al.* 2004), and electrolyte abnormalities and hypoglycemia (1 infant) (Doney *et al.* 1979).

Infant Deaths

There were 3 infant deaths following gestational exposure to cytarabine. One infant, born at 28 weeks of gestation, developed respiratory distress and died at age 1 day (Dilek *et al.* 2006). A second infant born at 34 weeks of gestation died of septicemia at age 21 days, and another infant born at term died of gastroenteritis at 90 days of age (Aviles and Niz 1988).

Follow Up Evaluations

Follow up evaluations of offspring gestationally exposed to cytarabine were available for 80 infants at ages from 5 months to 15 years; age at follow up was not specified for two children (Requena *et al.* 1995, Chelghoum *et al.* 2005). Normal growth and development were reported for all but 4 children. 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). One child had a speech delay (Cardonick *et al.* 2010). 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 164 singleton pregnancies (168 conceptuses)(**Table 76**). Overall, the raw apparent rate of major malformations among all cytarabine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 6% (8/143 conceptuses based on 131 liveborn infants and examination of the fetuses of 3 induced abortions, 1 spontaneous abortion, 7 stillbirths, and 1 maternal/fetal death). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Of the 34 pregnancies (34 conceptuses) exposed to cytarabine during the first trimester, major malformations were reported in 4 liveborn infants. These major malformations appeared to have similar characteristics including: absent or hypoplastic digits of hand or feet (4 infants), missing radii (2

infants) or a missing bone in the lower leg (1 infant), and atrial septal defects (2 infants). These malformations are consistent with fore- and hindlimb malformations observed in mice and rats and heart defects reported in mice following exposure to cytarabine during organogenesis. It has been proposed that cytarabine induces cranial and skeletal malformations similar to those observed with exposure to methotrexate or cyclophosphamide and that all of these malformations may be due to an induction of apoptosis (Vaux *et al.* 2003). The apparent rate of major malformations following first trimester exposure to cytarabine was 19% (4/21 conceptuses based on 19 liveborn infants and examination of the fetus for 1 induced abortion and 1 maternal/fetal death). In contrast, there were no major malformations attributable to exposure to cytarabine in the second and/or third trimester only (0/109 conceptuses based on 100 liveborn infants and examination of the fetus of 1 induced abortion, 1 spontaneous abortion, and 6 stillbirths). No major malformations were observed in the conceptuses from pregnancies without timing of exposure to cytarabine (0/13 conceptuses based on 12 liveborn infants and examination of 1 stillbirth).

Spontaneous abortion (at <22 weeks of gestation) occurred in 4 pregnancies (4 of 114 conceptuses; 4%) and stillbirth occurred in 9 pregnancies (9 of 110 conceptuses; 8%) of all pregnancies exposed in the second and/or third trimester only (**Table 76**). As a reference point, the rate of stillbirths (defined as spontaneous fetal loss at >20 weeks gestation) was 0.3 to 0.4% in the general United States population (MacDorman 2005). The stillbirth rate for cytarabine was among the higher apparent rates when compared to other chemotherapy agents (see **Table 77** to **Table 81**). While exposure to cytarabine may be a factor in the higher rate of stillbirths, the disease state of acute leukemia has been reported to lead to higher rates of spontaneous fetal loss (reviewed in (Fassas *et al.* 1984)). It has also been hypothesized that the condition of acute leukemia during pregnancy may increase the risk of spontaneous fetal death (Brenner *et al.* 2012).

5.13 DACARBAZINE

5.13.1 Mechanism of Action, Route of Administration, and Indications

Table 37: Pharmacology of dacarbazine in adult humans	
Molecular weight:	182.186
Protein binding:	~5%
Metabolism:	Extensively hepatic to the active metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide]
Half-life elimination:	Biphasic: Initial: 20-40 minutes, Terminal: 5 hours;. Patients with renal and hepatic dysfunction: Initial: 55 minutes, Terminal: 7.2 hours
Distribution:	Vd: 0.6 L/kg, exceeding total body water; suggesting binding to some tissue (probably liver)
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Urine (~40% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum,; Vd, volume of distribution.	

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. Additional information on the pharmacology of dacarbazine is located in **Table 37**.

Dacarbazine is indicated for treatment of melanoma and as a second-line therapy for Hodgkin disease (Bedford 2007).

5.13.2 Evidence of Placental and Breast Milk Transport

Placental transport in humans is not known. In animal studies, dacarbazine has been administered in combination therapy to pregnant baboons in an effort to measure the concentration of the drugs in maternal and fetal serum (Van Calsteren *et al.* 2010b). However, the authors were unable to assess the dacarbazine levels due to a lack of sample volume (Van Calsteren *et al.* 2010b).

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 was teratogenic when administered at 20 times the recommended human daily dose **[dose not indicated]** on day 12 of gestation (Bedford 2007).

In the peer-reviewed literature, dacarbazine was reported to induce 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 bw) (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 bw 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). Dacarbazine induced malformations in rat fetuses when administered during the period of organogenesis to pregnant

Sprague-Dawley rats (Thompson *et al.* 1975). Fetal skeletal anomalies, including delayed ossification and malformations, were observed at all dacarbazine dose levels evaluated (30, 50, and 70 mg/kg bw/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 bw) (Thompson *et al.* 1975). Neonatal survival rates were lowered when dacarbazine exposure (7.5, 15, or 30 mg/kg bw/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 bw (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 bw dose group, while the lower doses (2.5 or 5 mg/kg bw/day) were reported to have no adverse effects (Thompson *et al.* 1975).

5.13.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Dacarbazine was administered to 55 cancer patients (also called cases) during pregnancy identified from 9 case reports (9 cases), 4 case series (9 cases), 1 retrospective case series (10 cases), 2 retrospective surveys (6 cases), 2 retrospective cohort studies (2 cases) and 1 registry survey (20 cases) (Appendix Table 12). Dacarbazine was used to treat Hodgkin lymphoma (45 cases), melanoma (9 cases), and soft tissue sarcoma (2 cases).

A total of 57 pregnancies (58 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 first trimester in 9 pregnancies, and in the second and/or third trimester only in 48 pregnancies (49 conceptuses due to one set of twins). The total number of pregnancies exposed in the second and/or third trimester included a case series where age at initiation of exposure was reported as a range of 12-33 weeks of gestation (mean=22 weeks) (Jameel and Jamil 2007); it was assumed that these two pregnancies were likely exposed to dacarbazine in the second and/or third trimester only. Dacarbazine was administered as monotherapy to 5 cases (5 conceptuses) and as polytherapy to 52 pregnancies (54 conceptuses).

Termination of Pregnancy

Termination of pregnancy was reported for three pregnancies exposed to dacarbazine. No malformations were observed in an fetus of an induced abortion at gestation week 18 following exposure in the first trimester to dacarbazine, nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, and vinblastine (Peres *et al.* 2001); the fetus did have toxic degenerative changes in the liver and kidneys. In addition, the placenta had villus degeneration and vascular toxic degeneration (Peres *et al.* 2001). Induced abortion ended two additional pregnancies following second trimester exposure to dacarbazine monotherapy (Zemlickis *et al.* 1992b) or dacarbazine in combination with doxorubicin, bleomycin and vinblastine; no fetal data were provided.

Spontaneous Fetal Death

There were 2 stillbirths following gestational exposure to dacarbazine. Stillbirth occurred at gestation week 22 in one pregnancy following second trimester exposure to dacarbazine, doxorubicin and cyclophosphamide (Jameel and Jamil 2007); no examination of the fetus was reported. Stillbirth occurred in the 8th month of pregnancy following second and third trimester exposure to dacarbazine, bleomycin, doxorubicin and vinblastine (Dilek *et al.* 2006); no fetal data were reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in two infants with gestational exposure to dacarbazine .

Table 38: Major malformations diagnosed at birth possibly attributable to in utero exposure to dacarbazine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Floating thumb malformation, which consisted of partial agenesis of a metacarpal bone and hypoplasia of two phalanges	13% (1/8)
2nd and/or 3rd only	None	0% (0/45)

[a] Data based on liveborn infants as well as examination for the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

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 first trimester to dacarbazine, bleomycin, doxorubicin, and vinblastine. Thus, the apparent rate of major malformations following exposure to dacarbazine in the first trimester was 11% (1/9 conceptuses based on 8 liveborn infants and examination of the fetus of 1 induced abortion) (Table 38).

Syndactyly of the 4th and 5th fingers was reported in an infant with exposure in the second and third trimesters to dacarbazine, bleomycin, doxorubicin, and vinblastine (Cardonick *et al.* 2010). Since skeletal malformations are induced during the period of organogenesis in the first trimester, it is unlikely that this malformation was caused by exposure to dacarbazine in the second and third trimesters only. Thus, the adjusted apparent rat of major malformations following exposure to dacarbazine in the second and third trimesters was 0% (0/45 conceptuses based on 45 liveborn infants).

Minor Malformations

Minor malformations were observed in two liveborn infants. Plagiocephaly, a minor malformation, was reported in one infant with exposure in the second and third trimesters to dacarbazine, bleomycin, doxorubicin, and vinblastine (Cardonick *et al.* 2010). In addition, one infant had microphthalmia and severe hypermetropia, which was diagnosed at age 1 year (Li *et al.* 2007); the pregnancy was exposed in the 1st and 2nd trimesters and co-exposed to carmustine, cisplatin and tamoxifen (Li *et al.* 2007).

Pregnancy Complications and Newborn Health

The only pregnancy complication reported for gestational exposure to dacarbazine was intrauterine growth restriction (2 fetuses; (Fadilah *et al.* 2006, Gottschalk *et al.* 2009)).

There were 53 liveborn infants gestationally exposed to dacarbazine. Early preterm delivery (<34 weeks) was reported for 5 infants, late preterm delivery (34-36 weeks) was reported for 9 infants, and 14 infants were delivered at term. Data were insufficient to determine gestational age at birth for 25 infants. Of the preterm deliveries, 6 infants were delivered via spontaneous vaginal birth and 8 infants were born via C-section. Small for gestational age was determined for 7 infants (Klepfish *et al.* 2000, Dilek *et al.* 2006, Fadilah *et al.* 2006, Gottschalk *et al.* 2009, Pages *et al.* 2010) and 40 infants had normal

birth weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for the remaining 6 infants.

Adverse health effects were observed in 3 infants gestationally exposed to dacarbazine. Hypoglycemia was reported in 3 infants (Cardonick *et al.* 2010). One preterm newborn suffered from respiratory distress, bronchopulmonary dysplasia, a cytomegalovirus infection and necrotizing enterocolitis (Pages *et al.* 2010).

Infant Deaths

No infant deaths were reported following gestational exposure to dacarbazine.

Follow Up Evaluations

Follow up evaluations were reported for 39 infants ranging in age from 4 months to 16 years, including 2 children 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 57 pregnancies (58 conceptuses due to one set of twins) (**Table 77**). Overall, the raw apparent rate of major malformations among all dacarbazine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 4% (2/54 based on 53 liveborn infants and examination of the fetus of 1 induced abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in one infant with first trimester exposure to dacarbazine. 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). Distal limb skeletal malformations have also been reported in developmental toxicity studies of rats and rabbits following exposure to dacarbazine during organogenesis. Thus, the apparent rate of major malformations following exposure to dacarbazine during the first trimester was 11% (1/9 conceptuses). One major malformation was observed in one infant with exposure in the second and third trimesters to dacarbazine in polytherapy: syndactyly of the 4^{th} and 5^{th} fingers (Cardonick *et al.* 2010). However, the occurrence of syndactyly was unlikely to have resulted from chemotherapy exposure after the period of organogenesis (during the first trimester). Therefore, the adjusted apparent rate of major malformations possibly attributable to exposure to dacarbazine in the second and/or third trimester only is 0% (0/45 conceptuses based on 45 liveborn infants).

5.14 DAUNORUBICIN

Table 39: Pharmacology of daunorubicin in adult humans	
Molecular weight:	527.5231
Protein binding:	**[Information not located]**
Metabolism:	Primarily hepatic to daunorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides
Half-life elimination:	Distribution: 2 minutes; Elimination: 14-20 hours; Terminal: 18.5 hours; Daunorubicinol plasma half-life: 24-48 hours
Distribution:	Many body tissues, particularly the liver, kidneys, lung, spleen, and heart; not into CNS; crosses placenta; Vd: 40 L/kg
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (40%); urine (~25% as unchanged drug and metabolites)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CNS, central nervous system; Vd, volume of distribution	

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 is administered via intravenous injection. Additional information on the pharmacology of daunorubicin is located in **Table 39**.

It 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 in humans. Daunorubicin was detected in liver (0.015 ng/mL), kidney (0.021 ng/mL) and lung (0.02 ng/mL) tissues of a fetus that died at 29.5-30.5 weeks gestation (Germann *et al.* 2004). Tissue samples were collected at one time point after administration of the drug to the mother (Germann *et al.* 2004); the authors stated the interval between infusion and measurements was 48 hours + 5 days.

There are no published cases of breast milk transfer of daunorubicin in humans.

5.14.3 Laboratory Animal Developmental Toxicity

Information in the product label describes daunorubicin as embryotoxic and teratogenic in rabbits and rats (Bedford 2008); **[timing of exposures were not identified, but were presumed to be during organogenesis]**. Pregnant rats administered daunorubicin at 0.05 mg/kg bw (~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, and orrachischisis; **[timing and route of drug administration not indicated]**. 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 bw/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 through 15, daunorubicin

caused severe maternal toxicity and embryolethality at 2.0 mg/kg bw/day (~1/3rd of the recommend maximal human dose per body surface area), 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. Malformations were observed in 45% of rat fetuses following administration of daunorubicin to pregnant rats at doses of 1 to 3 mg/kg bw via intravenous injections on gestation day 7 or at 3 mg/kg bw/day via intraperitoneal injection for 3 days during organogenesis (reviewed in Shepard and Lemire 2004). The malformations included ocular anomalies, and defects of the heart, kidney and brain. Malformations were observed in 16% of rat fetuses, when 1 mg daunorubicin/kg bw 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 bw/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 bw administered to their mothers during pregnancy (Shepard and Lemire 2004).

5.14.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Daunorubicin was administered to 107 female cancer patients (also called cases) during pregnancy identified from 31 case reports (31 cases), 18 case series (37 cases), 1 retrospective case series (4 cases), 6 retrospective surveys (31 cases), 2 retrospective cohort studies (2 cases), and 1 registry survey (2 cases) (Appendix C Table 13). Among the 107 cases, daunorubicin was used to treat acute lymphocytic leukemia (24 cases), acute myelogeneous leukemia (67 cases), acute promyelocytic leukemia (8 cases), acute leukemia (type not specified; 4 cases), chronic myelogenous leukemia (also called chronic granulocytic leukemia, 2 cases), granulocytic sarcoma of the breast (1 case) and one case in which cancer type was not specified.

A total of 108 conceptuses were exposed to daunorubicin, including one twin pregnancy (Turchi and Villasis 1988). Daunorubicin was administered during the first trimester in 18 singleton pregnancies (18 conceptuses) and in the second and/or third trimester only in 83 pregnancies (84 conceptuses, including one set of twins). Timing of exposure was not specified for 5 singleton pregnancies (5 conceptuses); however, it was assumed that one of these pregnancies was likely exposed in the second and/or third 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 in the second and/or third trimester were calculated to be 84 pregnancies (85 conceptuses) and timing of exposure was not specified for 4 singleton pregnancies (4 conceptuses).

Termination of Pregnancy

Induced abortion terminated 14 singleton pregnancies (14 conceptuses) following gestational exposure to daunorubicin. No examination of the fetus was reported for 9 induced abortuses exposed to daunorubicin during the first trimester (Zemlickis *et al.* 1992b, Chelghoum *et al.* 2005, Molkenboer *et al.* 2005).

Normal fetuses were observed in two induced abortions following exposure in the second trimester to daunorubicin, cytarabine, vincristine, hydroxyurea, and 6-thioguanine (Doney *et al.* 1979) or

daunorubicin, cytarabine, 6-thioguanine, and vincristine (Lilleyman *et al.* 1977). No fetal data were reported for the remaining three induced abortions (Chelghoum *et al.* 2005).

Spontaneous Fetal Death

Spontaneous fetal death occurred in 13 singleton pregnancies (13 conceptuses) exposed to daunorubicin. Spontaneous abortion occurred in 4 singleton pregnancies exposed during the first trimester and no examination of fetuses were reported (Zuazu *et al.* 1991, Chelghoum *et al.* 2005). The spontaneous abortions followed exposure to the following polytherapy during the first trimester: daunorubicin and cytarabine (1 embryo) or daunorubicin, cytarabine, 6-thioguanine, and vincristine (1 embryo) (Zuazu *et al.* 1991) or daunorubicin, cytarabine and all-trans retinoic acid (1 embryo) or daunorubicin, cytarabine and mitoxantrone (1 embryo) (Chelghoum *et al.* 2005).

Spontaneous fetal death occurred in 10 singleton pregnancies following exposure to daunorubicin in the second and/or third trimester only, including 2 spontaneous abortions and 8 stillbirths. A normal fetus was reported following a spontaneous abortion at 20 weeks of gestation (Volkenandt *et al.* 1987); this pregnancy was exposed in the second trimester to daunorubicin and cytarabine. No examination of the fetus was reported for the remaining spontaneous abortion occurring in the second trimester to the following exposure to daunorubicin and cytarabine (Greenlund *et al.* 2001). Stillbirth was reported in 8 singleton pregnancies (8 conceptuses) following second and/or third trimester only, including 4 normal fetuses. A normal fetus was reported from a stillbirth following second trimester exposure to daunorubicin and cytarabine (Ali *et al.* 2003). A stillbirth of a normal fetus was associated with maternal preeclamptic toxemia following second trimester treatment with daunorubicin, cytarabine and 6-thioguanine (O'Donnell *et al.* 1979). A stillborn fetus had no obvious malformations following exposure in the second trimester to daunorubicin and cytarabine, followed by mitoxantrone and cytarabine in the second and third trimesters, then exposed to idarubicin and cytarabine in the third trimester (Reynoso and Huerta 1994). A fourth stillbirth of a macroscopically normal fetus followed third trimester exposure to daunorubicin, cytarabine, 6-thioguanine, and vincristine (Zuazu *et al.* 1991). No examination of the fetus was reported for the 4 remaining stillbirths which occurred following exposure: in the second trimester to daunorubicin and cytarabine (Ali *et al.* 2003), in the second trimester to daunorubicin, vincristine, asparaginase cytarabine and intrathecal methotrexate (Molkenboer *et al.* 2005), in the second and/or third trimester only exposure to daunorubicin and vincristine (Jameel and Jamil 2007), or in the third trimester exposure to daunorubicin monotherapy (Germann *et al.* 2004).

Three singleton pregnancies ended in maternal death following daunorubicin exposure. A normal fetus was reported for a maternal/fetal death that occurred at gestation week 23 following first and second trimester exposure to daunorubicin, cytarabine, vincristine and 6-mercaptopurine (Feliu *et al.* 1988). No fetal data were reported for two maternal and fetal deaths occurring following exposure during the second trimester to daunorubicin, vincristine and cytarabine (Greenlund *et al.* 2001) or to daunorubicin monotherapy (Zuazu *et al.* 1991).

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations occurred in 4 liveborn infants exposed in utero to daunorubicin, including one infant exposed during the first trimester. One infant had skeletal malformations of the distal limbs and cranium, and a cardiac defect following exposure during the first trimester to daunorubicin and 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. Thus, the apparent rate of major malformations following exposure to daunorubicin during the first trimester was 20% (1/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 maternal/fetal death) (**Table 40**).

Table 40: Major malformations diagnosed at birth possibly attributable to in utero exposure to daunorubicin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Mild hypotelorism, severe brachycephaly; hypoplasia of the anterior cranial base; supra-orbital structure, and naso-and orpharynx; premature closure of both coronal sutures and the metopic suture; bilateral four finger hands with hypoplastic thumbs; bilateral absent radii; small ostium secundum type atrial septal defect	20% (1/5)
2nd and/or 3rd only	None	0% (0/75)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths

Major malformations were reported in 3 liveborn infants following exposure to daunorubicin in the second and/or third trimester only. Polydactyly on one foot was reported in an infant exposed in the second trimester to daunorubicin, cytarabine and 6-thioguanine (Volkenandt *et al.* 1987); this malformation was likely due to family history of polydactyly. Down syndrome was reported in one infant (Roy *et al.* 1989) following second trimester exposure to daunorubicin, cytarabine and 6-thioguanine. Hypospadias was reported in one newborn following exposure in the third trimester to daunorubicin and cytarabine (De Carolis *et al.* 2006). It is unlikely that daunorubicin exposure in the second or third trimester only resulted any of these 3 major malformations. Distal limb skeletal malformations would have been induced by exposure to daunorubicin during the period of organogenesis; however, it is most likely that the incidence of polydactyly was due to a family history of this condition (Volkenandt *et al.* 1987). Down syndrome induced by chemical exposure would have been due to an exposure prior to conception. Regarding hypospadias, penile development is complete by approximately gestation week 15; however, the infant with hypospadias was exposed to daunorubicin in the third trimester. Thus, the adjusted apparent rate of major malformations following exposure to daunorubicin in the second and/or third trimester only was 0% (0/75 conceptuses based on 68 liveborn infants and examination of fetus of 2 induced abortuses, 1 spontaneous abortus and 4 stillbirths).

Minor Malformations

Three liveborn infants had minor malformations following in utero exposure to daunorubicin. A hemangioma was reported in an infant with second and third trimester exposure to daunorubicin, methotrexate, vincristine, cyclophosphamide, asparaginase, and 6-mercaptopurine (Van Calsteren *et al.* 2010a). 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 second trimester to daunorubicin and cytarabine, followed by third trimester exposure to mitoxantrone and cytarabine. Congenital adherence of the lens to the cornea was diagnosed at age 2 in a child who was exposed in the third trimester to daunorubicin, cytarabine and 6-thioguanine (Reynoso *et al.* 1987). In addition, chromosomal breakage and a ring chromosome were observed in an otherwise normal newborn (Schleuning and Clemm 1987).

Pregnancy Complications and Newborn Health

Several pregnancy complications were reported following exposure to daunorubicin. Intrauterine growth restriction was reported for 5 fetuses (Morishita *et al.* 1994, Hsu *et al.* 1995, Garcia *et al.* 1999), including one fetus with poor growth (Roy *et al.* 1989) and two fetuses with a preterm cessation of fetal growth (Murray *et al.* 1994, Scherf and Price 1996). Polyhydramios occurred in one pregnancy (Artlich *et al.* 1994), while 4 pregnancies experienced reductions in amniotic fluid (Scherf and Price 1996, Garcia *et al.* 1999, Hansen *et al.* 2001, Matsuo *et al.* 2004). Fetal tachycardia was reported in one pregnancy (Garcia *et al.* 1999). Fetal distress occurred in 2 pregnancies (Hsu *et al.* 1995, Ali *et al.* 2009a). Premature rupture of membranes occurred in 5 cases (Okun *et al.* 1979, Morishita *et al.* 1994, Ali *et al.* 2009a, Udink ten Cate *et al.* 2009), including in one case likely caused by medical evaluation of the placenta (Volkenandt *et al.* 1987). Spontaneous preterm labor occurred in 7 cases (Doney *et al.* 1979, Tobias and Bloom 1980, Sanz and Rafecas 1982, Reynoso *et al.* 1987, Hansen *et al.* 2001). In one case, labor was induced because the mother was seriously ill (Roy *et al.* 1989). As mentioned above, toxemia due to preeclampsia caused one stillbirth (O'Donnell *et al.* 1979).

A total of 77 liveborn infants were gestationally exposed to daunorubicin. Early preterm delivery (<34 weeks) was reported for 25 infants, late preterm delivery (34 to <37 weeks) was reported for 17 infants and 21 infants were delivered at term. Data were not sufficient to determine gestational age at delivery for 14 infants. Of the preterm infants, 12 infants were born via spontaneous vaginal delivery, 5 infants were born via induced vaginal delivery and 21 infants were born via C-section. Route of delivery was not specified for 4 infants. Small for gestational age was determined for 8 infants and 47 infants were normal weight based on sex, gestational age and body weight at birth. Data were insufficient to determine small for gestational age for the remaining 22 infants.

Breathing difficulties occurred in a total of 13 newborns (Murray *et al.* 1994, Scherf and Price 1996, Garcia *et al.* 1999, Hansen *et al.* 2001, De Carolis *et al.* 2006, Dilek *et al.* 2006, Papantoniou *et al.* 2008, Ali *et al.* 2009a), including one infant with bilateral pneumothorax and seizures (Cantini and Yanes 1984) and another infant with choanal stenosis and pneumothorax (Artlich *et al.* 1994). One of the infants with respiratory distress also had meconium aspiration (Hansen *et al.* 2001). Another infant with respiratory distress died of pulmonary hemorrhage on day 1 (Dilek *et al.* 2006). Transient myelosuppression was observed in 10 infants and all were born preterm (Doney *et al.* 1979, Okun *et al.* 1979, Murray *et al.* 1994, Reynoso and Huerta 1994, Hsu *et al.* 1995, Scherf and Price 1996, Garcia *et al.* 1999, Matsuo *et al.* 2004, Biener *et al.* 2009, Udink ten Cate *et al.* 2009). Jaundice was observed in 3 infants (Hansen *et al.* 2001, Matsouka *et al.* 2008, Papantoniou *et al.* 2008). Hyponatremia (sodium deficiency) and hypoglycemia were observed in a preterm infant who experienced seizures and an intracranial hemorrhage (Garcia *et al.* 1999). Another infant had electrolyte abnormalities and hypoglycemia (Doney *et al.* 1979). One newborn was treated for congestive heart failure (Okun *et al.* 1979); this infant was also hydropic, and had an enlarged liver and spleen, slight cardiomegaly, and a petechial rash on her abdomen and extremities. Other health effects included: pale color, tone-decreased and lethargy (Ali *et al.* 2009c), hepatopathy and elevated creatinine (Matsuo *et al.* 2004), seizures (Cantini and Yanes 1984), a premature appearance (Tobias and Bloom 1980) and a urinary tract infection (Udink ten Cate *et al.* 2009). A set of twins was treated for diarrhea and the female twin had hypotonia (Turchi and Villasis 1988). One placenta had myeloblastic infiltration (Volkenandt *et al.* 1987)

Infant Deaths

One early preterm infant with respiratory distress died of pulmonary hemorrhage on day 1 (Dilek *et al.* 2006).

Follow Up Evaluations

Follow up evaluations were available for 52 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 for 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 107 pregnancies (108 conceptuses, including one set of twins) (**Table 78**). Overall, the apparent rate of major malformations among all daunorubicin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 5% (4/85 conceptuses based on 77 liveborn infants and examination of the fetus of 2 induced abortuses, 1 spontaneous abortus, 4 stillbirths and 1 maternal/fetal death). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in only one liveborn infant following gestational exposure to daunorubicin, cytarabine and vincristine in the first trimester (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. The skeletal malformations observed were consistent with malformations observed in other human conceptuses exposed to cytarabine polytherapy as well as developmental toxicity studies of cytarabine in laboratory animals (see Section 5.12 Cytarabine). Similarly, aberrant cardiac development has been documented in developmental toxicity studies of daunorubicin in laboratory animals. Thus, the apparent rate of major malformations following exposure to daunorubicin during the first trimester was 20% (1/5 conceptuses based on 4 liveborn infants and examination of the fetus of one maternal and fetal death).

Major malformations were observed in three liveborn infants following exposure to daunorubicin in the second and/or third trimester only. However, it was unlikely that exposure to daunorubicin in the second trimester was likely to cause Down syndrome (Roy *et al.* 1989) or polydactyly in an infant with a family history of polydactyly (Volkenandt *et al.* 1987), or hypospadias following third trimester exposure (De Carolis *et al.* 2006). An infant had polydactyly on the right foot and a family history of polydactyly (Volkenandt *et al.* 1987). Thus, the adjusted apparent rate of major malformations following exposure to daunorubicin in the second and/or third trimester only was 0% (0/75 conceptuses based on 68 liveborn infants and examination of the fetus of 2 induced abortuses, 1 spontaneous abortus and 4 stillbirths). No major malformations were observed in the 5 liveborn infants exposed to daunorubicin for which timing of exposure was not specified (0/5 conceptuses based on 5 liveborn infants).

There were a few other notable pregnancy outcomes following gestational exposure to daunorubicin. The apparent rate of spontaneous abortion following exposure to daunorubicin during the first trimester was 50% (4/8 conceptuses, not including terminations of pregnancy (9 conceptuses) or maternal/fetal deaths (1 conceptus). It has also been hypothesized that acute leukemia during pregnancy may increase the risk of spontaneous fetal loss (Brenner *et al.* 2012). Daunorubicin is reported to cause cardiotoxicity in adult cancer patients administered the drug. Fetal tachycardia was reported in one singleton pregnancy (Garcia *et al.* 1999) and one newborn was treated for congestive heart failure (Okun *et al.* 1979).

5.15 DOCETAXEL

5.15.1 Mechanism, route of administration, and indications

Table 41: Pharmacology of docetaxel in adult humans	
Molecular weight:	807.885
Protein binding:	~94% to 97%, primarily to alpha1-acid glycoprotein, albumin, and lipoproteins
Metabolism:	Hepatic; oxidation via CYP3A4 to metabolites
Half-life elimination:	Terminal: ~11 hours
Distribution:	Extensive extravascular distribution and/or tissue binding; Vd: 80-90 L/m^2, Vdss: 113 L (mean steady state)
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (~75%, <8% as unchanged drug); urine (<5%)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; Vd, volume of distribution; Vdss, volume of distribution at steady state	

Docetaxel is a semi-synthetic analog of paclitaxel, which is isolated from the needles of the European yew tree. Docetaxel inhibits microtubule function by binding to microtubules and promoting 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 of each drug on microtubule dynamics (reviewed in (Herbst and Khuri 2003)). Docetaxel is administered intravenously. Additional information on the pharmacology of docetaxel is located in **Table 41**.

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. (2010c) reported that 100 mg/m^2 docetaxel administered intravenously to the mother was not detected in fetal plasma in the first 76 hours after drug infusion. Docetaxel was detected just above the lower limit of quantification in 3 of 10 amniotic fluid samples and fetal tissues contained 5%-50% of maternal tissue concentrations of docetaxel three hours after infusion. Levels in maternal and fetal tissues were equal after 24 and 76 hours (Van Calsteren *et al.* 2010c).

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 bw/d in rats and 3.0 mg/kg bw/d in rabbits when administered during the period of organogenesis (1/50 and 1/300, respectively, the daily maximum recommended human dose on a mg/m^2 basis). Docetaxel did not induce teratogenic effects in fetuses, even at the highest

doses intravenously administered to rat (1.8 mg/m^2/d) or rabbit dams (1.2 mg/m^2/d) (abstract by (Brunel *et al.* 1995)).

5.15.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Docetaxel was administered to 21 female cancer patients (also called cases) during pregnancy identified from 8 case reports (8 cases), 2 case series (3 cases), 1 retrospective case series (4 cases) and 1 registry survey (6 cases) (Appendix C Table 14). Among these patients, docetaxel was used to treat cancers of the breast (19 cases), lung (1 case) and ovary (1 case).

A total of 21 singleton pregnancies (21 conceptuses) were exposed to docetaxel. Docetaxel was administered during the first trimester in one pregnancy (2 conceptuses), and in the second and/or third trimester in 19 pregnancies (19 conceptuses). Docetaxel was used as monotherapy in 8 cases, including 6 cases were it following treatment with vinorelbine (1 case), doxorubicin and cyclophosphamide (2 cases) or doxorubicin, cyclophosphamide and paclitaxel (3 cases). It was used as polytherapy in 13 cases.

Termination of Pregnancy

No terminations of pregnancy were reported following gestational exposure to docetaxel.

Spontaneous Fetal Death

No spontaneous abortions or stillbirths were reported were reported following gestational exposure to docetaxel.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in two liveborn infants exposed to docetaxel. No major malformations were observed in the two liveborn infants exposed to docetaxel during the first trimester.

Table 42. Major malformations diagnosed at birth possibly attributable to in utero exposure to docetaxel

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses)
During 1st	None	0% (0/2)
2nd and/or 3rd only	Pyloric stenosis	5% (1/19)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations were observed in two infants exposed to docetaxel in the second and/or third trimester only. Pyloric stenosis was reported in a newborn exposed in the second and third trimester to docetaxel monotherapy, following polytherapy with doxorubicin, cyclophosphamide, and paclitaxel (Cardonick *et al.* 2010). In another infant, left-sided ventriculomegaly was diagnosed prenatally prior to exposure to docetaxel and cisplatin in the second trimester (Rouzi *et al.* 2009). Ventriculomegaly increased after exposure to docetaxel polytherapy , 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). Docetaxel polytherapy was not the cause of the ventriculomegaly because it was diagnosed prior to administration of chemotherapy. Thus, the adjusted rate of major malformations caused by second and/or third trimester only exposure to docetaxel was (1/19 conceptuses based on 19 liveborn infants) (**Table 42**).

Minor Malformations

Two infants had minor malformations that resolved without treatment following gestational exposure to docetaxel. Suspected holoprosencephaly was diagnosed in a newborn exposed during the second and third trimesters to docetaxel monotherapy following exposure to doxorubicin and cyclophosphamide (Cardonick *et al.* 2010); at follow up evaluation at age 2.6 years, this infant was normal with prominent lateral ventricles. Another infant had mild hydrocephalus, which was diagnosed prenatally at approximately gestation week 17 (second trimester), three weeks after initiation of doxorubicin and cyclophosphamide, and prior administration of docetaxel monotherapy beginning at gestation week 26 through the third trimester (Potluri *et al.* 2006); this case of mild hydrocephalus regressed spontaneously over several months.

Pregnancy Complications and Newborn Health

Pregnancy complications were reported in a few cases. Reductions in amniotic fluid occurred in four fetuses, including in one fetus where anhydramnios was diagnosed prior to chemotherapy (Rouzi *et al.* 2009) Two pregnancies with anhydramnios also had intrauterine growth restriction, and co-exposed to trastuzumab in the second (Sekar and Stone 2007, Gottschalk *et al.* 2011) or second and third trimester (Sekar and Stone 2007). A fourth fetus had oligohydramnios and intrauterine growth restriction in combination with placental insufficiency (Massey Skatulla *et al.* 2012); this fetus also suffered from a pathological fetal heart rate, reverse flow in the umbilical artery, fetal centralization and negative A wave in the venous duct. Preeclampsia was reported for two pregnancies (Potluri *et al.* 2006), including one case with preeclampsia and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome (Massey Skatulla *et al.* 2012).

A total of 21 liveborn infants were gestationally exposed to docetaxel. Early preterm delivery (<34 weeks) was reported for 4 infants, late preterm delivery (34 to <37 weeks) was reported for 7 infants, and 4 infants were delivered at term. Gestational age at delivery was not specified for 6 pregnancies. Of the preterm infants, 2 infants were delivery via spontaneous vaginal delivery and 9 infants were delivered via C-section. Small for gestational age was determined for 4 infants and 14 infants had normal body weight based on sex, gestational age and body weight at delivery (Olsen *et al.* 2010). Data were not sufficient to determine small for gestational age in the remaining 3 infants.

Only one newborn had health issues. Transient myelosuppression was reported for two infants: neutropenia (1 infant) (Cardonick *et al.* 2010) and thrombocytopenia (1 infant) (Massey Skatulla *et al.* 2012). The infant with thrombocytopenia also required cardiopulmonary resuscitation, and had hypoglycemia and a single focal convulsion (Massey Skatulla *et al.* 2012).

Infant Deaths

No infant deaths were reported.

Follow Up Evaluations

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 21 singleton pregnancies (21 conceptuses) (**Table 79**). Overall, the apparent rate of major malformations among all docetaxel-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 10% (2/21 conceptuses based on 21 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). There were no major malformations following exposure to docetaxel during the first trimester. Thus, the apparent rate of major malformations was 0% (0/2 conceptuses based on 2 liveborn infants). Only one major malformation following exposure in the second and third trimesters could be possibly attributable to docetaxel: pyloric stenosis. The remaining malformation (ventriculomegaly) was observed prior to administration of chemotherapy, and, therefore, was not attributable to docetaxel polytherapy in the second and third trimester. Thus, the adjusted rate of major malformations following exposure to docetaxel in the second and/or third trimester was 5% (1/19 conceptuses based on 19 liveborn infants).

Of the four singleton pregnancies that experienced reductions in amniotic fluid following exposure to docetaxel, anhydramnios was likely caused by the co-administration of trastuzumab in two pregnancies (Sekar and Stone 2007, Gottschalk *et al.* 2011) and a third pregnancy experienced placental insufficiency (Massey Skatulla *et al.* 2012). Infants exposed to docetaxel had a high rate of small for gestational age birth weights (**Table 79**).

5.16 DOXORUBICIN

5.16.1 Mechanism of Action, Route of Administration, and Indications

Table 43: Pharmacology of doxorubicin in adult humans	
Molecular weight:	543.5221
Protein binding:	70% to 76% in plasma
Metabolism:	Primarily hepatic to doxorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides
Half-life elimination:	Distribution: 5-10 minutes; Elimination: 1-3 hours (doxorubicin), 3-3.5 hours (metabolites); Terminal: 17-48 hours; Female: 35 hours
Distribution:	Vd: 809-1214 L/m^2; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (~40% to 50% as unchanged drug); urine (~5% to 12% as unchanged drug and metabolites)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CNS, central nervous system; Vd, volume of distribution	

Doxorubicin (adriamycin) is an anthracycline antibiotic that intercalates between DNA base pairs inhibiting DNA and RNA synthesis. The cytoxic properties of doxorubicin are, in part, due to its interaction with the enzyme topoisomerase II to form DNA-cleavable complexes, as well as the generation of free radicals following the binding and reduction of doxorubicin at the cell surface, which are thought to be the possible mechanism for its cardiotoxicity. Doxorubicin is administered via intravenous injection. Additional information on the pharmacology of doxorubicin is located in **Table 43**.

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 kidney (Wilms 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 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, doxorubicin was detected in fetal liver, kidney and lung at 15 hours after dose administration in a fetus aborted at gestation week 17 (D'Incalci *et al.* 1983). 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 tissues of a stillborn fetus 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.* 2010d). 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.* 2010b). No doxorubicin was detected in fetal blood samples in baboons at 24 hours post-dose.

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

5.16.3 Laboratory Animal Developmental Toxicity

Doxorubicin induced embryolethal and teratogenic effects in laboratory animals with malformations induced at doses as low as 0.8 mg/kg bw/day in the rat (estimated as 1/14 the human dose **[of 60-75 mg/m^2]** based upon surface area) (Pharmacia & UpJohn Company 2010). The period of organogenesis was most vulnerable to doxorubicin exposure. For example, intraperitoneal injection of 1-2 mg doxorubicin/kg bw 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 bw/day (reviewed in 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 bw/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 bw/day on gestation days 9.5 and 10.5, relative to control and doses of 1-3 mg/kg bw/day (Menegola *et al.* 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

Number of Cases, Publications, and Types of Cancer Treated

Doxorubicin was administered to 424 female cancer patients during pregnancy identified from 64 case reports (66 cases), 28 case series (137 cases), 4 retrospective case series (55 cases), 7 retrospective surveys (35 cases), 2 retrospective cohort studies (9 cases) and 1 registry survey (128 cases), (Appendix C Table 15). Among these 424 patients, doxorubicin was used to treat breast cancer (245 cases), ovarian cancer (4 cases), malignant granular cell myoblastoma (1 case), adenoid cystic carcinoma (1 case), small

cell carcinoma of the cervix (1 case) and vaginal cancer (neuroendocrine carcinoma, 1 case). It was administered to pregnant patients to treat various types of sarcoma, including: sarcoma (type not specified; 1 case), embryonal sarcoma (1 case), Ewing sarcoma (7 cases), high grade sarcoma (2 cases), Kaposi sarcoma (1 case), osteosarcoma (1 case), rhabdomyosarcoma (1 case), soft tissue sarcoma (2 cases), and sarcoma, undifferentiated (1 case). In addition, doxorubicin was used in the treatment of lymphoma patients including: Hodgkin lymphoma (52 cases), and non-Hodgkin lymphoma (44), B-cell lymphoma (1 case), diffuse B-cell lymphoma (2 cases), large B-cell lymphoma (1 case), Burkitt lymphoma (5 cases), T-cell leukemia-lymphoma (1 case) and subcutaneous panniculitis-like T-cell lymphoma (1 case). Doxorubicin was also administered to pregnant patients to treat acute leukemia (subtype not specified, 1 case), acute lymphocytic leukemia (17 cases), acute myelogeneous leukemia (18 cases) and acute promyelocytic leukemia (3 cases), chronic myelogenous leukemia (1 case), and erythroleukemia (1 case). No cancer type was specified for 4 patients.

A total of 427 pregnancies with 430 conceptuses were exposed to doxorubicin, including three twin pregnancies (Nantel *et al.* 1990, Lycette *et al.* 2006, Cardonick *et al.* 2010) and three patients who had two pregnancies each (Aviles and Niz 1988, Dilek *et al.* 2006). Doxorubicin was administered during the first trimester to 42 cases with 42 singleton pregnancies (42 conceptuses). The drug was administered in the second and/or third trimester only to 382 cases with 385 pregnancies (388 conceptuses due to 3 sets of twins), include 49 singleton pregnancies for which individual patient timing of exposure was not provided but was assumed to be second and/or third trimester (Hahn *et al.* 2006, Jameel and Jamil 2007). It was assumed that these 49 cases were likely exposed in the second and/or third trimester since the reported age of initiation of chemotherapy ranged from 11-34 weeks (median 23 weeks)(Hahn *et al.* 2006) or 12-33 weeks (mean = 24 weeks)(Jameel and Jamil 2007)Doxorubicin was predominantly administered as polytherapy (413 cases, 419 conceptuses). The drug was administered as monotherapy in 6 cases (6 conceptuses) and type of therapy (mono- versus polytherapy) was not specified in 3 cases (3 conceptuses).

Termination of Pregnancy

Termination of pregnancy was reported for 4 singleton pregnancies exposed to doxorubicin, including 3 pregnancies exposed during the first trimester. Induced abortion terminated one normal fetus that was exposed during the first trimester to doxorubicin, nitrogen mustard, vincristine, procarbazine, bleomycin, vinblastine, and dacarbazine (Peres *et al.* 2001). Although the fetus was not deformed, the authors reported toxic degeneration of the liver and kidneys (Peres *et al.* 2001). No fetal data were reported for the remaining 2 singleton pregnancies terminated by induced abortion following exposure during the first trimester to doxorubicin, cytarabine and vincristine (Fassas *et al.* 1984) or doxorubicin, cyclophosphamide, and vincristine (Zuazu *et al.* 1991).

One induced abortion was reported following exposure in the second trimester to doxorubicin, bleomycin, vinblastine and dacarbazine (D'Incalci *et al.* 1983); no fetal data were reported.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 8 singleton pregnancies following gestational exposure to doxorubicin, including 2 spontaneous abortions, 6 stillbirths and one maternal/fetal death. Two spontaneous abortions were reported following exposure to doxorubicin polytherapy during the first trimester and no fetal data were provided. These spontaneous abortions occurred following first trimester exposure to: doxorubicin and vincristine (Peres *et al.* 2001), and doxorubicin, cytarabine and vincristine (Awidi *et al.* 1983).

Six singleton pregnancies ended in stillbirth following exposure to doxorubicin in the second and/or third trimester only. Normal fetuses were observed in 3 stillbirths occurring at: gestation week 30 following second trimester exposure to doxorubicin, vincristine, cyclophosphamide, and rituximab (Cardonick *et al.* 2010), at gestation week 31 following exposure during the third trimester to doxorubicin and vincristine (Karp *et al.* 1983), and at gestation week 26 following second trimester exposure cytarabine and 6-thioguanine (Zemlickis *et al.* 1992b). One stillbirth with no examination of the fetus occurred at gestation week 26 following second trimester exposure cyclophosphamide, ifosfamide, etoposide, cytarabine, vincristine and rituximab (Peterson *et al.* 2010); the fetus experienced oligohydramnios and intrauterine growth restriction prior to death. No fetal data were reported for the remaining 2 stillbirths following exposure to doxorubicin in the second and/or third trimester only, including: a stillbirth at gestation week 22 following second trimester exposure to doxorubicin, cyclophosphamide, vincristine, and dacarbazine (Jameel and Jamil 2007) and a stillbirth in the 8th month of pregnancy after second and third trimester exposure bleomycin, vinblastine, and dacarbazine (Dilek *et al.* 2006).

In addition, one maternal death resulted in the death of the fetus following exposure in the second trimester to doxorubicin monotherapy (Roboz *et al.* 1979); no fetal data were reported.

Rate of Occurrence of Congenital Malformations

Major malformations

Table 44: Major malformations diagnosed at birth possibly attributable to in utero exposure to doxorubicin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Floating thumb malformation (e.g. partial agenesis of a metacarpal bone and hypoplasia of two phalanges)	13% (5/38)
	Bilateral loss of radius and 5th digit as well as an atrial septum defect	
	Multiple skeletal deformities of the hand and cranium as well as ventriculomegaly, colpocephaly, and a bicuspid aortic valve	
	Imperforate anus and rectovaginal fistula	
	Microcephaly, hydrocephalus, blepharophimosis	
2nd and/or 3rd only	Clubfoot	1% (2/383)
	Pyloric stenosis	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Major malformations were observed in 10 liveborn infants gestationally exposed to doxorubicin, including 5 infants exposed during the first trimester. Skeletal malformations of the digits were reported in 3 infants with first trimester exposure to doxorubicin. One infant exposed during 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); this infant was exposed prenatally to doxorubicin, bleomycin, vinblastine, and dacarbazine. Bilateral loss of radius and 5th digit as well as an atrial septum defect were observed in an infant who was exposed during the first trimester to doxorubicin, cytarabine and vincristine (Ebert *et al.* 1997). Multiple skeletal deformities of the hand, flat nasal bridge, high arched palate, ventriculomegaly, colpocephaly, and a bicuspid aortic valve were reported for an infant exposed during the first trimester to doxorubicin, cyclophosphamide and 5-fluorouracil (Paskulin *et al.* 2005). One infant had

microcephaly, hydrocephalus and blepharophimosis following exposure during the first trimester to doxorubicin, cyclophosphamide and cisplatin (Kim *et al.* 1996); blepharophimosis is a condition where the individual has bilateral ptosis (dropping lower eyelids) with reduced lid size, a flat nasal bridge, and a hypoplastic orbital rim. An imperforate anus and rectovaginal fistula was reported in another newborn exposed during the first and second trimesters to doxorubicin, cyclophosphamide and cobalt radiation therapy (Murray *et al.* 1984). Thus, the apparent rate of major malformations following exposure to doxorubicin during the first trimester was 13% (5/39 conceptuses based on 38 liveborn infants and examination of the fetus of 1 induced abortion) (**Table 44**).

Major malformations were reported in 6 liveborn infants exposed to doxorubicin in the second and/or third trimester only. A small main pulmonary fistula was observed in an infant following second and third trimester exposure to cyclophosphamide and doxorubicin (Cardonick *et al.* 2010). Syndactyly of the 4th and 5th fingers occurred in one infant exposed in the second and third trimesters to doxorubicin, bleomycin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Bilateral partial syndactyly of digits II and III occurred in one infant following second and third trimester exposure to doxorubicin, nitrogen mustard, vincristine, procarbazine, bleomycin and vinblastine as well as second trimester exposure to radiation therapy (Van Calsteren *et al.* 2010a). Clubfoot and Down syndrome were reported in one infant each after second and third trimester exposure to doxorubicin, cyclophosphamide and 5-fluorouracil (Hahn *et al.* 2006). Pyloric stenosis occurred in one infant exposed in the second and third trimesters to doxorubicin, cyclophosphamide, docetaxel and paclitaxel (Cardonick *et al.* 2010). However, it is not likely that pulmonary fistula or the syndactyly were induced by exposure to chemotherapy after the period of organogenesis in the first trimester. Similarly, Down syndrome could result from damage to the parental germ cells pre-conception but not later in gestation. Thus, the adjusted apparent rate of major malformations following exposure to doxorubicin in the second and/or third trimester only was 1% (2/383 conceptuses based on 380 liveborn infants and examination of the fetuses of 3 stillbirths).

Minor Malformations

Minor malformations occurred in 9 liveborn infants gestationally exposed to doxorubicin. All minor malformations were reported following exposure to doxorubicin in the second and/or third trimester only. One infant had plagiocephaly following second and third trimester exposure to doxorubicin, bleomycin, vinblastine and dacarbazine (Cardonick *et al.* 2010). Bilateral ureteral reflex occurred in an infant exposed in the second and/or third trimester to doxorubicin, cyclophosphamide and 5-fluorouracil (Hahn *et al.* 2006). One infant had a hemangioma on its abdomen following exposure in the second and third trimesters to doxorubicin and cyclophosphamide (Ring *et al.* 2005b); the authors deemed this anomaly was not caused by chemotherapy (Ring *et al.* 2005b). **[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 *et al.* 2005b).]** Double cartilage rings were reported in an infant with second and third trimester exposure to doxorubicin, 5-fluorouracil and cyclophosphamide as well as radiation therapy in the first and second trimesters (Van Calsteren *et al.* 2010a). Hip subluxation was reported in another infant exposed in second and third trimesters to doxorubicin and cyclophosphamide (Van Calsteren *et al.* 2010a). Pectus excavatum occurred in one infant following second and third trimester exposure to doxorubicin, nitrogen mustard, vincristine, procarbazine, bleomycin and vinblastine (Van Calsteren *et al.* 2010a).

Three infants had minor malformations that were resolved without intervention. Suspected holoprosencephaly was reported for a newborn exposed in the second and third trimesters to

doxorubicin, cyclophosphamide and docetaxel (Cardonick *et al.* 2010); however, this infant was normal with prominent lateral ventricles at age 2.6 years. A minor ventricular septal defect occurred in a newborn exposed in the third 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 infants was gestationally exposed in the second trimester to doxorubicin and cyclophosphamide followed by docetaxel monotherapy in the second and third trimesters.

Pregnancy Complications and Newborn Health

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, Lambert *et al.* 1991, Merimsky *et al.* 1999, Ring *et al.* 2005b, Fadilah *et al.* 2006, Ustaalioglu *et al.* 2010), including two with reductions in amniotic fluid (Nakajima *et al.* 2004, Peterson 2008, Cordoba *et al.* 2010). Oligohydramnios was reported for 3 additional pregnancies (Meyer-Wittkopf *et al.* 2001, Shieh and Mehta 2011). As mentioned above, one singleton pregnancy experienced intrauterine growth restriction and oligohydramnios prior to stillbirth (Peterson *et al.* 2010). Preeclampsia was reported in 8 pregnancies (Bartsch *et al.* 1988, Lambert *et al.* 1991, Anselmo *et al.* 1999, Berry *et al.* 1999, Kuerer *et al.* 2002, Gonzalez-Angulo *et al.* 2004, Potluri *et al.* 2006, Chakravarty *et al.* 2011), and maternal hypotension occurred in one case (Turchi and Villasis 1988). Spontaneous preterm labor was reported in 13 pregnancies (Tobias and Bloom 1980, Fassas *et al.* 1984, Nantel *et al.* 1990, Willemse *et al.* 1990, Moore and Taslimi 1991, Kim *et al.* 1996, Berry *et al.* 1999, Decker *et al.* 2006, Mir *et al.* 2012), including 3 pregnancies which also experienced premature rupture of membranes (Webb 1980, Karp *et al.* 1983, Meador *et al.* 1987). Transient preterm labor was reported in two pregnancies (Meyer-Wittkopf *et al.* 2001, Lycette *et al.* 2006). Fetal distress was reported in two singleton pregnancies (D'Emilio *et al.* 1989, Veneri *et al.* 1996).

A total of 417 infants were exposed to doxorubicin in utero. Early preterm delivery (<34 weeks) was reported for 35 infants, late preterm delivery (34 to <37 weeks) was reported for 64 infants, and 71 infants were delivered at term. Data were insufficient to determine the gestational age at birth for 247 infants. Of the preterm infants, 32 infants were born via spontaneous vaginal birth, 8 were born via induced vaginal birth, 46 were born via C-section and no route of delivery was specified for 13 preterm infants. Small for gestational age was determined for 26 infants and 274 infants had normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 117 infants.

Respiratory distress and transient breathing difficulties occurred in 31 infants (Haerr and Pratt 1985, Willemse *et al.* 1990, Veneri *et al.* 1996, Berry *et al.* 1999, Peres *et al.* 2001, Nakajima *et al.* 2004, Ring *et al.* 2005b, Lam 2006, Hahn *et al.* 2009, Cardonick *et al.* 2010), including two infants with respiratory distress who also required surfactant delivery (Bartsch *et al.* 1988, Kerr 2005). Among the infants with breathing difficulties, extreme hypotonia accompanied hypocapnia in one infant (Cardonick *et al.* 2010) and another newborn experienced asystole immediately after birth (Willemse *et al.* 1990). Transient myelosuppression was reported in 11 newborns, including: 4 infants with anemia (Aviles and Niz 1988, Nakajima *et al.* 2004, Cardonick *et al.* 2010), two infants with decreased or complete absence of B-cells ((Decker *et al.* 2006, Friedrichs *et al.* 2006); both infants were co-exposed to rituximab), 3 infants with leukopenia (Khurshid and Saleem 1978, Berry *et al.* 1999, Garcia *et al.* 1999), 1 infant with neutropenia (Cardonick *et al.* 2010) and another infants with neutropenia and thrombocytopenia (Hahn *et al.* 2006, Cardonick *et al.* 2010). One infant had polycythemia (Dara *et al.* 1981). Two newborns experienced substantial hair loss (Berry *et al.* 1999). Jaundice was reported in 14 infants (Dara *et al.* 1981, Rawlinson

et al. 1984, Dreicer and Love 1991, Lambert *et al.* 1991, Peres *et al.* 2001, Nakajima *et al.* 2004, Kerr 2005, Cardonick *et al.* 2010). Other health effects observed in the live born infants included: hypoglycemia (4 infants) (Kerr 2005, Cardonick *et al.* 2010), and calcium-deficiency requiring intravenous calcium (1 infant)(Haerr and Pratt 1985). Two newborns had gastroesophageal reflux (Cardonick *et al.* 2010) and two additional infants required temporary feeding tubes (Nakajima *et al.* 2004, Cardonick *et al.* 2010). Two infants had cerebral hemorrhage (Veneri *et al.* 1996, Hahn *et al.* 2006). Infections were reported in four neonates, including two infants with sepsis (Willemse *et al.* 1990, Cardonick *et al.* 2010), one infant with necrotizing enterocolitis (Garcia *et al.* 1999) and one infant with bronchopneumonia and sepsis (Peres *et al.* 2001).

Adverse placenta effects were reported in at least 5 singleton pregnancies yielding liveborn infants. One placenta had tumor deposits (Ateser *et al.* 2007). Another placenta had multiple infarctions, but no leukemic infiltration (D'Emilio *et al.* 1989). Extensive infarction was reported for another placenta (Lambert *et al.* 1991). Another placenta was reported to be small (350 g); the full term infant weighed 2860 g **[gestational age not specified].**

Infant Deaths

One infant died at 13 months from a severe autoimmune disorder following exposure in the second and third trimesters to doxorubicin and cyclophosphamide (Cardonick *et al.* 2010); this infant was small for gestational age at birth and experienced meconium aspiration, thrombocytopenia and a rash as a newborn.

Follow Up Evaluations

Of the 323 infants with follow up evaluations at 10 weeks to 19 years of age, normal growth and development were reported for all but 7 children. 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, including one with recurrent otitis media (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 (a total of 5 children), reactive airway disease (2 children), asthma (1 child), selective IgA deficiency not requiring treatment (1 child), and chronic broncholitis (1 child) (Cardonick *et al.* 2010).

5.16.5 Summary of Pregnancy Outcomes for doxorubicin

Exposure to doxorubicin was documented for 427 pregnancies with a total of 430 conceptuses, including 3 sets of twins (**Table 78**). Overall, the apparent rate of major malformations among all doxorubicin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 2% (11/421 conceptuses based on 417 liveborn infants and examination of the fetuses of 1 induced abortion and 3 stillbirths). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in 4 newborns exposed to doxorubicin during the first trimester. Three infants had skeletal malformations involving the digits or the digits and the cranial bones, and another infant had an imperforate anus and

rectovaginal fistula. These malformations in humans are consistent with malformations reported in developmental toxicity studies of doxorubicin in animals exposed during the period of organogenesis. The occurrence of microcephaly, hydrocephalus and blepharophimosis in one infant was likely due to doxorubicin polytherapy, including co-treatments cyclophosphamide and cisplatin. Hydrocephalus and abnormal development of the eyes were reported in developmental toxicity studies in animals using cyclophosphamide or cisplatin. Thus, the apparent rate of major malformations following first trimester exposure is 13% (5/39 conceptuses based on 38 conceptuses and examination of the fetus of 1 induced abortion). Five infants were born with major malformations following exposure to doxorubicin in the second and/or third trimester only. However, three of these malformations were not likely due to exposure to doxorubicin in the second or third trimesters because syndactylies would be induced during the period of organogenesis and Down syndrome would reflect insults to the parental germ cells. Thus, the adjusted apparent rate of major malformations following exposure to doxorubicin in the second and/or third trimester only was 1% (2/384 conceptuses based on 383 liveborn infants and examination of the fetuses of 3 stillbirths).

5.17 EPIRUBICIN

5.17.1 Mechanism of Action, Route of Administration, and Indications

Table 45: Pharmacology of epirubicin in adult humans	
Molecular weight:	543.522
Protein binding:	~77% to albumin
Metabolism:	Extensively via hepatic and extrahepatic (including red blood cells) routes
Half-life elimination:	Triphasic; Terminal (mean): 33 hours
Distribution:	Vdss: 21-27 L/kg
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (34% to 35%); urine (20% to 27%)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; Vdss, volume of distribution at steady state	

Epirubicin (epirubicin hydrochloride) is an anthracycline DNA intercalating 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 DNA and RNA and, subsequently, proteins. The intercalation induces DNA cleavage by the enzyme topoisomerase II. Epirubicin also inhibits DNA synthesis by interfering with the DNA helicase enzyme, the enzyme responsible for separating strands of DNA for replication, and it generates cytotoxic free radicals. Epirubicin is administered intravenously. Additional information on the pharmacology of epirubicin is located in **Table 45**.

Epirubicin is indicated for the treatment of breast cancer.

5.17.2 Evidence of Placental and Breast Milk Transport

Placental transport of epirubicin in humans is currently unknown. However, placental transport of epirubicin has been documented in laboratory animal studies. In the baboon, the fetal plasma levels of epirubicin were 4.0±1.6% of maternal plasma levels when tested at multiple time-points within three hours of intravenous dose administration to the mother (Van Calsteren *et al.* 2010b); three of the eight 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 in the baboon study, and fetal tissue levels averaged 8.7±8.1% of maternal tissue concentrations (Van Calsteren *et al.* 2010b). A similar rate of transplacental transfer (4.8±3.8%) was observed following intravenous injection of epirubicin to pregnant mice (Van Calsteren *et al.* 2010d). It is not known if epirubicin is transferred into breast milk.

Breast milk transport of epirubicin in humans is currently unknown. The manufacturers product label reports that epirubicin was excreted into the milk of rats administered intravenous epirubicin (0.50 mg/kg bw/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 bw/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 bw/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 bw/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 bw/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 bw/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 bw/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 (Mayne 2006).

5.17.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Epirubicin was administered to 67 female cancer patients (also called cases) during pregnancy identified from 9 case reports (9 cases), 5 case series (30 cases), 1 retrospective case series (4 cases), 1 retrospective cohort study (1 case), 4 retrospective surveys (18 cases), and 1 registry survey (5 cases) (Appendix C Table 16). Among these patients, epirubicin was used to treat breast cancer (58 cases), non-Hodgkin lymphoma (6 cases) and acute lymphocytic leukemia (1 case); cancer type was not specified for 2 patients.

A total of 67 singleton pregnancies (67 conceptuses) were exposed to epirubicin. Epirubicin was administered during the first trimester to 7 and in the second and/or third trimester only in 62 cases. It was used as monotherapy in 26 cases and as polytherapy in 41 cases.

Termination of Pregnancy

A malformed fetus was terminated by induced abortion following first trimester exposure to epirubicin, cyclophosphamide and 5-fluorouracil as well as radiation therapy, followed by exposure to cyclophosphamide, 5-fluorouracil and methotrexate in the second 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.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 5 pregnancies exposed to epirubicin, including 2 spontaneous abortions and 2 stillbirths. No examination of the fetus was reported for the two spontaneous abortions occurred following exposure during the first trimester to epirubicin, 5-fluorouracil and cyclophosphamide (1 embryo) or vincristine and methotrexate (1 embryo) (Giacalone *et al.* 1999).

No examination of the fetus was reported for two singleton pregnancies ending in stillbirth following second trimester exposure to epirubicin and cyclophosphamide (Giacalone *et al.* 1999) or epirubicin and vincristine (Peres *et al.* 2001).

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 4 liveborn infants and 1 induced abortus following in utero exposure to epirubicin.

Table 46: Major malformations diagnosed at birth possibly attributable to in utero exposure to epirubicin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	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	20% (1/5)
2nd and/or 3rd only	Polycystic kidney	3% (2/62)
	Clubfoot	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

The only reported occurrence of major malformations following first trimester exposure to epirubicin was in an induced abortus following the first trimester exposure to epirubicin, cyclophosphamide and 5-fluorouracil as well as radiation therapy, followed by exposure to cyclophosphamide, 5-fluorouracil and methotrexate in the second 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. Thus, the apparent rate of major malformations following exposure to epirubicin during the first trimester was 20% (1/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 induced abortion) (Table 46).

Major malformations were observed in 3 liveborn infants in the second and/or third trimester only exposure to epirubicin. Polycystic kidney was reported in an infant with second trimester exposure to epirubicin monotherapy (Azim *et al.* 2008). Clubfoot and a left eye hemangioma, a minor malformation, were reported in an infant exposed in the second and third trimesters epirubicin and cyclophosphamide (Cardonick *et al.* 2010). Rectal atresia was observed in one infant with gestational exposure to epirubicin monotherapy in the second and third trimesters beginning in gestation week 23 (Van Calsteren *et al.* 2010a) However, rectal atresia was not likely due to exposure to epirubicin beginning at gestation week 23 because this malformation is induced by a vascular accident at gestational week 13 to 14 (Kisra *et al.* 2005). Thus, the adjusted rate of major malformations following exposure to epirubicin in the second and/or third trimester only is 7% (2/58 conceptuses based on 58 liveborn infants).

Minor Malformations

Minor malformations were observed in 3 liveborn infants following gestational exposure to epirubicin. A small bilateral protuberance on phalanx 5 was observed in an infant following gestational exposure in the second and third trimesters to epirubicin, 5-fluorouracil and cyclophosphamide (Van Calsteren *et al.* 2010a). Hemangiomas were reported in two infant. One infant had a left eye hemangioma following exposure in the second and third trimesters epirubicin and cyclophosphamide (Cardonick *et al.* 2010). Another infant had a hemangioma located on the abdomen following second and third trimester

exposure to epirubicin and cyclophosphamide (Ring *et al.* 2005b); **[it is possible that the infant with the hemangioma on the abdomen was, instead, treated with cyclophosphamide and either doxorubicin or 5-fluorouracil and methotrexate; the authors did not report the treatments of individual patients (Ring *et al.* 2005b).]**

Pregnancy Complications and Newborn Health

Pregnancy complications were observed in a few cases following in utero exposure to epirubicin. Premature rupture of fetal membranes (Ginopoulos *et al.* 2004) and eclamptic seizures (Muller *et al.* 1996) were reported for one pregnancy each. Spontaneous preterm labor preceded preterm delivery in two cases (Andreadis *et al.* 2004, Sharma *et al.* 2009). Intrauterine growth restriction due to placental insufficiency occurred in one fetus (Ring *et al.* 2005a).

A total of 62 liveborn infants were exposed to epirubicin during gestation. Early preterm delivery (>34 weeks gestation) was reported for 2 infants, late preterm delivery (34 to <37 weeks gestation) was reported for 18 infants and 7 infants were delivered at term. Data were insufficient to determine the gestational age at birth for 35 infants. Of the preterm infants, 4 infants were born via spontaneous vaginal delivery, 2 infants were born via induced vaginal delivery and 14 infants were born via C-section. Small for gestational age was determined for 3 infants and 33 infants had normal body weights based on sex, gestational age and body weights at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 26 infants.

Breathing difficulties were observed in three infants, including respiratory distress (n=2 infants) (Ring *et al.* 2005b) and mild transient tachypnea requiring oxygen treatment (n=1 infant) (Ginopoulos *et al.* 2004). One newborn had leukopenia (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).

Infant Deaths

One infant died following gestational exposure to epirubicin. One newborn died 8 days after birth with no obvious malformations following exposure in the third trimester to epirubicin, 5-fluorouracil and cyclophosphamide (Giacalone *et al.* 1999); no cause of death was determined.

Follow Up Evaluations

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 67 singleton pregnancies (67 conceptuses) (**Table 78**). Overall, the apparent rate of major malformations among all epirubicin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 8% (4/63 conceptuses based on 62 liveborn infants and examination of the fetus of 1 induced abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major skeletal malformations were observed in one induced abortus following epirubicin polytherapy in the first trimester. Developmental toxicity studies of epirubicin in rats did report skeletal malformations, but not syndactylies; however, these studies were unable to test dose

levels similar to humans due to embryotoxicity. It is possible that the syndactylies were induced by epirubicin polytherapy or by the toxicity of the co-treatments (cyclophosphamide and 5-fluorouracil during the first trimester. Thus, the apparent rate of major malformations following exposure to epirubicin during the first trimester was 20% (1/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 induced abortion).

Of the major malformations that were observed in three liveborn infants exposed to epirubicin in the second and/or third trimester, only polycystic kidney (1 infant) and clubfoot (1 infant) were likely caused by gestational exposure to epirubicin after the first trimester. It was not likely that exposure to epirubicin exposure in the late second trimester contributed to the reported occurrence of rectal atresia. Thus, the adjusted apparent rate of major malformations following exposure to epirubicin in the second and/or third trimester only was 3% (2/58 conceptuses).

5.18 ETOPOSIDE

5.18.1 Mechanism of Action, Route of Administration, and Indications

Table 47: Pharmacology of etoposide in adult humans	
Molecular weight:	588.5588
Protein binding:	94% to 98%
Metabolism:	Hepatic, via CYP3A4 and 3A5, to various metabolites; in addition, conversion of etoposide to the O-demethylated metabolites (catechol and quinine) via prostaglandin synthases or myeloperoxidase occurs, as well as glutathione and glucuronide conjugation via GSTT1/GSTP1 and UGT1A1
Half-life elimination:	Terminal: 4-11 hours
Distribution:	Average Vd: 7-17 L/m^2; poor penetration across the blood-brain barrier; CSF concentrations <5% of plasma concentrations
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Urine (56%; 45% as unchanged drug) within 120 hours; feces (44%) within 120 hours
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CSF, cerebral spinal fluid; IV, intravenous; Vd, volume of distribution	

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 (Baxter 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. Additional pharmacology information on etoposide is located in **Table 47**.

Etoposide 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 reported in one lactating patient. One case report 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 (Azuno *et al.* 1995). 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 (Baxter 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 (Baxter 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 bw/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 bw/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

Number of Cases, Publications, and Types of Cancer Treated

Etoposide was administered to 45 female cancer patients (also called cases) during pregnancy identified from 20 case reports (20 cases), 7 case series (12 cases), 2 retrospective case series (6 cases), 1 retrospective survey (1 case), 1 retrospective cohort study (2 cases), and 1 registry survey (4 cases) (Appendix C Table 17). Among these patients, etoposide was primarily used to treat ovarian cancer (20 cases), non-Hodgkin lymphoma (11 cases), Burkitt lymphoma (2 cases), and Hodgkin lymphoma (2 cases). It was also used to treat acute myelogenous leukemia (4 cases), acute lymphocytic leukemia (1 case), adenocarcinoma (of unknown primary cancer) (1 case), choriocarcinoma of the uterus (1 case), lung cancer (1 case), alveolar rhabdomyosarcoma (1 case) and neuroblastoma (1 case).

A total of 45 singleton pregnancies (45 conceptuses) were exposed to etoposide. Etoposide was administered during the first trimester in 4 cases and in the second and/or third trimester only in 41 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.

Termination of Pregnancy

One induced abortion terminated a singleton pregnancy following exposure in the second trimester to etoposide, daunorubicin and cytarabine (Chelghoum *et al.* 2005); no examination of the fetus was reported.

Spontaneous Fetal Death

Spontaneous fetal death occurred in two singleton pregnancies. Stillbirth of a normal fetus occurred at gestational week 26 following exposure in the second trimester to etoposide and cisplatin (Peres *et al.* 2001). Another stillbirth at gestation week 26 followed oligohydramnios at gestation week 18 and intrauterine growth restriction at gestation week 22, and no examination of the fetus was reported (Peterson *et al.* 2010). This pregnancy was exposed in the second trimester to etoposide, cyclophosphamide, doxorubicin, ifosfamide, cytarabine, vincristine, and rituximab (Peterson *et al.* 2010).

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations occurred in 2 liveborn infants with gestational exposure to etoposide and both infants were exposed in the second and/or third trimester only. One newborn had ventriculomegaly

and cerebral atrophy following exposure in the second trimester to etoposide, bleomycin and cisplatin (Elit *et al.* 1999); ventriculomegaly was first observed prenatally following administration of chemotherapy. Genetic hearing loss (the infant's parents were carriers) and a spontaneous mutation for neurofibromatosis were identified in an infant exposed in the second and third trimesters to etoposide, bleomycin and cisplatin (Cardonick *et al.* 2010). However, the spontaneous mutation for neurofibromatosis was not caused by exposure to etoposide in the second or third trimester because it would have occurred in a parental germ cell prior to conception. Thus, the adjusted apparent rate of major malformations following exposure to etoposide in the second and/or third trimester only was 3% (1/39 based on 38 liveborn infants and examination of the fetus of one stillbirth). No major malformations were reported in the four liveborn infants exposed to etoposide during the first trimester (0/4 conceptuses based on 4 liveborn infants) (**Table 48**).

Table 48: Major malformations diagnosed at birth possibly attributable to in utero exposure to etoposide

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses)
During 1st	None	0% (0/4)
2nd and/or 3rd only	Cerebral atrophy and ventriculomegaly	3% (1/39)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Minor Malformations

Minor malformations were observed in one newborn gestationally exposed to etoposide. The infant had a mild glandular hypospadias (considered a first degree hypospadias) (Ghaemmaghami *et al.* 2009); the infant was exposed during the second trimester to etoposide, bleomycin and cisplatin.

Pregnancy Complications and Newborn Health

A variety of pregnancy complications were observed following etoposide exposure during pregnancy. Preeclampsia occurred in two singleton pregnancies (Horbelt *et al.* 1994, Siu *et al.* 2002, Benjapibal *et al.* 2010), premature rupture of membranes was reported in one singleton pregnancy (Ghaemmaghami and Hasanzadeh 2006), and spontaneous preterm labor was reported in three pregnancies (Raffles *et al.* 1989, Moore and Taslimi 1991, Brudie *et al.* 2011). A reduction in amniotic fluid was observed in 3 singleton pregnancies yielding liveborn infants (Buller *et al.* 1992, Scherf and Price 1996, Ghaemmaghami *et al.* 2009). An inhibition of fetal growth was observed in 8 pregnancies, including intrauterine growth restriction (Buller *et al.* 1992, Arango *et al.* 1994, Hsu *et al.* 1995, Ghaemmaghami *et al.* 2009, Benjapibal *et al.* 2010, Peterson *et al.* 2010), 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. (1994) and Scherf et al. (1996) appear to be the same case, but are considered as two separate case reports in this evaluation.]** As mentioned above, a reduction in amniotic fluid and intrauterine growth restriction preceded a stillbirth following second trimester exposure to etoposide (Peterson *et al.* 2010). One fetus experienced intermittent sinusoidal heart rate patterns (Hsu *et al.* 1995).

There were 42 liveborn infants with in utero exposure to etoposide. Early preterm delivery (<34 weeks) was reported for 7 infants, late preterm delivery (34 to <37 weeks) was reported for 12 infants, and 16 infants were carried to term. Data were insufficient to determine gestational age a birth for 7 infants. Of the preterm infants, 4 infants were born via spontaneous vaginal delivery, 14 infants were born via C-section and route of delivery was not specified for one infant. Small for gestational age was determined

for 10 infants and 24 infants had normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 8 infants.

Breathing difficulties were reported for six infants (Raffles *et al.* 1989, Murray *et al.* 1994, Scherf and Price 1996, Elit *et al.* 1999, Malhotra and Sood 2000, Lam 2006), including one infant with severe respiratory distress and pneumothorax (Raffles *et al.* 1989). Transient myelosuppression was reported in six infants (Raffles *et al.* 1989, Horbelt *et al.* 1994, Murray *et al.* 1994, Hsu *et al.* 1995, Scherf and Price 1996, Peres *et al.* 2001). One infant had jaundice (Peres *et al.* 2001) and another infant had jaundice and hypoglycemia (Tseng and ChangChien 2004). One infant, who experienced both respiratory distress and leukopenia with neutropenia in the first 2 weeks of life, also had alopecia at age 10 days (Raffles *et al.* 1989). One placenta had foci of villous edema (Buller *et al.* 1992); the placenta was associated with a normal infant born at term, who experienced oligohydramnios and intrauterine fetal growth retardation in late pregnancy.

Infant Deaths

No infant deaths were reported following gestational exposure to etoposide.

Follow Up Evaluations

Follow-up evaluations were reported for 28 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 had 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 another 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 45 singleton pregnancies (45 conceptuses) (**Table 80**). Overall, the apparent rate of major malformations among all etoposide-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 5% (2/42 conceptuses based on 41 liveborn infants and examination of the fetus of one stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). No major malformations occurred in the 4 infants born following in utero exposure during the first trimester. Thus, the total occurrence of major malformations following exposure to etoposide during the first trimester is 0% (0/4 conceptuses). Major malformations were reported in 2 newborns exposed to etoposide in the second and/or third trimester. However, only one of the malformations was likely caused by gestational exposure to etoposide after the period of organogenesis: ventriculomegaly, which was diagnosed prenatally after administration of etoposide polytherapy, and cerebral atrophy (Elit *et al.* 1999). The mutation for neurofibromatosis reported in an infant was not attributable to exposure to etoposide in the second and third trimesters. Thus, the adjusted apparent rate of major malformations following exposure to etoposide in the second and/or third trimester only was 3% (1/39 conceptuses based on 39 liveborn infants and examination of fetus of one stillbirth). In utero exposure to etoposide appeared to result in a high apparent rate of small for gestational age infants (24%; 10/42 liveborn infants). While etoposide is reported to cause fetal growth restriction in animal developmental toxicity studies when exposed during organogenesis, the majority of the small for gestational age infants (9 infants) were exposed to etoposide in the second and/or third trimester only.

5.19 HYDROXYUREA

5.19.1 Mechanism of Action, Route of Administration, and Indications

Hydroxyurea is an anti-neoplastic agent that belongs to the class of chemotherapy drugs known as anti-metabolites. It inhibits the enzyme ribonucleotide reductase, which blocks the conversion of ribonucleotides to deoxyribonucleotide, 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 co-treatment with other chemotherapeutic agents (Yarbro 1992) or radiation therapy (Bristol-Myers-Squibb 2010); however, treatment with radiation is generally not recommended for pregnant women. Hydroxyurea is administered orally one to three times per day. Additional information on the pharmacology of hydroxyurea (parent compound) is located in **Table 49**.

Table 49: Pharmacology of hydroxyurea in adult humans

Molecular weight:	76.0546
Protein binding:	**[Information not located]**
Metabolism:	60% via hepatic and gastrointestinal tract
Half-life elimination:	3-4 hours
Distribution:	Readily crosses blood-brain barrier; distributes into intestine, brain, lung, kidney tissues, effusions and ascites
Time to peak, serum (C_{max}):	1-4 hours
Excretion:	Urine

Data from Brunton et al. (2011). Abbreviations: Cmax, time to peak levels in serum.

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 in non-pregnant patients for primary cell carcinomas of the head and neck, excluding the lip. Hydroxyurea is also indicated for the non-cancerous health condition of sickle cell anemia 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

Human placental transport of hydroxyurea is not known. However, hydroxyurea is known to cross the placenta in rats, monkeys, and rabbits (Wilson *et al.* 1975, DeSesso and Goeringer 1990). 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 teratogenic 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 (approximately 0.8 and 0.3 times, respectively, the maximum recommended daily dose in humans per mg/m^2 (Bristol-Myers-Squibb 2010)).

In the peer-reviewed literature, higher doses of hydroxyurea were associated with increased cell death of limb buds and the neural tube, and decreased postnatal locomotor activity in rat offspring following gestational exposure to 2000 mg/kg bw on gestation day 14 (Fritz and Hess 1980), impaired cardiac development and neural tube defects in hamster fetuses after a single intravenous dose to the dam on of 50 mg on gestation day 8 **[400-500 mg/kg bw/day based on bw of 100-125 gm]** (Ferm 1966), and adversely affected cardiovascular function in rabbit embryos exposed via a single subcutaneous injection of 750 mg/kg bw to the mother on gestation day 12 (Millicovsky and DeSesso 1980). In addition, hydroxyurea induced embryotoxicity manifested as decreased fetal viability of rat fetuses following maternal intraperitoneal doses of 137 or 150 mg/kg bw/d on gestation days 9 to 12 (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

Number of Cases, Publications, and Types of Cancer Treated

Hydroxyurea was administered to 33 female cancer patients (also called cases) during pregnancy identified from 13 case reports (13 cases), 5 case series (10 cases), 2 retrospective cohort studies (3 cases) and 2 retrospective surveys (7 cases) (Appendix C Table 18). Among these patients, hydroxyurea was used to treat chronic myeloid leukemia (30 cases), acute myeloid leukemia (2 cases) and adult T-cell lymphoma/leukemia (1 case).

A total of 33 pregnancies yielding 35 conceptuses were exposed to hydroxyurea, including 2 twin pregnancies (Thauvin-Robinet *et al.* 2001, De Carolis *et al.* 2006, Pye *et al.* 2008). Hydroxyurea was administered during the first trimester in 14 cases (15 conceptuses due to one set of twins). The drug was administered in the second and/or third trimester only in 19 cases (20 conceptuses due to one set of twins), including 4 cases that began hydroxyurea treatment between gestation weeks 12-33 (Jameel and Jamil 2007). Hydroxyurea was administered as monotherapy to 26 cases (28 conceptuses), including 8 cases (10 conceptuses) that were switched from imatinib to hydroxyurea upon identification of the pregnancy, one case (2 conceptuses) that was switched from hydroxyurea to interferon alpha at gestation week 27, and one case that was administered hydroxyurea as monotherapy prior to imatinib monotherapy in the second trimester (Appendix C Table 18). Hydroxyurea was administered as polytherapy in 7 cases (7 conceptuses).

Termination of Pregnancy

Two singleton pregnancies (2 conceptuses) were terminated following exposure to hydroxyurea polytherapy. No examination of the fetus was reported for an induced abortion which followed first trimester exposure to hydroxyurea, daunorubicin, 6-thioguanine and cytarabine (Zemlickis *et al.* 1992b). A normal fetus was reported from an induced abortion following exposure in the second trimester to hydroxyurea, daunorubicin, cytarabine, vincristine, and 6-thioguanine (Doney *et al.* 1979).

Spontaneous Fetal Death

Two pregnancies exposed to hydroxyurea ended in stillbirth. A stillbirth of a grossly normal fetus occurred in gestation week 26 following eclampsia (Delmer *et al.* 1992); the pregnancy was exposed to hydroxyurea monotherapy throughout the entire pregnancy. Meningocele was observed in a stillborn fetus born at gestation week 34 that was treated with imatinib monotherapy in the first and second trimesters, then switched to hydroxyurea monotherapy after the first trimester (Pye *et al.* 2008). Meningocele refers to a protrusion of the meninges (the covering of the spinal cord) through a defect in the cranium or spinal column.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations following in utero exposure to hydroxyurea were observed in 2 liveborn infants and examination of the fetus of1 stillbirth.

Table 50: Major malformations diagnosed at birth possibly attributable to in utero exposure to hydroxyurea

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Premature closure of skull sutures	8% (1/13)
2nd and/or 3rd only	Pyloric stenosis	5% (1/21)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Only one malformation occurred following first trimester exposure to hydroxyurea: premature closure of the skull sutures in a liveborn infant exposed to hydroxyurea monotherapy during the first trimester through term, following first trimester exposure to imatinib monotherapy. Thus, the apparent rate of malformations following exposure to hydroxyurea in the first trimester was 8% (1/13 conceptuses based on 12 liveborn infants and examination of the fetus of 1 stillborn fetus) (**Table 50**).

Three major malformations were observed in two liveborn infants and one stillbirth exposed in the second and/or third trimester only to hydroxyurea, including hypospadias (1 liveborn infant), pyloric stenosis (1 liveborn infant), and meningocele (cleft spinal cord; 1 stillborn fetus), as mentioned above (Pye *et al.* 2008). Based on the timing of normal development, exposure to hydroxyurea in the third trimester only did not cause hypospadias or meningocele. Penile development is completed by the end of the 14th gestation week, and perturbations leading to spinal cord malformations would occur in the first 4 to 5 weeks of gestation (Moore and Persaud 2003). Thus, the adjusted apparent rate of malformations possibly attributable to exposure to hydroxyurea in the second and/or third trimester only was 5% (1/21 conceptuses based on 19 liveborn infants and examination of the fetus of 1 induced abortion and 1 stillbirth).

Minor Malformations

No minor malformations were observed following in utero exposure to hydroxyurea.

Pregnancy Complications and Newborn Health

A few pregnancy complications and infant health issues are reported in pregnancies exposed to hydroxyurea. Eclampsia at gestation week 26 likely caused the birth of a grossly normal stillborn fetus

(Delmer *et al.* 1992). 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). There were no reports of intrauterine growth restriction.

There were 31 liveborn infants with in utero exposure to hydroxyurea. Early preterm delivery (<34 weeks) was reported for 3 infants, late preterm delivery (34-36 weeks) was reported for 7 infants, and 16 infants were delivered at term (>37 weeks). Data were insufficient to identify age at birth for the remaining 5 infants. Of the 10 preterm infants, 2 infants were delivered via spontaneous vaginal birth, 1 infant was delivered via induced vaginal birth, and 6 infants (including 2 sets of twins) were delivered via C-section; route of delivery was not specified for one preterm infant. One infant was small for gestational age and 21 infants had normal weight for gestational age based upon data reported for sex, body weight and gestational age at birth of each infant (Olsen *et al.* 2010). The data reported were insufficient to identify small for gestation age in the remaining 9 infants. Jaundice was observed in two newborns (Peres *et al.* 2001). One infant suffered from electrolyte abnormalities and hypoglycemia (Doney *et al.* 1979).

Infant Deaths

One premature infant died 10 days after birth from intracranial hemorrhage (Dilek *et al.* 2006); this infant was born at 28 weeks of gestation with no malformations.

Follow Up Evaluations

Follow up evaluations were available for 22 infants at ages ranging from 1 month to 53 months. Age at follow-up was not specified for one infant (Fitzgerald and McCann 1993). Normal growth and development were reported for all but one child (Doney *et al.* 1979). 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 was reported for 33 pregnancies and 35 conceptuses due to two set of twins (**Table 76**). Overall, the raw apparent rate of major malformations among all hydroxyurea-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 12% (4/34 based on 31 liveborn infants and examination of the fetus of 1 induced abortion and 2 stillbirths). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). In all cases with major malformations following gestational exposure to hydroxyurea, the patients were taking imatinib monotherapy when their pregnancies were first detected; thus, some or all of these malformations may be due to imatinib exposure during the first trimester (Pye *et al.* 2008). The one major malformation observed following exposure during the first trimester to hydroxyurea monotherapy (premature closure of cranial sutures in one liveborn infant) was similar to observations of partial ossification of cranial bones reported in developmental toxicity studies of rats exposed to the drug during organogenesis. Thus, the apparent rate of malformations following exposure to hydroxyurea in the first trimester was 8% (1/13 conceptuses based on 12 liveborn infants and examination of the fetus of 1 stillbirth). Of the three major malformations observed following second and/or third trimester only exposure to hydroxyurea, the report of meningocele in a stillborn fetus and hypospadias in a liveborn infant were not likely due to exposure to hydroxyurea after the period of organogenesis. Thus, the adjusted apparent rate of malformations possibly attributable to exposure to hydroxyurea in the second and/or third trimester only was 5% (1/21 conceptuses based on 19 liveborn infants and examination of the fetus of 1 induced abortion and 1 stillbirth).

Although not included in this monograph, pregnancy outcomes have also been reported for patients treated with hydroxyurea for non-cancerous health conditions during pregnancy. In one larger case series that included non-cancerous conditions, one major malformation (hip dysplasia; 1 infant) and two minor malformations (1 infant each had pilonidal sinus and unilateral renal dilation) were observed in 24 liveborn infants and the examination of the fetus of 2 stillbirths (Thauvin-Robinet *et al.* 2001).

5.20 IDARUBICIN

5.20.1 Mechanism of Action, Route of Administration, and Indications

Idarubicin (4-demethoxydaunorubicin) is an anthracycline DNA-intercalating agent and an analog of daunorubicin. Idarubicin has a high lipophilicity, which allows a higher rate of cellular uptake than other anthracyclines. It inhibits DNA and RNA synthesis and interacts with the enzyme topoisomerase II to cause DNA cleavage (Teva 2011b). Idarubicin is administered by intravenous injection. Additional information on the pharmacology of idarubicin is located in **Table 51**.

Idarubicin is indicated for the treatment of acute myeloid leukemia (Teva 2011b).

Table 51: Pharmacology of idarubicin in adult humans

Molecular weight:	497.497
Protein binding:	94% to 97%
Metabolism:	Hepatic to idarubicinol (pharmacologically active)
Half-life elimination:	Oral; 14-35 hours; IV: 12-27 hours
Distribution:	Vd: 64 L/kg (some reports indicate 2250 L); extensive tissue binding: CSF
Time to peak, serum (C_{max}):	1-5 hours
Excretion:	Oral: Urine (~5% of dose; 0.5% to 0.7% as unchanged drug, 4% as idarubicinol); hepatic (8%) IV: Urine (13% as idarubicinol, 3% as unchanged drug); hepatic (17%)

Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; IV, intravenous; Vd, volume of distribution

5.20.2 Evidence of Placental and Breast Milk Transport

Placenta and breast milk transport of idarubicin in humans is not known. It has been hypothesized that the high liposolubility and the long half-life of idarubicin may facilitate placental transport (Achtari and Hohlfeld 2000). 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.

5.20.3 Laboratory Animal Developmental Toxicity

Preclinical studies reported in the product label observed that idarubicin was embryotoxic and teratogenic **[types of malformations not reported]** in rats, when administered orally to pregnant rats at a dose of 1.2 mg/m^2/day (one tenth the human dose); this dose was nontoxic to dams (Teva 2011b). Embryotoxicity, but not teratogenicity, was observed following administration of a maternally toxic dose of 2.4 mg idarubicin/m^2/day in rabbits; this compares to two tenths the human dose) (Teva 2011b).

Teratogenic effects of idarubicin are also described in the peer-reviewed literature. Adult female rats treated with idarubicin (0.2 mg/kg bw intravenously) prior to conception and during early pregnancy had increased early fetal loss and fetuses with decreased ossification (reviewed in Shepard and Lemire 2004). 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 µM idarubicin resulted in 100% dead embryos, while exposure to 0.025 µM

induced abnormalities in70% of embryos and a reduction in somite number and embryonic DNA content (Menegola *et al.* 1997). Abnormalities observed in rat embryos following ex vivo exposure to 0.025 µM idarubicin were effects on brain development (e.g., swollen rhombencephelon, reduced telencephon), reduced branchial bars, and short tails (Menegola *et al.* 1997). Exposure to 0.0125 µM idarubicin did not induce teratogenic effects.

5.20.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Idarubicin was administered to 23 female cancer patients (also called cases) during pregnancy identified from 13 case reports (13 cases), 1 case series (1 case), 1 retrospective case series (4 cases), 1 retrospective cohort study (2 cases) and 1 retrospective survey (3 cases) (Appendix C Table 19). Among these patients, idarubicin was used to treat acute leukemia: acute lymphocytic (2 cases), acute myelogenous (12 cases), acute promyelocytic (4 cases), and acute leukemia, type not specified (4 cases).

A total of 23 singleton pregnancies (23 conceptuses) were exposed to idarubicin. Idarubicin was administered during the first trimester in one pregnancy and in the second and/or third trimester only in 16 pregnancies (16 conceptuses). Timing of exposure was not specified in 5 pregnancies (5 conceptuses). Idarubicin was administered as polytherapy in all 23 cases.

Termination of Pregnancy

Three pregnancies were ended by induced abortion following exposure to idarubicin polytherapy. No examination of the fetus was reported for an induced abortus exposed in the first trimester to idarubicin and cytarabine (Chelghoum *et al.* 2005). Likewise, no examination of the fetus was reported for the remaining 2 induced abortuses, who were exposed in the second trimester to idarubicin and cytarabine (Chelghoum *et al.* 2005).

Spontaneous Fetal Death

Three pregnancies exposed to idarubicin polytherapy ended in stillbirth, and all three were exposed in the second and/or third trimester only. One stillbirth of a normal fetus occurred following exposure during the third trimester to idarubicin and cytarabine (Reynoso and Huerta 1994); this pregnancy was previously exposed to cytarabine and daunorubicin in the second trimester, cytarabine and mitoxantrone in the second and third trimesters. No examination of the fetus was reported for a third stillbirth, which occurred in the eighth month of gestation following exposure in the second and third trimester to idarubicin and cytarabine (Paşa *et al.* 2009). A normal fetus was reported for a second stillbirth following in utero exposure to idarubicin and cytarabine for which timing of exposure to idarubicin was not specified (Peres *et al.* 2001); this pregnancy also experienced oligohydramnios and intrauterine growth restriction.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations occurred in one infant gestationally exposed to idarubicin. This infant was born with a ventricular septal defect 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 following exposure to idarubicin and cytarabine during the second trimester, and cytarabine in the third trimesters (Niedermeier *et al.* 2005). It is unlikely that the ventricular septal defect and skeletal

malformations were induced by idarubicin polytherapy beginning at gestation week 21 because these types of malformations are induced during the period of organogenesis. Thus, the adjusted apparent rate of major malformations following exposure to idarubicin in the second and/or third trimester only was 0% (0/14 conceptuses based on 13 liveborn infants and examination of the fetus of one stillbirth).

No major malformations were observed 5 singleton pregnancies for which timing of exposure to idarubicin was not specified (0/5 conceptuses based on 4 liveborn infants and examination of the fetus of 1 stillbirth). There were no data reported for the apparent rate of major malformations following exposure to idarubicin during the first trimester.

Minor Malformations

Two infants had minor malformations following gestational exposure to idarubicin. 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 second and third trimesters to idarubicin and all-trans retinoic acid (Siu *et al.* 2002). A patent ductus arteriosus was reported in another infant born, who was born at 28 weeks of gestation following exposure during the second trimester to idarubicin and all-trans retinoic acid (Carradice *et al.* 2002); the patent ductus arteriosus observed in this infant closed after treatment with indomethacin.

Pregnancy Complications and Newborn Health

A variety of pregnancy complications were observed following gestational exposure to idarubicin. Oligohydramnios occurred in three pregnancies (Peres *et al.* 2001, Carradice *et al.* 2002, Matsuo *et al.* 2004). Intrauterine growth retardation was observed in four pregnancies (Claahsen *et al.* 1998, Peres *et al.* 2001, Baumgartner *et al.* 2009), including one case where it was secondary to placental insufficiency and was accompanied by fetal ascites (Carradice *et al.* 2002). Cardiomyopathy and cerebral ventriculomegaly were reported in one fetus with intrauterine growth restriction (Baumgartner *et al.* 2009). At gestation week 26, ultrasound of another fetus detected right ventricle dilation and a small left ventricle as well as mild systolic dysfunction in both ventricles (Niedermeier *et al.* 2005). The following pregnancy complications preceded preterm birth in three cases: spontaneous preterm rupture of membranes (1 pregnancy) (Carradice *et al.* 2002), spontaneous preterm labor and fetal distress (1 pregnancy) (Yucebilgin *et al.* 2004), and early signs of preeclampsia (1 pregnancy) (Siu *et al.* 2002). Fetal distress was observed in an additional singleton pregnancy (Claahsen *et al.* 1998).

There were a total of 17 liveborn infants with gestational exposure to idarubicin. Early preterm delivery (<34 weeks) was reported for 7 infants, late preterm delivery was reported for 5 infants and one infant was delivered at term. Data were insufficient to determine the gestational age at birth for 4 infants. Of the preterm infants, 11 infants were delivered via C-section and route of delivery was not specified for one infant. Small for gestational age was determined for 3 infants and 9 infants had normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were not sufficient to determine small for gestational age for the remaining 5 infants.

Regarding infant health effects, two liveborn infants suffered from heart problems after birth. Acute cardiac failure occurred in a newborn on day 1 and resolved on day 3 with treatment (Achtari and Hohlfeld 2000); the authors attributed the cardiac failure to second 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). Moderate dilation of the right atrium and right ventricle was reported in another

newborn, who also suffered from 2 small secundum atrial septal defects, and a small patent ductus arteriosus (Siu *et al.* 2002).

Breathing difficulties were reported for five newborns (Achtari and Hohlfeld 2000, Carradice *et al.* 2002, Siu *et al.* 2002, Baumgartner *et al.* 2009, Ganzitti *et al.* 2010), including one preterm newborn in poor condition with pulmonary hypoplasia and bilateral pneumothoraces (Carradice *et al.* 2002). Cyanosis of the extremities at birth was observed in one infant (Niedermeier *et al.* 2005). Myelosuppression occurred in two infants (Matsuo *et al.* 2004, Baumgartner *et al.* 2009). One of the infants with myelosuppression also had hepatopathy and elevated creatinine kinase levels, which normalized within a week (Matsuo *et al.* 2004). 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).

Infant Deaths

No infant deaths were reported following gestational exposure to idarubicin.

Follow Up Evaluations

Follow up evaluations were available for 12 children ranging in age from 1.5 months to 6 years with normal growth reported for all but 1 child. 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 23 singleton pregnancies (23 conceptuses) (**Table 78**). Overall, the apparent rate of major malformations among all idarubicin-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 6% (1/19 based on 17 liveborn infants and examination of the fetuses of 2 stillbirths). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). The only pregnancy exposed in the first trimester was terminated by induced abortion and no examination of the fetus was reported (Chelghoum *et al.* 2005). Thus, there were no data to determine the apparent rate of major malformations following exposure to idarubicin during the first trimester.

Major malformations were reported for only one infant exposed in the second and third trimester to idarubicin polytherapy. The major malformations included a ventricular septal defect (surgically repaired at 5 month of age), skeletal malformations (e.g. short limbs and digits) as well as shallow sacral pit and macrognathia (Niedermeier *et al.* 2005). These skeletal and cardiac malformations were not likely caused by exposure to idarubicin polytherapy beginning in gestation week 21. Thus, the adjusted apparent rate of major malformations following second and/or third trimester exposure to idarubicin was 0% (0/13 conceptuses based on 12 liveborn infants and examination of the fetus of 1 stillbirth). Similarly, no major malformations were reported for the 5 conceptuses for whom timing of exposure to idarubicin was not specified (4 liveborn infants and examination of the fetus of 1 stillbirth).

Anthracycline antibiotics, such as idarubicin, are reported to cause cardiotoxicity in adult cancer patients administered these drugs. Of note, aberrant cardiac function was observed in two fetuses (Niedermeier *et al.* 2005, Baumgartner *et al.* 2009) and 2 newborns (Achtari and Hohlfeld 2000, Siu *et al.* 2002) following exposure to idarubicin in the second and/or third trimester only. Further investigation of possible effects of idarubicin on heart development and function are needed.

5.21 IFOSFAMIDE

5.21.1 Mechanism of Action, Route of Administration, and Indications

Table 52: Pharmacology of ifosfamide in adult humans	
Molecular weight:	261.087
Protein binding:	Negligible
Metabolism:	Hepatic to active metabolites isofosforamide mustard, 4-hydroxy-ifosfamide, acrolein, and inactive dichloroethylated and carboxy metabolites; acrolein is the agent implicated in development of hemorrhagic cystitis
Half-life elimination:	High dose (3800-5000 mg/m^2): ~15 hours; lower dose (1600-2400 mg/m^2): ~7 hours
Distribution:	Vd: 5.7-49 L; penetrates CNS, but not in therapeutic levels
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	High dose (5000 mg/m^2): Urine (70% to 86%; 61% as unchanged drug); lower dose (1600-2400 mg/m^2): Urine (12% to 18% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CNS, central nervous system; Vd, volume of distribution	

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. Additional information on the pharmacology of ifosfamide is located in **Table 52**.

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

Placental transfer of ifosfamide in humans was not detected in one case series. The study reported that maternal blood levels of ifosfamide were highest (~20 µg/mL) at 24 hours after initiation of a 5 g/m^3 injection administered over 48 hours to a pregnant sarcoma patient (Mir *et al.* 2012). However, the authors reported that ifosfamide was not detected in amniotic fluid or cord blood (<5 µg/mL) (Mir *et al.* 2012).

The manufacturer's product information reported that ifosfamide is excreted in breast milk **[not specified whether breast milk transport was observed in humans or laboratory animals]** (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 ifosfamide/m^2 on gestation days 6 to 15 caused embryolethal effects, and embryotoxic effects were observed following doses of 18 mg/m^2 over the same dosing period. In mice, administration of 30 mg ifosfamide/m^2 on gestation day 11 resulted in increased resorptions and fetal anomalies. In rabbits, ifosfamide was embryotoxic and teratogenic at doses of 88 mg/m^2/day on gestation days 6 to 18 (Baxter Healthcare Corporation 2007).

Teratogenic effects of ifosfamide are also described in the peer-reviewed literature. As reviewed in Shepard and Lemire (Shepard and Lemire 2004), administration of ifosfamide (2.5 or 5.0 mg/kg bw) during mating and the first 7 days of gestation in rats resulted in decreased viability of fetuses at term and an increase in stillbirths and hydrocephalus were observed with doses up to 10 mg/kg bw. An increase in central nervous system defects was 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 ectrodactylia (the congenital absence of part or all of one or more fingers or toes) (Shepard and Lemire 2004). Skeletal defects and hydrocephalus were observed in fetal Swiss Webster mice on gestation day 19 following exposure of the pregnant dam to ifosfamide at doses of 20 mg/kg via intraperitoneal injection on gestation day 11 (Bus and Gibson 1973). Skeletal malformations included: shortened limbs, fused or missing digits, absent or not ossified skull bones and sternebrae and limbs, and shortened or kinked tail. Fused vertebrae were observed on gestation day 19 following exposure to 10 or 20 mg/kg bw ifosfamide on gestation day 11. Furthermore, ifosfamide administered on gestation day 11 significantly increased resorption rates and decreased the total number of fetuses at the 20 mg/kg bw dose and decreased body weight at doses of 10 and 20 mg/kg bw compared to control when evaluated on gestation day 19 (Bus and Gibson 1973). Ifosfamide administered subcutaneously at 45 mg/kg bw on postnatal day to mouse pups resulted in altered growth and development, including a significant reduction in body weight measured on postnatal day 15 (Bus and Gibson 1973).

5.21.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Ifosfamide was administered to 11 female cancer patients (also called cases) during pregnancy identified from 5 case reports (5 cases) and 2 case series (6 cases) (Appendix C Table 20). Ifosfamide was used to treat 2 cases of Burkitt lymphoma and 9 cases of sarcoma, including Ewing sarcoma (4 cases), high-grade sarcoma (2 cases), embryonal sarcoma (1 case), osteosarcoma (1 case), and rhabdomyosarcoma (1 case).

A total of 11 singleton pregnancies (11 conceptuses) were exposed to ifosfamide. Ifosfamide was administered in the first trimester in 1 pregnancy (1 embryo) and in the second and/third trimester only in 10 pregnancies (10 conceptuses). Ifosfamide was administered as polytherapy during all 11 pregnancies (11 conceptuses).

Termination of pregnancy

No terminations of pregnancy were reported following gestational exposure to ifosfamide.

Spontaneous Fetal Death

Spontaneous fetal death occurred in one pregnancy exposed to ifosfamide. Stillbirth at gestation week 26 was reported for a singleton pregnancy experiencing following the administration of ifosfamide polytherapy in the second trimester beginning at gestation week 16 (Peterson *et al.* 2010); no examination of the fetus was reported. This pregnancy was exposed to ifosfamide polytherapy that included: ifosfamide, cyclophosphamide, doxorubicin, etoposide, cytarabine, vincristine and rituximab. Oligohydramnios and intrauterine growth restriction were observed at gestation week 18 and 22.

Rate of Occurrence of Congenital Malformations

Major Malformations

No major malformations were reported following gestational exposure to ifosfamide. Thus the apparent rate of major malformations following exposure to ifosfamide during the first trimester was 0% (0/1 conceptus based on one liveborn infant). Similarly, the apparent rate of major malformations following exposure to ifosfamide in the second and/or third trimester only was 0% (0/9 conceptuses based on 9 liveborn infants).

Minor Malformations

No minor malformations were reported following gestational exposure to ifosfamide.

Pregnancy Complications and Newborn Health

Pregnancy complications observed following in utero exposure to ifosfamide included reductions in amniotic fluid (3 singleton pregnancies; (Fernandez *et al.* 1989, Nakajima *et al.* 2004, Mir *et al.* 2012)) and intrauterine growth restriction (3 singleton pregnancies; (Fernandez *et al.* 1989, Nakajima *et al.* 2004) (Merimsky *et al.* 1999). In addition, reductions in amniotic fluid and intrauterine growth restriction occurred in one pregnancy ending in a stillbirth (Peterson *et al.* 2010).

There were 10 liveborn infants with gestational exposure to ifosfamide. Early preterm delivery (<34 weeks) was reported for 4 infants, late preterm delivery (34-36 weeks) was reported for 5 infants and 1 infant was born at term (≥37 weeks). Of the preterm infants, 4 infants were delivered via spontaneous vaginal delivery and 5 infants were born via C-section. Small for gestational age was determined for 3 infants (Fernandez *et al.* 1989, Merimsky and Le Cesne 1998, Mir *et al.* 2012) and 7 infants had normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010).

Infant health effects observed following gestational exposure to ifosfamide included respiratory difficulties, which were observed in two preterm infants (Nakajima *et al.* 2004, Lam 2006). One infant treated for respiratory difficulties was also treated for jaundice and low hemoglobin (Nakajima *et al.* 2004). Another preterm infant had had bilateral intraventricular hemorrhages and a left occipital meningeal hematoma (Fernandez *et al.* 1989). This newborn also experienced anuria and died at age 7 days.

Infant Deaths

One infant death was reported following gestational exposure to ifosfamide. One premature infant had bilateral intraventricular hemorrhages and a left occipital meningeal hematoma (Fernandez *et al.* 1989). This newborn, who had suffered from oligohydramnios and intrauterine growth restriction during pregnancy, also experienced anuria. The infant died at age 7 days and the autopsy revealed extensive cerebral lesions (Fernandez *et al.* 1989).

Follow Up Evaluations

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 preterm infant with mildly delayed motor skills (Lam 2006).

5.21.5 Summary of Pregnancy Outcomes for ifosfamide

In utero exposure to ifosfamide was documented for 11 pregnancies (11 conceptuses) (**Table 77**). Overall, the apparent rate of major malformations among all ifosfamide-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 0% (0/10 conceptuses based on 10 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Thus the apparent rate of major malformations following exposure to ifosfamide during the first trimester was 0% (0/1 conceptuses based on one liveborn infant). Similarly, the apparent rate of major malformations following exposure to ifosfamide in the second and/or third trimester only was 0% (0/9 conceptuses based on 9 liveborn infants).

5.22 IMATINIB

5.22.1 Mechanism of Action, Route of Administration, and Indications

Table 53: Pharmacology of imatinib in adult humans

Molecular weight:	493.612
Protein binding:	Parent drug and metabolite; ~95% to albumin and alpha1-acid glycoprotein
Metabolism:	Hepatic via CYP3A4 (minor metabolism via CYP1A2, CYP2D6, CYP2C9, CYP2C19); primary metabolite (active): N-demethylated piperazine derivative (CGP74588); severe hepatic impairment (bilirubin>3-10 times ULN) increases AUC by 45% to 55% for imatinib and its active metabolite, respectively
Half-life elimination:	Parent drug:~18 hours; N-desmethyl metabolite: ~40 hours
Distribution:	**[Information not located]**
Time to peak, serum (C_{max}):	2-4 hours
Excretion:	Feces (68% primarily as metabolites, 20% as unchanged drug); urine (13% primarily as metabolites, 5% as unchanged drug)

Data from Brunton et al. (2011). Abbreviations: AUC, area under the curve; Cmax, time to reach maximal concentration in serum; ULN, upper limit of normal.

Imatinib mesylate (also called imatinib, STI 571, Glivec or Gleevec) is a protein-tyrosine kinase inhibitor. Tyrosine kinases regulate several cellular activities, including proliferation, differentiation and survival, and the deregulation of tyrosine kinases can lead to cancer. Imatinib acts by binding to the kinase and blocks the binding of adenosine triphosphate (ATP), thus inhibiting activation of the tyrosine kinase by blocking the transfer of phosphate from ATP to the tyrosine residues, and inhibiting cell proliferation and inducing cell death (Novartis 2009, Waller 2010). Imatinib 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 (Nishimura *et al.* 2003, Deininger *et al.* 2005). Imatinib is administered orally. Additional information on the pharmacology of imatinib is located in **Table 53**.

Imatinib is indicated for chronic myelocytic leukemia (also called chronic granulocytic leukemia), chronic eosinophilic leukemia and acute lymphoblastic leukemia (Novartis 2009). Imatinib is also used to treat gastrointestinal stromal tumors, which are caused by a mutated c-kit tyrosine kinase (Novartis 2009, Deshaies *et al.* 2010).

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. (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.* 2009b). Imatinib is detected in human breast

milk collected 10 to 16 hours following last maternal dose (Russell *et al.* 2007, Ali *et al.* 2009b). 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 area under the curve (AUC)). In addition, imatinib caused significant post-implantation loss in female rats at doses ≥45 mg/kg bw/day (approximately equal to the human dose of 400 mg/day based on body surface area) marked by early fetal resorptions, stillbirths, nonviable pups and/or neonatal pup death in the first five days of life. No fetal loss was reported for rats at doses of ≤30 mg imatinib/kg bw/day and there was no lasting impact of imatinib on fertility in the first generation rats (Novartis 2009).

Imatinib is anti-angiogenic in animal models through inhibitory effects on PDGFR, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). It has been hypothesized that the incidence of exomphalos and/or skeletal system defects in infants exposed to imatinib during pregnancy may be due to effects mediated via the PDFGRα (Apperley 2009). PDGFRs play an important role in mammalian organogenesis (Hoch and Soriano 2003). Mice engineered with mutated, nonfunctional PDGFRα receptors displayed omphalocele, i.e., exomphalos, vertebral and rib fusion abnormalities, kidney and urogenital abnormalities, cardiac defects, and facial clefts (comparable to cleft palate) (Soriano 1997).

5.22.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Imatinib was administered to 152 pregnant cancer patients (also called cases) identified from 13 case reports (13 cases), 8 case series (14 cases), and 1 retrospective survey (125 cases) (Appendix C Table 21). The majority of the cases were treated with imatinib for chronic myelocytic leukemia (114 cases). In addition, imatinib was used to treat gastrointestinal stromal tumors (4 cases), and 33 cases in which the health conditions were not specified by the authors (Pye *et al.* 2008); this retrospective survey was included in the NTP monograph because the majority of the cases (143 of 180 cases) were treated for cancer.

There were 155 pregnancies exposed to imatinib due to 3 patients having 2 pregnancies (AlKindi *et al.* 2005, Garderet *et al.* 2007, Dolai *et al.* 2009) and a total of 157 conceptuses exposed to imatinib due to two sets of twins (Meera *et al.* 2008, Pye *et al.* 2008). Imatinib was administered during the first trimester in 149 pregnancies (151 conceptuses due to two sets of twins), including 16 singleton pregnancies cases for whom timing of exposure was not specified (Pye *et al.* 2008). **[For those cases not specifying timing of exposure, exposure to imatinib was assumed to have occurred during the first**

trimester until pregnancy was detected because the drug is generally not prescribed to women who are known to be pregnant]. The drug was administered in the second and/or third trimester only in 6 pregnancies (6 conceptuses). Imatinib was clearly reported as been administered as monotherapy in 46 cases, and was administered as polytherapy in two cases with either dasatinib (Berveiller *et al.* 2012) or interferon alpha (Eskander *et al.* 2011). In some cases treated with imatinib monotherapy, imatinib was discontinued upon identification of the pregnancy and the patient was switched to treatment with hydroxyurea (8 cases and 9 conceptuses due to 1 set twins), or interferon (5 cases, 5 conceptuses). Co-treatment was not reported for the remaining 109 cases, which were likely also imatinib monotherapy (Pye *et al.* 2008).

Termination of Pregnancy

Thirty-six pregnancies exposed to imatinib were terminated by induced abortion (Pye *et al.* 2008, Berveiller *et al.* 2012). Of the terminated pregnancies, 29 were exposed during the first trimester and timing was not specified for 7 pregnancies **[which were also assumed to be first trimester]**. Major malformations were observed in autopsies of 3 terminated singleton pregnancies. One induced abortus had cleft palate and polydactyly and another fetus had warfarin embryopathy with a depressed nasal bridge, choanal stenosis, Dandy Walker cyst, a ventricular septal defect, coarctation of the aorta, and gastroschisis (Pye *et al.* 2008). The fetus with suspected warfarin embryopathy was co-exposed to warfarin and other non-cancer chemotherapeutic agents during pregnancy (Pye *et al.* 2008); thus, malformations observed in this induced abortus were not attributable to imatinib. The third singleton pregnancy exposed to imatinib was terminated because of unspecified abnormal findings detected on the prenatal ultrasound along with elevated alpha fetoprotein, but no examination of the fetus was reported (Pye *et al.* 2008); elevated levels of alpha fetoprotein suggest a high probability of fetal neural tube defects **[thus, counted as a major malformation]**. A normal fetus from another induced abortion was reported to have hydrops with subcutaneous edema, plural effusion, and ascites (Berveiller *et al.* 2012); this pregnancy was exposed to imatinib early in the first trimester and then switched to dasatinib in gestation week 5, after detection of the pregnancy. No data were available examination of the fetuses for the remaining 33 fetuses of induced abortions exposed to imatinib during pregnancy. Thus, examination of the fetuses of 4 induced abortions revealed that 2 fetuses had major malformations possibly attributable to imatinib.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 20 pregnancies exposed to imatinib, including 19 spontaneous abortions and 1 stillborn fetus following exposure during the first trimester (AlKindi *et al.* 2005, Pye *et al.* 2008). No individual data on examination of fetuses was available for any of the spontaneous abortions, which were exposed to imatinib monotherapy (1 pregnancy) (AlKindi *et al.* 2005) or co-treatments were not specified (n=18 pregnancies) (Pye *et al.* 2008).

Meningocele, a major malformation, was reported in one stillborn fetus exposed in the first trimester to imatinib, then subsequently to hydroxyurea after the first trimester (Choudhary *et al.* 2006, Pye *et al.* 2008). Meningocele refers to a protrusion of the meninges (the covering of the spinal cord) through a defect in the cranium or spinal column.

Rate of Occurrence of Congenital Malformations

Major Malformations

Table 54: Major malformations diagnosed at birth possibly attributable to in utero exposure to imatinib

Trimester exposed	Major malformations observed[a]	Apparent rate (affected/total conceptuses[b])
During 1st	Small exomphalos and scoliosis	11% (11/100)
	Exomphalos, hemivertebrae, right shoulder anomaly, right kidney agenesis, left duplex kidney and hypoplastic lungs	
	Exomphalos, hemivertebrae and right renal agenesis	
	Hypospadias (2 infants)	
	Premature closure of cranial sutures	
	Pyloric stenosis	
	Communicating hydrocephalus, cerebral hypoplasia, an atrial septal defect, overriding aorta, ascites, and pericardial effusion	
	Cleft palate and polydactyly	
	Abnormal ultrasound and elevated alpha fetoprotein	
	Meningocele	
2nd and/or 3rd only	None	0% (0/6)

[a] One embryo per major malformation, unless noted in parentheses
[b] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations following in utero exposure to imatinib were observed in 8 liveborn infants and the examination of 3 induced abortions and 1 stillbirth. All major malformations occurred in fetuses of pregnancies that were exposed to imatinib in the first trimester (Pye *et al.* 2008). Three liveborn infants had exomphalos (umbilical hernia) accompanied by a skeletal malformation or exomphalos, a skeletal malformation and right kidney agenesis: a small exomphalos and scoliosis with no co-treatments during pregnancy (1 infant); exomphalos, hemivertebrae (spinal malformation caused by underdevelopment of one side of the vertebrae), right shoulder anomaly as well as right kidney agenesis, left duplex kidney and hypoplastic lungs with no co-treatments during pregnancy (1 infant); and exomphalos, hemivertebrae and right renal agenesis with first trimester exposure to imatinib, then interferon (1 infant). Hypospadias was reported in two liveborn infants, including one infant from a pregnancy that was subsequently exposed to hydroxyurea (timing of exposure NS). Premature closure of the skull sutures (craniosynostosis) was reported for a liveborn infant that was subsequently exposed to hydroxyurea for the remainder of the pregnancy. Pyloric stenosis was observed in one liveborn infant from a pregnancy that was subsequently exposed to hydroxyurea in the third trimester (Heartin *et al.* 2004, Pye *et al.* 2008). An eighth liveborn infant with major malformations had communicating hydrocephalus, cerebral hypoplasia, an atrial septal defect, overriding aorta, ascites, and pericardial effusion; this premature infant died 45 minutes after delivery, and no co-treatments during pregnancy were specified.

As mentioned above, major malformations were observed in the examination of the fetuses of 2 induced abortions and 1 stillbirth; all cases were exposed in the first trimester and reported in the same survey retrospective (Pye *et al.* 2008). Cleft palate and polydactyly was observed in a fetus from an induced abortion with no co-treatments during pregnancy. Abnormally high alpha-feto proteins were reported for an induced abortion; elevated alpha-feto proteins generally indicate a neural tube defect. Finally, a meningocele was observed via ultrasound and confirmed upon birth of a stillborn fetus with co-treatment of hydroxyurea after the first trimester. In utero co-treatment with warfarin, not imatinib, was likely responsible for the malformations observed in the another induced abortus: warfarin

embryopathy with a depressed nasal bridge, choanal stenosis, Dandy Walker cyst, a ventricular septal defect, coarctation of the aorta, and gastroschisis. Thus, the apparent rate of malformations following exposure to imatinib in the first trimester is 11% (11/100 conceptuses based on 95 liveborn infants and examination of the fetuses of 4 induced abortions and 1 stillbirth) (**Table 54**).

No malformations (either major or minor) were observed in the 6 liveborn infants with in utero exposure to imatinib in the second and/or third trimester only. Thus, the apparent rate of malformations following exposure to imatinib in the first trimester is 0% (0/6 conceptuses based on 6 liveborn infants).

Minor Malformations

One infant had a minor malformation, a non-patent mid-line perineal pit (Russell *et al.* 2007); this infant was exposed to imatinib during the entire pregnancy with no co-treatments.

Pregnancy Complications and Newborn Health

There were very few pregnancy complications or infant health effects following in utero exposure to imatinib. Pregnancy complications included: spontaneous preterm labor (1 pregnancy) (Meera *et al.* 2008) and signs of placental insufficiency (1 pregnancy) (Skoumalova *et al.* 2008).

There were 101 liveborn infants with in utero exposure to imatinib. Early preterm delivery (<34 weeks) was reported for 3 infants (including one set of twins), late preterm delivery (34 to <37 weeks) was reported for 6 infants (including a set of twins), and 25 infants were born at term. Data were insufficient to identify age at birth for the remaining 67 infants. Of the 9 preterm infants, 4 infants were delivered via spontaneous vaginal delivery (including one set of twins) 1 infant was delivered via induced vaginal delivery and 3 infants were delivered via C-section (including one set of twins); route of delivery was not specified for one preterm infant. Small for gestational age was observed for 2 infants and 23 infants had normal birth weights based upon data reported for sex, body weight and gestational age at birth of each infant (Olsen *et al.* 2010). The data reported were insufficient to identify small for gestational age in the remaining 76 infants.

Infant Deaths

Two infant deaths occurred in pregnancies exposed to imatinib. One infant from a set of premature twins died at 5 days; the infant had a normal karyotype and no apparent malformations (Meera *et al.* 2008). Another preterm infant with communicating hydrocephalus and other malformations died 45 minutes after birth (Pye *et al.* 2008).

Follow Up Evaluations

Of the 26 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 *et al.* 2005, Skoumalova *et al.* 2008).

5.22.5 Summary of Pregnancy Outcomes for Imatinib

In utero exposure to imatinib was documented for 155 pregnancies, including two sets of twins (157 conceptuses) (**Table 81**). Overall, the apparent rate of major malformations among all imatinib-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 11% (12/106 conceptuses based on 101 liveborn infants and examination of the fetus of 4 induced abortions

and 1 stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major congenital malformations were observed in 12 conceptuses exposed to imatinib during the first trimester. The human and animal data suggest that imatinib exposure during the first trimester of pregnancy may induce a specific pattern of major malformations as observed in 3 infants, including: exomphalos (umbilical hernia) accompanied by a skeletal malformation with or without urogenital malformations (i.e., right kidney agenesis) (Pye *et al.* 2008). Five additional major malformations observed in an induced abortus and liveborn infants following gestational exposure to imatinib involved defects of the cranial and/or spinal column, including: elevated alpha-feto proteins (indicating a possible spinal cord defect), cleft palate, premature closure of cranial sutures, meningocele, and communicating hydrocephalus in an infant with cardiac defects. Malformations of one induced abortus were attributed to co-treatment with warfarin, not imatinib. Thus, the adjusted apparent rate of major malformations following exposure to imatinib during the first trimester was 11% (11/100 conceptuses based on 95 liveborn infants and examination of the fetus of 4 induced abortions, 1 spontaneous abortion and 1 stillbirth).

Imatinib exerts inhibitory actions on several tyrosine kinases. One hypothesis for the incidence of exomphalos and/or skeletal system defects in infants gestationally-exposed to imatinib may be effects of imatinib mediated via the PDFGRα (Apperley 2009). Mice engineered with mutated, nonfunctional PDGFRα receptors displayed similar birth defects as congenital malformations seen in human infants exposed to imatinib in utero, including: omphalocele, (i.e., exomphalos), vertebral and rib fusion abnormalities, kidney and urogenital abnormalities, cardiac defects, and facial clefts (comparable to cleft palate) (Soriano 1997). Furthermore, there is evidence from clinical trials as well as laboratory studies that imatinib may disrupt bone remodeling by suppressing osteoclasts, stimulating proliferation, but not maturation of osteoblasts (Vandyke *et al.* 2010), which could have an effect on skeletal development.

5.23 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).

Table 55: Pharmacology of interferon alpha in adult humans

Molecular weight:	17,500-23,000 (range for all interferon alpha)
Protein binding:	**[Information not located]**
Metabolism:	**[Information not located]**
Half-life elimination:	IM and SC: ~2-3 hours; IV: ~2 hours
Distribution:	Vd: 12 to 40 L
Time to peak, serum (C_{max}):	IV: 30 minutes
Excretion:	Not detected in urine (catabolized in the kidney)

Data from Schering Corporation (2007) and Wills (Wills 1990). Abbreviations: Cmax, time to reach maximal concentration in serum; IM, intramuscular; IV, intravenous; SC, subcutaneous; Vd, volume of distribution.

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, intramuscular, intralesional or intravenous injection. Additional information on the pharmacology of interferon alpha is located in **Table 55**.

Recombinant alpha interferons are indicated for hairy cell leukemia, malignant melanoma, follicular lymphoma, and Philadelphia chromosome positive (Ph-positive) chronic myelogenous leukemia (Roth and Foon 1986, Bekisz *et al.* 2004). 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. (1995) reported that fetal blood and amniotic levels of interferon alpha were below the level of detection (<2 international units (IU)/ml) 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 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. (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 has been associated with significant, dose-dependent increases in abortions in laboratory animals at doses well above the recommended human dose. For example, interferon alpha 1a induced abortions in pregnant rhesus monkeys when administered during organogenesis or late gestation at doses of 1, 5, or 25 million IU/kg/d (20 to 500 times the human weekly dose based on body surface area) (Roche 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).

In the peer-reviewed literature, 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 resulted in lower fetal weights and delays in ossification.

5.23.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Interferon alpha was administered to 41 female cancer patients (also called cases) during pregnancy identified from 15 case reports (15 cases), 11 case series (23 cases) and 2 retrospective surveys (3 cases) (Appendix C Table 22). Among these patients, interferon alpha was used to treat chronic myeloid leukemia (33 cases), hairy cell leukemia (2 cases), melanoma (4 cases), and one patient each with Hodgkin lymphoma and multiple myeloma.

A total of 41 pregnancies yielding 43 infants were born to these patients, including two sets of twins (De Carolis *et al.* 2006, Egberts *et al.* 2006). Interferon alpha was administered during the first trimester to 19 patients (20 conceptuses due to one set of twins) and in the second and third trimester only to 20 patients (21 conceptuses due to one set of twins). Timing of exposure was not specified in 2 cases (Pye *et al.* 2008). Interferon alpha was administered as monotherapy to 37 patients (38 infants) (Appendix C Table 22), including 6 patients who were switched from imatinib to interferon alpha upon identification of the pregnancy (Koh and Kanagalingam 2006, Garderet *et al.* 2007, Pye *et al.* 2008, Skoumalova *et al.* 2008, Klamova *et al.* 2009), 1 patient who was switched from dasatinib to interferon alpha upon identification of the pregnancy (Conchon *et al.* 2010), and 2 additional patients who were switched from interferon to other treatments (De Carolis *et al.* 2006, Gottschalk *et al.* 2009). Interferon was administered as polytherapy to 2 patients (2 infants) (Baykal *et al.* 2000, Eskander *et al.* 2011).

Termination of Pregnancy

No terminations of pregnancy were reported.

Spontaneous Fetal Death

No spontaneous abortions or stillbirths were reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations following in utero exposure to interferon alpha were observed in only 1 liveborn infant. Exomphalos, right renal agenesis, and hemivertebrae were observed in one infant who was

exposed to interferon (timing of exposure not specified) after exposure to imatinib in the first trimester (Pye *et al.* 2008). This constellation of major malformations was likely due to in utero exposure to imatinib, not interferon, because two other infants exposed to imatinib monotherapy in the first trimester had similar malformations. Thus, the apparent rate of major malformations attributable to interferon alpha at any time during pregnancy was 0% (0/20 conceptuses based on 20 liveborn infants). No major malformations were observed following exposure in the second and/or third trimester only (0/21 conceptuses based on 21 liveborn infants). Similarly, no major malformations were observed in the two liveborn infants for whom timing of exposure was not specified.

Minor Malformations

No minor malformations were reported.

Pregnancy Complications and Newborn Health

Pregnancy complications were reported for two pregnancies. Intrauterine fetal growth restriction occurred at gestation week 28 following first trimester exposure to interferon, second trimester exposure to dacarbazine and second and third trimester exposure to cisplatin (Gottschalk *et al.* 2009). Intrauterine growth retardation and severe oligohydramnios occurred in another pregnancy with exposure to interferon in the first through third trimesters of pregnancy (Mubarak *et al.* 2002).

There were 43 liveborn infants with in utero exposure to interferon alpha. Early preterm delivery (<34 weeks) was reported for 3 infants, late preterm delivery (34 to <37 weeks) was reported for 8 infants (including 2 sets of twins), and 30 infants were delivered at term (≥37 weeks). Data were insufficient to identify the gestational age at birth for 2 infants. Of the 11 preterm infants, 2 infants were delivered via spontaneous vaginal birth, 2 infants (1 set of twins) were delivered via induced vaginal birth, and 7 infants were delivered via C-section (including one set of twins). Small for gestational age was identified for 4 infants and 22 infants had normal body weight based on data reported for sex, gestational age and body weight at birth of each infant. The data were insufficient to identify small for gestational age in the remaining 17 infants. There were no newborn health issues with the exception of one infant with transient thrombocytopenia (Mubarak *et al.* 2002).

Infant Deaths

No infant deaths were observed.

Follow Up Evaluations

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 (Mubarak *et al.* 2002, Skoumalova *et al.* 2008, Gottschalk *et al.* 2009). Normal growth and development were reported for all 25 children.

5.23.5 Summary of Pregnancy Outcomes for interferon alpha

In utero exposure to interferon alpha was documented for 41 pregnancies, including two set of twins (43 conceptuses) (**Table 81**). Overall, the apparent rate of major malformations among all interferon alpha-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 2% (1/43 conceptuses based on 43 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). No major malformations were attributable to interferon alpha among the 43 liveborn infants exposed in utero. One infant, who was exposed to interferon (timing of exposure not specified) and imatinib in the

first trimester, had a constellation of major malformations consistent with imatinib exposure. Furthermore, no malformations were observed in developmental toxicity studies of interferon alpha in laboratory animals.

In addition, there was one case report of a melanoma patient with a normal pregnancy outcome following treatment during the second and third trimester of pregnancy with interferon beta, which is a Type I interferon similar to interferon alpha (Ishida *et al.* 2009) (Appendix C Table 22). Similar to the pregnancy outcomes following gestational exposure to interferon alpha, no major malformations were observed in pregnancies of women treated with interferon beta for multiple sclerosis, a non-cancerous health condition (Lu *et al.* 2012); interferon beta was not reviewed in this monograph.

5.24 METHOTREXATE

5.24.1 Mechanism of Action, Route of Administration, and Indications

Methotrexate is in the group of antineoplastic agents known as antimetabolites. It inhibits the enzyme dihydrofolic acid reductase, which is essential in the synthesis of purine nucleotides and thymidylate. Inhibition of the synthesis of these compounds interferes with DNA replication and repair and cellular replication. It may be administered by intramuscular, intravenous, intra-arterial, or intrathecal injection. Additional information on the pharmacology of methotrexate is located in **Table 56**.

Table 56: Pharmacology of methotrexate in adult humans

Molecular weight:	454.4393
Protein binding:	~50%
Metabolism:	Partially metabolized by intestinal flora (after oral administration); hepatic aldehyde oxidase converts methotrexate to 7-hydroxy methotrexate; polyglutamates are produced intracellularly in a dose-and duration-dependent manner, and are just as potent as methotrexate; polyglutamates are slowly eliminated by the cell once formed and can be converted back to methotrexate.
Half-life elimination:	Low dose: 3-10 hours; High dose: 8-15 hours
Distribution:	Penetrates slowly into 3rd space fluids (e.g., pleural effusions, ascites), exits more slowly from these compartments than from plasma; sustained concentrations retained in kidney and liver; Vd: 0.18 L/kg (initial); 0.4-0.8 L/kg (steady state)
Time to peak, serum (C_{max}):	Oral: 1-2 hours; IM: 30-60 minutes
Excretion:	Urine: 80 to 90% as unchanged drug; 5 to 7% as 7-hydryoxy methotrexate); feces <10%)

Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CSF, cerebral spinal fluid; IM, intramuscular; Vd, volume of distribution.

Indications for methotrexate include gestational choriocarcinoma, chorioadenoma destruens, hydatidiform mole, meningeal leukemia (prophylaxis and treatment), breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungiodes, lung cancer, non-Hodgkin lymphoma, and osteosarcoma (Hospira 2008c). Methotrexate is used to treat non-cancerous diseases, such as the severe, recalcitrant disabling cases of psoriasis (Bedford 2012) and rheumatoid arthritis, including polyarticular-course juvenile rheumatoid arthritis (Duramed 2005). Methotrexate is also used as an abortifacient in humans (Kulier *et al.* 2004, Bartz and Goldberg 2009), particularly for ectopic (also called tubal) pregnancies (Lipscomb 2007).

5.24.2 Evidence of Placental and Breast Milk Transport

Placental milk transport of methotrexate in humans has been reported. In one case report, methotrexate was detected in cord blood at a concentration of 1.86 $x10^{-9}$ M following delivery by a woman who was treated weekly with methotrexate therapy (20 mg/m^2) for acute lymphoblastic leukemia (Schleuning and Clemm 1987).

Breast milk transfer of methotrexate in humans was reported in one case. Johns et al. (1972) detected low levels of methotrexate in breast milk of a one-month postpartum woman following administration of 15 mg/m^2 (22.5 mg/day) for choriocarcinoma. They collected urine, blood, and milk samples at 2-

hour intervals. The peak plasma concentration (1.8×10^{-7} M) occurred at 6 hours and the milk concentration (5.0×10^{-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 3.5 days of incubation with 5-40 µg **[0.005-0.04 mg]** methotrexate resulted in ratio changes of brain weight and cerebellum cell numbers (Zamenhof 1985). No defects were observed at doses below 10 mg methotrexate/kg bw in ICR mice administered a dose-range of 0.3 to 50 mg methotrexate per single intraperitoneal injection on gestation day 10 (Skalko and Gold 1974). However, higher doses caused an increase in embryolethality and teratogenicity in mice, including ectrodactyly and cleft palate at the highest doses (25 and 50 mg/kg) (Skalko and Gold 1974). In vitro studies of rat embryos treated with methotrexate in culture medium at concentrations as low as 0.05 µg/mL **[0.05 mg/mL]** reported malformations of the rhombencephalic and telencephalic brain regions within 48 hours (Schmid 1984). Other malformations were observed in the caudal trunk, heart and forelimb regions and in the vascular structures (Schmid 1984). Intravenous administration of methotrexate to pregnant Wistar rats induced embryolethality at a dose of 0.3 mg/kg bw on gestation Day 11 (Wilson *et al.* 1975). In contrast, methotrexate administered intravenously to pregnant rhesus monkeys at 3.0 mg/kg bw/day on gestation days 29 to 32 caused embryonic growth retardation, but no teratogenicity (Wilson *et al.* 1975). Methotrextate induced malformations in 94% of New Zealand white rabbit offspring when administered intravenous at 19.2 mg/kg bw 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

Number of Cases, Publications, and Types of Cancer Treated

Methotrexate was administered to 84 female cancer patients (also called cases) during pregnancy identified from 25 case reports (25 cases), 11 case series (16 cases), 4 retrospective case series (23 cases), 2 retrospective cohort studies (4 cases), 5 retrospective surveys (15 cases), and one registry survey (1 case) (Appendix C Table 23). Among these patients, methotrexate was used to treat acute lymphocytic leukemia (32 cases), acute myelogenous leukemia (also, called acute granulocytic leukemia; 7 cases), acute myelomonocytic leukemia (1 case), non-Hodgkin lymphoma (8 cases), and Burkitt lymphoma (3 cases). Methotrexate was also used to treat breast cancer (25 cases), and choriocarcinoma (6 cases, include 1 case each of the ovary, uterus and vagina, respectively), and Ewing sarcoma (1 case). The cancer type was not specified for one case.

A total of 84 pregnancies (87 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, Turchi and Villasis 1988, Nantel *et al.* 1990). Methotrexate was administered during the first trimester in 29 pregnancies (29 conceptuses) and in the second and/or third trimester only in 56 pregnancies (59

conceptuses due to three sets of twins). Methotrexate was most frequently administered as polytherapy (80 cases, 84 conceptuses). It was administered as monotherapy in 4 cases (4 conceptuses), including one case who was treated with a single dose of methotrexate after treatment with 6-mercaptopurine (Frenkel and Meyers 1960).

Termination of Pregnancy

Three pregnancies were terminated following exposure to methotrexate. One pregnancy was terminated by induced abortion following first trimester exposure to methotrexate (Molkenboer *et al.* 2005); no examination of the fetus was reported.

Two pregnancies were terminated following second trimester exposure to methotrexate. An induced abortion terminated a fetus with major malformations following exposure in the second trimester to methotrexate, cyclophosphamide and 5-fluorouracil (Leyder *et al.* 2010); however, this fetus was also exposed to chemotherapy in the first trimester, including epirubicin, cyclophosphamide, and 5-fluorouracil, as well as radiation therapy. Malformations observed in this fetus 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). Finally, a normal fetus was reported for an induced abortion following exposure in the second trimester to methotrexate and cyclophosphamide (Armitage *et al.* 1977).

Spontaneous Fetal Death

Spontaneous fetal loss occurred in 6 pregnancies including 4 spontaneous abortions and 2 stillbirths. Spontaneous abortions were reported for 4 pregnancies following first trimester exposure and co-treatment with: cyclophosphamide and 5-fluorouracil (Zemlickis *et al.* 1992b, Ring *et al.* 2005b), 6-mercaptopurine and vincristine (Bergstrom and Altman 1998), or epirubicin and vincristine (Giacalone *et al.* 1999); no examination of the fetus was reported.

A normal fetus was reported for a stillbirth following first trimester exposure to methotrexate, cyclophosphamide and 5-fluorouracil (Peres *et al.* 2001). Finally, another stillbirth occurred following second trimester exposure to methotrexate and co-exposure to vincristine, asparaginase, daunorubicin, and cytarabine (Molkenboer *et al.* 2005); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 1 liveborn infant and 1 induced abortion following gestational exposure to methotrexate. One liveborn infant had microencephaly, hypertelorism, low-set ears, micrognathia, and a right palmar simian crease (Bawle *et al.* 1998); this infant was exposed from the first through third trimesters and co-exposed to 5-fluorouracil and radiation therapy in the second trimester. Thus, the apparent rate of major malformations following exposure to methotrexate in the first trimester was 4% (1/24 based on 23 liveborn infants and examination of the fetus of 1 stillbirth) (**Table 57**).

Table 57: Major malformations diagnosed at birth possibly attributable to in utero exposure to methotrexate		
Trimester exposed	**Major malformations observed**	**Apparent rate of (affected/total conceptuses[a])**
During 1st	Microencephaly, hypertelorism, low-set ears, micrognathia, and a right palmar simian crease	4% (1/24)
2nd and/or 3rd only	0	0% (0/58)
[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths		

Major malformations were observed in a fetus from an induced abortion following exposure to methotrexate in the second trimester with co-treatments cyclophosphamide and 5-fluorouracil (Leyder *et al.* 2010). However, this fetus was also exposed to chemotherapy in the first trimester, including epirubicin, cyclophosphamide, and 5-fluorouracil, as well as radiation therapy. Therefore, the malformations were most likely due to first trimester exposure to other cytotoxic chemotherapy agents. These malformations 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). Thus, the apparent rate of major malformations following exposure to methotrexate in the second and/or third trimester was 0% (0/58 based on 56 liveborn infants and examination of the fetus of 2 induced abortions).

Minor Malformations

Minor malformations were observed in three infants exposed to methotrexate during gestation. An inguinal hernia occurred in an infant with first and second trimester exposure to methotrexate 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 second and third trimester to methotrexate, vincristine, daunorubicin, cyclophosphamide, asparaginase and 6-mercaptopurine (Van Calsteren *et al.* 2010a), and another infant was exposed in the second and/or third trimester to combination therapy with methotrexate, cyclophosphamide and 5-fluorouracil (Ring *et al.* 2005b). Ring et al. (2005b) stated that they did not believe the hemangioma was due to chemotherapy exposure in utero. **[It is possible that one 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 *et al.* 2005b).]** In addition, chromosomal analysis of an apparently normal infant reported some chromosome breakage and a ring chromosome (Schleuning and Clemm 1987).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications occurred following in utero exposure to methotrexate. Pregnancy complications included preeclampsia (2 pregnancies) (Coopland *et al.* 1969, Bergstrom and Altman 1998), elevated maternal blood pressure (1 pregnancy) (Turchi and Villasis 1988), premature rupture of membranes (5 pregnancies) (Doney *et al.* 1979, Okun *et al.* 1979, Karp *et al.* 1983, Meador *et al.* 1987, Udink ten Cate *et al.* 2009), and spontaneous preterm labor (9 pregnancies) (Berrebi *et al.* 1983, Nantel *et al.* 1990, Willemse *et al.* 1990, Moore and Taslimi 1991, Giannakopoulou *et al.* 2000, Hansen *et al.* 2001, Brudie *et al.* 2011), including two cases with both premature rupture of membranes and spontaneous preterm labor (Karp *et al.* 1983, Meador *et al.* 1987). 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.* 2005b). Transient oligohydramnios occurred in one pregnancy (Hansen *et al.* 2001).

There were 79 liveborn infants gestationally exposed to methotrexate. Early preterm delivery (<34 weeks) was reported for 16 infants, late preterm delivery (34-36 weeks) was reported for 11 infants, and 28 infants were delivered at term. Data were insufficient to determine the timing of delivery of 24 infants. Of the preterm infants, 12 infants were delivered via spontaneous vaginal delivery, 2 infants via induced vaginal delivery, and 12 infants via C-section; data were insufficient to determine the route of delivery for the remaining 1 infant. Small for gestational age was determined for 10 newborns and 49 infants had normal body weights based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age in the remaining 20 infants.

Breathing difficulties were reported in 5 newborns (Willemse *et al.* 1990, Giannakopoulou *et al.* 2000, Hansen *et al.* 2001, Ring *et al.* 2005b), including one infant who had asystole and apnea at birth (Willemse *et al.* 1990). Another infant received oxygen treatment and positive airway pressure after meconium aspiration at birth (Hansen *et al.* 2001). Transient myelosuppression was observed in 5 infants (Khurshid and Saleem 1978, Okun *et al.* 1979, Dara *et al.* 1981, Aviles and Niz 1988, Aviles *et al.* 1991) and 2 of these infants had jaundice (Dara *et al.* 1981, Hansen *et al.* 2001). One infant with transient myelosuppression also was hydropic with abdominal distension and slight cardiomegaly, and was treated for congenital heart failure (Okun *et al.* 1979). One otherwise normal infant had 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).

Infant Deaths

There were two infant deaths following gestational exposure to methotrexate. One infant died of septicemia at age 21 days and another infant died of gastroenteritis at age 90 days (Aviles and Niz 1988).

Follow Up Evaluations

There were 52 infants with follow-up evaluations at ages ranging from 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 (Gulati *et al.* 1986).

5.24.5 Summary of Pregnancy Outcomes for methotrexate

In utero exposure to methotrextate occurred in 85 pregnancies, including three sets of twins (88 conceptuses) (**Table 76**). Overall, the raw apparent rate of major malformations among all methotrexate-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 2% (2/82 based on 79 liveborn infants and examination of the fetuses of 2 induced abortions and 1 stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Of the 29 singleton pregnancies exposed in the first trimester, only one newborn had major malformations (Bawle *et al.* 1998). The craniofacial malformations reported in this infant were similar to the malformations reported in infants born following unsuccessful methotrexate-induced abortions in the first trimester (Bawle *et al.* 1998). Malformations and hypoplasia of the cranium and skeletal system and stunted growth have been reported in developmental toxicity studies of methotrexate in many laboratory animals (Hyoun *et al.* 2012). Thus, these types of malformations have been proposed as a possible methotrexate syndrome likely due to exposure to methotrexate between 6 and 8 weeks of gestation in humans (Vaux *et al.* 2003, Hyoun *et al.* 2012). The apparent rate of major malformations following first trimester exposure to

methotrexate was 4% (1/23 liveborn infants and examination of the fetus of 1 stillbirth). In contrast, there were no major malformations attributable to exposure to methotrexate in the second and/or third trimester only (0/58 conceptuses based on 56 liveborn infants and examination of the fetuses of 2 induced abortuses).

5.25 MITOXANTRONE

5.25.1 Mechanism of Action, Route of Administration, and Indications

Table 58: Pharmacology of mitoxantrone in adult humans	
Molecular weight:	444.485
Protein binding:	78%
Metabolism:	Hepatic; pathway not determined
Half-life elimination:	Terminal: 23-215 hours (median: ~75 hours); may be prolonged with hepatic impairment
Distribution:	Vd: 14 L/kg; Vdss: >1000 L/m2; distributes extensively into tissue (pleural fluid, kidney, thyroid, liver, heart) and red blood cells
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (25%); urine (6% to 11%; 65% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; Vd, volume of distribution; Vdss, volume of distribution at stead state	

Mitoxantrone is an anthracycline intercalating agent that damages DNA by causing cross-links and strand breaks after binding. Mitoxantrone also interferes with RNA and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling DNA (APP Pharmaceuticals 2010). Mitoxantrone is administered via intravenous injection. Additional information on the pharmacology of mitoxantrone is located in **Table 58**.

Mitoxantrone is 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 in humans is not known. 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 (D'Incalci *et al.* 1982) and laboratory animal models (Van Calsteren *et al.* 2010b, Van Calsteren *et al.* 2010d).

Mitoxantrone was detected in human breast milk following maternal administration of the drug. Detectable levels of mitoxantrone were present in breast milk at 21 and 28 days post-administration of 6 mg/m^2 to the mother on 3 consecutive days (Azuno *et al.* 1995). 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 mitoxantrone is designated a human teratogen based on its mechanism of action and the development effects of other anthracycline intercalating agents (i.e., doxorubicin and ametantrone) (APP Pharmaceuticals 2010). Mitoxantrone did not induce teratogenic effects in rats and rabbits at the maximum doses tested, which were 2% and 5% of the maximal human dose on a body surface area basis, respectively. Fetal growth retardation in rats and increased incidence of premature delivery in rabbits administered mitoxantrone during the period of organogenesis at ≥ 0.01 mg/kg bw/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 bw/day to the dam (Petrere *et al.* 1986). No teratogenic effects were observed in the fetuses of pregnant rats treated over 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

Number of Cases, Publications, and Types of Cancer Treated

Mitoxantrone was administered to 17 patients (also called cases) during pregnancy identified from 7 case reports (7 cases), 2 case series (3 cases), 1 retrospective case series (3 cases), 1 retrospective cohort study (2 cases) and 1 retrospective survey (2 cases) (Appendix C Table 23). Among these patients, mitoxantrone was administered to treat acute myelogenous leukemia (9 cases), acute promyelocytic leukemia (2 cases), acute leukemia (type not specified; 3 cases), non-Hodgkin lymphoma (1 case) and breast cancer (2 cases).

A total of 17 singleton pregnancies (17 conceptuses) were exposed to mitoxantrone. Mitoxantrone was administered during the first trimester in one case (1 conceptus), and in the second and/or third trimester only in 13 cases (13 conceptuses). The timing of exposure was not specified for 3 cases (3 conceptuses). Mitoxantrone was used in polytherapy for all cases.

Termination of Pregnancy

One induced abortion ended a pregnancy following second trimester exposure to mitoxantrone and cytarabine (Chelghoum *et al.* 2005); no examination of the fetus was reported.

Spontaneous Fetal Death

Spontaneous fetal death was reported in two pregnancies exposed to mitoxantrone, including one spontaneous abortion and one stillbirth. A spontaneous abortion occurred following first trimester exposure to mitoxantrone and cytarabine (Chelghoum *et al.* 2005); no examination of the fetus was reported. A grossly normal fetus was reported from a stillbirth (Reynoso and Huerta 1994). The pregnancy ending in stillbirth was exposed during the second and third trimesters to mitoxantrone and cytarabine following exposure in the second trimester to daunorubicin and cytarabine, and was switched to idarubicin and cytarabine for the consolidation therapy in the third trimester.

Rate of Occurrence of Congenital Malformations

Major Malformations

No major malformations were reported following gestational exposure to mitoxantrone. Thus, the apparent rate of major malformations following exposure to mitoxantrone in the second and/or third trimester only was 0% (0/12 conceptuses based on 11 liveborn infants and examination of the fetus of 1 stillbirth). Also, no malformations were observed in 3 liveborn infants for whom timing of gestational exposure to mitoxantrone was not specified.

Minor Malformations

Minor malformations were observed in one infant with gestational exposure to mitoxantrone. Bilateral hydronephrosis with dilation of the left proximal ureter was reported in an infant exposed to mitoxantrone and cytarabine in the third trimester, following exposure to daunorubicin and cytarabine in the second trimester (Garcia *et al.* 1999).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications occurred following exposure to mitoxantrone in utero. One patient experienced transient spontaneous preterm labor early in the third trimester 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 intrauterine growth restriction was reported in 3 fetuses (Hsu *et al.* 1995, Garcia *et al.* 1999, Baumgartner *et al.* 2009). Two singleton pregnancies experienced fetal heart abnormalities, including: cardiomyopathy (Baumgartner *et al.* 2009) and fetal tachycardia (Garcia *et al.* 1999). The fetus with cardiomyopathy also suffered from transient ventriculomegaly after initiation of chemotherapy treatment (Baumgartner *et al.* 2009). Fetal distress was observed in two pregnancies as intermittent sinusoidal fetal heart rate patterns (Yucebilgin *et al.* 2004) and an abnormal cardiotocogram and low biophysical profile score (Mavrommatis *et al.* 1998).

A total of 14 liveborn infants were gestationally exposed to mitoxantrone. Early preterm delivery (<34 weeks) was reported for 5 infants, late preterm delivery (34 to <37 weeks) was reported for 6 infants. Data were not sufficient to determine the gestational age at delivery for 3 infants. Of the preterm infants, one infant was born via induced vaginal delivery and 10 infants were delivered via C-section. Small for gestational age was determined for 4 infants and 7 infants were normal based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for the remaining 3 infants.

Newborn health effects following gestational exposure to mitoxantrone included respiratory difficulties (4 infants) (Reynoso and Huerta 1994, Mavrommatis *et al.* 1998, Garcia *et al.* 1999, Giacalone *et al.* 1999, Baumgartner *et al.* 2009). Four newborns had transient myelosuppression, including anemia (Hsu *et al.* 1995, Baumgartner *et al.* 2009), neutropenia and thrombocytopenia (Garcia *et al.* 1999), and thrombocytopenia and leukocytopenia (Gondo *et al.* 1990). 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.

Infant Deaths

No infant deaths were reported following gestational exposure to mitoxantrone.

Follow Up Evaluations

Follow up evaluations were available for 13 offspring ranging in age from 2 months to 29 years. Normal growth and development were reported for all but one infant. One infant suffered from failure to thrive and did not gain weight until age 3 months (Garcia *et al.* 1999).

5.25.5 Summary of pregnancy outcome following in utero exposure to mitoxantrone

In utero exposure to mitoxtantrone was reported for 17 singleton pregnancies (17 conceptuses) (**Table 78**). Overall, the apparent rate of major malformations among all mitoxantrone-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 0% (0/15 conceptuses based on 14 liveborn infants and examination of the fetus of 1 stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). The occurrence of major malformations following exposure to mitoxantrone in the second and/or third trimester only was 0% (0/12 conceptuses based on 11 liveborn infants and examination of the fetus of 1 stillbirth). There were no major malformations observed in the 3 infants for whom timing

of exposure was not specified and no examination of the fetus was reported for the spontaneous abortion in the only pregnancy reported with first trimester exposure to mitoxantrone.

The anthracycline antibiotics agents, including mitoxantrone, are reported to cause cardiotoxicity in adult cancer patients administered these drugs. Abnormal cardiac function was reported for 2 fetuses exposed to mitoxantrone (Garcia *et al.* 1999, Baumgartner *et al.* 2009).

5.26 NITROGEN MUSTARD (Mechlorethamine)

5.26.1 Mechanism of Action, Route of Administration, and Indications

Table 59: Pharmacology of nitrogen mustard in adult humans	
Molecular weight:	156.055
Protein binding:	**[Information not located]**
Metabolism:	Rapid hydrolysis and demethylation, possibly in plasma
Half-life elimination:	<1 minute
Distribution:	**[Information not located]**
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Urine (50% as metabolites, <0.01% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum	

Nitrogen mustard (mechlorethamine) is an anti-neoplastic alkylating agent that inhibits rapidly proliferating cells (Merck 2010). Nitrogen mustard acts via the crosslinking of its active metabolites to DNA, which results in inhibition of DNA synthesis and function (Perry and Mckinney 2008). Nitrogen mustard is administered via intravenous injection. Additional information on the pharmacology of nitrogen mustard is located in **Table 59**.

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 2010). 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 2010).

5.26.2 Evidence of Placental and Breast Milk Transport

Placental and breast milk transport of nitrogen mustard in humans is unknown.

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 nitrogen mustard at 1 mg/kg bw (2-3 times the maximum recommended human dose) produced congenital malformations in rats and ferrets (Merck 2010).

Teratogenic effects of nitrogen mustard are also described in the peer-reviewed literature. Nitrogen mustard induced malformations in rat fetuses when administered to pregnant Wister rats by a single intraperitoneal injection on gestation day 11 or 12 at doses of 0.5- 0.7 mg/kg bw (Chaube *et al.* 1968). Malformations included: encephalocele or exencephaly, cleft palate, retarded or clubbed for or rear leg, ectrodactyly, polydactyly, syndactyly, brachydactyly and short, kinky or absent tail (Chaube *et al.* 1968). In addition, Charles River CD rat conceptuses removed from the dams on gestation day 11 and cultured in vitro for two days in 1 to 5 µg/ml nitrogen mustard showed severe growth retardation (Sanyal *et al.* 1981).

5.26.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Nitrogen mustard was administered to 31 female cancer patients (also called cases) during pregnancy identified from 7 case reports (7 cases), 6 case series (7 cases), 3 retrospective case series (10 cases), 3 retrospective cohort studies (6 cases), and 1 retrospective survey (1 case) (Appendix C Table 24). Nitrogen mustard was used to treat Hodgkin lymphoma (28 cases) and acute lymphocytic leukemia (1 case). Cancer type was not specified in two cases.

A total of 31 singleton pregnancies (31 conceptuses) were exposed to nitrogen mustard. Nitrogen mustard was administered during the first trimester in 18 pregnancies (18 conceptuses), and in the second and/or third trimester only in 13 pregnancies (13 conceptuses). Nitrogen mustard was administered as monotherapy in 7 cases, including two cases co-administered radiation therapy (2 conceptuses) and one case co-administered x-rays. Nitrogen mustard was administered as polytherapy in 24 cases (24 conceptuses).

Termination of Pregnancy

Four pregnancies exposed to nitrogen mustard were medically terminated. Examination of a fetus of an induced abortion at gestation week 13 revealed a normal fetus with very small, malpositioned kidneys (Mennuti *et al.* 1975); the pregnancy was exposed during the first trimester to nitrogen mustard, vincristine and procarbazine. Examination of a fetus of another induced abortion revealed a normal fetus with toxic degeneration of the liver and kidneys (Peres *et al.* 2001); the pregnancy was exposed during the first trimester to nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarbazine. No examination of the fetus was reported in the remaining 2 induced abortions, which were exposed in the first trimester to nitrogen mustard, vincristine, and procarbazine (Blatt *et al.* 1980, Zemlickis *et al.* 1992b).

Spontaneous Fetal Death

Spontaneous abortion occurred in two pregnancies exposed to nitrogen mustard. A fetus from a spontaneous abortion was grossly normal following exposure to nitrogen mustard monotherapy during early first trimester, followed by exposure to 6-mercaptopurine monotherapy in the first trimester (Hoover and Schumacher 1966). A second spontaneous abortion occurred following exposure to nitrogen mustard, vincristine, and procarbazine during the first trimester (Zemlickis *et al.* 1992b); fetal data were not reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Table 60: Major malformations diagnosed at birth possibly attributable to in utero exposure to nitrogen mustard

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Only 4 digits per foot, webbing between 3rd and 4th digits, bowing of the right tibia, and an abnormal right pinna	13% (2/15)
	Hydrocephaly	
2nd and/or 3rd only	None	0% (0/13)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Major malformations were reported in 3 liveborn infants with gestational exposure to nitrogen mustard, including 2 liveborn infants exposed during the first trimester. 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 first trimester to nitrogen mustard, vincristine and procarbazine. One infant with hydrocephaly died 4 hours after birth (Zemlickis *et al.* 1992b); this pregnancy was exposed during the first trimester to nitrogen mustard, procarbazine and vincristine. Thus, the apparent rate of major malformations following exposure to nitrogen mustard during in the first trimester was 13% (2/15 conceptuses based on 12 liveborn infants and examination of the fetuses of 2 induced abortions and 1 spontaneous abortion) (**Table 60**).

Bilateral syndactyly of digits II and III was observed in an infant following second and third trimester exposure to nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarbazine and second trimester exposure to radiation therapy (Van Calsteren *et al.* 2010a). However, skeletal malformations such as syndactyly occur during the period of organogenesis in the first trimester; therefore, syndactyly was not likely caused by exposure to chemotherapy treatment in the second and third trimesters only. Thus, the adjusted rate of major malformations following second and/or third trimester exposure was 0% (0/13 conceptuses based on liveborn infants).

Minor Malformations

A minor malformation was observed in one liveborn infant. Pectus excavatum was observed in a liveborn infant exposed during the second and third trimesters to nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarbazine (Van Calsteren *et al.* 2010a).

Pregnancy Complications and Newborn Health

Only one pregnancy complication was reported among the liveborn infants with in utero exposure to nitrogen mustard: spontaneous preterm labor (1 conceptus) (Johnson and Filshie 1977).

There were 25 liveborn infants gestationally exposed to nitrogen mustard. Early preterm delivery (<34 weeks) was reported for 4 infants, late preterm delivery (34-36 weeks) was reported to 2 infants, and 13 infants were delivered at term. Data were insufficient to determine gestational age at delivery for 6 infants. Of the preterm infants, 5 infants were delivered via spontaneous vaginal delivery and data were insufficient to determine the route of delivery for one infant. Small for gestational age was determined

for 1 infant and 12 infants had normal body weight based on sex, gestational age, and body weight at birth. Data were insufficient to determine small for gestational age for 12 infants.

Four liveborn infants had health effects at birth. One newborn had jaundice, anemia and hepatomegaly at birth, but progressively improved (Deuschle and Wiggins 1953). Mild anemia occurred in another infant (Johnson and Filshie 1977). Cerebral hemorrhage was reported in an early preterm infant (Garrett 1974). Another infant was bronchoscoped for excess mucus shortly after birth and was sluggish for a few hours, but then progressed well (Zoet 1950).

Infant Deaths

There were three infant deaths following gestational exposure to nitrogen mustard. One early preterm infant died at age 2 days (Boland 1951); the pregnancy was exposed during the first trimester to nitrogen mustard monotherapy. As described above, one infant with hydrocephalus died 4 hours after birth (Zemlickis *et al.* 1992b). A third infant died of severe gastroenteritis at age 3 months (Dilek *et al.* 2006); this infant was exposed during the first trimester to nitrogen mustard, vincristine and procarbazine.

Follow Up Evaluations

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 31 singleton pregnancies (31 conceptuses) (**Table 77**). Overall, the apparent rate of major malformations among all nitrogen mustard-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 11% (3/28 based on 25 liveborn infants and examination of the fetuses of 2 induced abortions and 1 spontaneous abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations occurred in two infants with first trimester exposure. 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) and another infant had hydrocephaly (Zemlickis *et al.* 1992b). In developmental toxicity studies in rats, administration of nitrogen mustard during organogenesis induced skeletal malformations, including syndactylies. Thus, the apparent rate of major malformations following exposure during the first trimester to nitrogen mustard was 11% (2/15 conceptuses based on 12 liveborn infants and examination of the fetuses of 2 induced abortions and 1 spontaneous abortion).

Bilateral syndactyly was observed in one liveborn infant exposed to nitrogen mustard in the second and third trimesters (Van Calsteren *et al.* 2010a) ; however, this skeletal malformation was not likely caused by exposure to chemotherapy outside of the period of organogenesis. Thus, the adjusted rate of major malformations following second and/or third trimester exposure was 0% (0/13 conceptuses based on liveborn infants).

5.27 PACLITAXEL

5.27.1 Mechanism of Action, Route of Administration, and Indications

Table 61: Pharmacology of paclitaxel in adult humans	
Molecular weight:	853.9129
Protein binding:	89% to 98%
Metabolism:	Hepatic via CYPC8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel)
Half-life elimination:	1- to 6-hour infusion: Mean (beta): 6.4 hours; 3-hour infusion: Mean (terminal): 13.1-20.2 hours; 24-hour infusion: Mean (terminal): 15.7-52.7 hours
Distribution:	Vd: Widely distributed into body fluids and tissues; affected by dose and duration of infusion; Vdss: 1- to 6-hour infusion: 67.1 L/m^2 24-hour infusion: 227-688 L/m^2
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (~70%, 5% as unchanged drug); urine (14%)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum, Vd, volume of distribution; Vdss, volume of distribution at steady state	

Paclitaxel 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 2010c). 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. Additional information on the pharmacology of paclitaxel is located in **Table 61**.

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 2010c).

5.27.2 Evidence of Placental and Breast Milk Transport

Placental transfer in humans is not known. Transplacental transfer of paclitaxel was reported in the baboon model administered paclitaxel at 100 mg/m^2 intravenous injection during pregnancy and necropsied at 1 and 3.2 hours post-dose. Levels of paclitaxel in fetal plasma measured approximately 100 times less than levels in maternal plasma over the sampling period. Levels of paclitaxel in fetal tissues were 15% to non-detectable of levels in maternal organs and placenta, and the drug could not be detected in brain or cerebral spinal fluid (Van Calsteren *et al.* 2010c). The authors observed that although the fetus was exposed to very low levels of paclitaxel or docetaxel (a related taxane), the drugs may persist in fetal tissues for a long time resulting in a low level, long exposure. For example, docetaxel was detected at 72 hours post-dose; the last sampling period for paclitaxel was 3.2 hours post-dose (Van Calsteren *et al.* 2010c).

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 reduce the amount of paclitaxel passing from the placenta into the fetus, thus sparing the developing fetus toxic effects of paclitaxel (Smit *et al.* 1999). In wild type CF-1 mice administered 10 mg paclitaxel/kg bw intravenously, the ratio of levels of paclitaxel in fetal tissue relative to maternal serum was 0.02 at 1 hour post-dose (Smit *et al.* 1999). Specifically, when pregnant mice were administered paclitaxel

intravenously at 10 mg/kg bw 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 at one hour post dosing (Smit *et al.* 1999). Levels of paclitaxel in fetal plasma were below the level of detection in the C57/Bl6J mouse model (Van Calsteren *et al.* 2010d). Cremophor EL, a vehicle administered to improve the water solubility of paclitaxel, was reported to contribute to the drug's nonlinear clearance behavior in both mice and humans (Sparreboom *et al.* 1996). It is speculated that cremophor may be capable of reversing the P-glycoprotein drug resistance, or may induce a lipoprotein disassociation product that could act as a high affinity drug transporting reservoir that would lower the levels of unbound paclitaxel in the serum (Sparreboom *et al.* 1996).

Breast milk transfer of paclitaxel in humans is not known (Bristol-Myers Squibb 2010c). However, studies in laboratory animals suggest that breast milk transport of paclitaxel may occur. Intravenous administration of carbon 14-labeled paclitaxel 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 2010c).

5.27.3 Laboratory Animal Developmental Toxicity

Paclitaxel is embroylethal in rabbits, mice, rats and chicks as per the product label (Bristol-Myers Squibb 2010c). Paclitaxel induced resorptions and fetal death in rabbits when administered during organogenesis at a dose of 3.0 mg/kg bw/day (0.2 times the daily maximum recommended human dose on a mg/m^2 basis) (Bristol-Myers Squibb 2010c).

In a review of the peer-reviewed literature, paclitaxel reportedly caused a reduction in the number of implantations and live fetuses of mice intravenously exposed to 1.0 mg paclitaxel/kg bw before pregnancy and during the first week of gestation. No teratogenic effects were observed in mice treated with up to 0.6 mg/kg bw/day of paclitaxel during organogenesis (Shepard and Lemire 2004). Paclitaxel was also reported to be teratogenic in rats and chicks (Scialli *et al.* 1995, Scialli *et al.* 1997). 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 bw on gestation day 8), free paclitaxel reduced fetal body weight, implantation number, and it induced malformations at 2.0 mg/kg bw, 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 bw of the encapsulated drug produced effects similar to 2 mg/kg bw of the free (non-encapsulated) drug.

5.27.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Paclitaxel was administered to 36 female cancer patients (also called cases) during pregnancy identified from 17 case reports (17 cases), 4 case series (8 cases), and 1 registry survey (12 cases) (Appendix C Table 25). Among these 37 cases, paclitaxel was used to treat cancers of the breast (14 cases), ovary (12 cases), cervix (8 cases), lung (2 cases), and tongue squamous cell carcinoma (1 case).

A total of 36 pregnancies and 38 conceptuses were exposed to paclitaxel due to two set of twins; (Lycette *et al.* 2006, Cardonick *et al.* 2010). All 36 pregnancies (38 conceptuses) were administered

paclitaxel in the second and/or third trimester only. Paclitaxel was administered as monotherapy in 6 cases, including one case each treated with paclitaxel monotherapy following epirubicin monotherapy (Gadducci *et al.* 2003) or doxorubicin and cyclophosphamide (Lycette *et al.* 2006). It was administered as polytherapy in 30 cases (32 conceptuses).

Termination of Pregnancy

No terminations of pregnancy were reported.

Spontaneous Fetal Death

No spontaneous abortions or stillbirths were reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Table 62: Major malformations diagnosed at birth possibly attributable to in utero exposure to paclitaxel

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	None	No data
2nd and/or 3rd only	Pyloric stenosis	3% (1/38)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations were reported in one liveborn infant with gestational exposure to paclitaxel. Pyloric stenosis was reported in an infant exposed in the second and third trimesters to paclitaxel, and to doxorubicin, and cytarabine followed by docetaxel monotherapy (Cardonick *et al.* 2010) (Table 62).

Minor Malformations

No minor malformations were reported following gestational exposure to paclitaxel.

Pregnancy Complications and Newborn Health

A variety of pregnancy complications occurred in pregnancies exposed to paclitaxel. Oligohydramnios occurred during 2 singleton pregnancies (2 fetuses) (Shieh and Mehta 2011), including one pregnancy with normal placental function that experienced cessation of fetal abdominal growth and fetal renal failure (Bader *et al.* 2007b). One pregnancy each had preeclampsia (Gonzalez-Angulo *et al.* 2004) and pregnancy-induced hypertension (Raghunath and Shashi 2006). Spontaneous preterm labor occurred in one singleton pregnancy (Azim *et al.* 2009b) and two pregnancies had transient preterm labor that was treated and subsided (Lycette *et al.* 2006, Li *et al.* 2011). 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).

A total of 38 liveborn infants were gestationally exposed to paclitaxel. Early preterm delivery (<34 weeks) was reported for 5 infants, late preterm delivery (34 to <37 weeks) was reported for 13 infants, and 6 infants were delivered at term (22.7%). Data were insufficient to determine the gestational age at delivery for 14 infants. Of the preterm infants, all 18 infants were delivered via C-section. Small for gestational age was reported for 5 infants and 28 infants had normal weight based on sex, gestational

age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 5 infants.

Newborn health issues included respiratory distress (4 infants) (Bader *et al.* 2007b, Hubalek *et al.* 2007, Garcia-Gonzalez *et al.* 2008, Fruscio *et al.* 2012). Two infants had anemia (Hubalek *et al.* 2007, Cheung *et al.* 2009) and one infant had neutropenia (Cardonick *et al.* 2010). Jaundice was reported in two infants (Cheung *et al.* 2009, Cardonick *et al.* 2010). Another infant had transient renal failure, hypotension, and was treated for bacterial sepsis (Bader *et al.* 2007b). 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.* 2007b). An intraventricular hemorrhage was observed in a preterm infant (Fruscio *et al.* 2012).

Infant Deaths

No infant deaths were reported following gestational exposure to paclitaxel.

Follow Up Evaluations

Follow up evaluations were reported for 34 infants ranging in age from 12 weeks to 11 years. All children had normal growth and development with the exception of one. One twin had attention deficit disorder at 11 years of age; the twin sibling was normal (Cardonick *et al.* 2010).

5.27.5 Summary of Pregnancy Outcomes for paclitaxel

In utero exposure to paclitaxel was reported for 37 pregnancies, including two sets of twins (39 conceptuses) (**Table 79**). Overall, the apparent rate of major malformations among all paclitaxel-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 3% (1/39 conceptuses based on 39 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). There were no pregnancies exposed to the drug in the first trimester. A major malformation was observed in one liveborn infants following exposure to paclitaxel in the second and/or third trimester only. Thus, the apparent rate of major malformations following exposure to paclitaxel in the second and/or third trimester only was 3% (1/39 conceptuses).

5.28 PROCARBAZINE

5.28.1 Mechanism of Action, Route of Administration, and Indications

Table 63: Pharmacology of procarbazine in adult humans	
Molecular weight:	221.3021
Protein binding:	**[Information not located]**
Metabolism:	Hepatic and renal
Half-life elimination:	1 hour
Distribution:	Crosses blood-brain barrier; equilibrates between plasma and CSF
Time to peak, serum (C_{max}):	1 hour
Excretion:	Urine and respiratory tract (<5% as unchanged drug, 70% as metabolites)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum, CSF, cerebral spinal fluid	

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. Additional information on the pharmacology of procarbazine is located in **Table 63**.

Procarbazine is indicated for Hodgkin and non-Hodgkin lymphomas as well as in the treatment of malignant gliomas.

5.28.2 Evidence of Placental and Breast Milk Transport

Placental transport of procarbazine is not documented in either humans or animals. However, it is known that procarbazine can pass the blood-brain barrier and that it equilibrates between the plasma and the cerebral spinal fluid (Brunton and Chabner 2011). Evidence suggestive of placental transport of procarbazine are cytogenetic damage in fetal blood cells in mice and methylation of fetal tissue DNA in rats exposed to the agent during gestation 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 bw 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 bw on gestation day 22 (Wiestler *et al.* 1984).

Breast milk transport of procarbazine in humans or animals is not known.

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 bw/day. 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 bw. Malformations included: limb, digit, and tail defects; jaw defects;

clefts of the palate, lip, and face; malformations of the brain, skull and spine; acephaly and omphalocele. Lower doses caused embryo lethality and malformations when administered during the period of organogenesis. Procarbazine also induced malformations when administered at doses of 5-10 mg/kg bw 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 bw 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. (2003) treated pregnant rats with 25 or 50 mg procarbazine/kg bw by gavage on gestation day 14. They reported that both dose levels resulted in a reduction in live fetuses and an increase in resorptions, and a reduction in some physical measurements of the fetuses, e.g., body weight, tail length, and occipito-coccygeal length, but 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 bw/day on gestation days 12 to 15, the offspring had reduced weights of the neocortex brain region when evaluated at postnatal day 21 (Johnson *et al.* 1985).

5.28.4 Human fetal exposure and developmental effects

Number of Cases, Publications, and Types of Cancer Treated

Procarbazine was administered to 32 female cancer patients during pregnancy identified from 8 case reports (8 cases), 3 case series (4 cases), 2 retrospective case series (9 cases), 2 retrospective cohort studies (4 cases), and 3 retrospective surveys (7 cases) (Appendix C Table 26). Among these patients, procarbazine was used to treat Hodgkin lymphoma (28 cases), non-Hodgkin lymphoma (1 case), diffuse histiocytic lymphoma (1 case), and two cases did not specify cancer type.

A total of 31 singleton pregnancies were exposed to procarbazine (31 conceptuses). It was administered during the first trimester in 20 pregnancies (20 conceptuses) and in the second and/or third trimester only in 12 pregnancies (12 conceptuses). Procarbazine was most commonly administered as polytherapy (31 cases) and was administered as monotherapy in only 1 case.

Termination of Pregnancy

Six pregnancies were medically terminated following first trimester exposure. A normal fetus with small, malpositioned kidneys was reported for an induced abortion performed at gestation week 13 of a singleton pregnancy (Mennuti *et al.* 1975); the pregnancy was exposed during the first trimester to procarbazine, nitrogen mustard and vincristine. Examination of a fetus from another induced abortion revealed toxic degeneration of the liver and kidneys, but no malformations (Peres *et al.* 2001); the pregnancy was exposed during the first trimester to procarbazine, nitrogen mustard, vincristine, doxorubicin, bleomycin, vinblastine and dacarbazine. Examination of the fetus was not reported for the remaining 4 induced abortions exposed to procarbazine polytherapy in the first trimester (Thomas and Peckham 1976, Blatt *et al.* 1980, Zuazu *et al.* 1991, Zemlickis *et al.* 1992b).

Spontaneous Fetal Death

One spontaneous abortion followed exposure during the first trimester to procarbazine and co-treatments nitrogen mustard and vincristine (Zemlickis *et al.* 1992b); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations were observed in 5 liveborn infants gestationally exposed to procarbazine, including 4 infants exposed in the first 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 during the first trimester to procarbazine, nitrogen mustard and vincristine. Cleft lip and cleft palate were reported in an infant with exposure in the first trimester to procarbazine, lomustine and vincristine and co-treatment with vinblastine from first through third 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 first trimester to procarbazine, vinblastine and vincristine. Hydrocephalus occurred in another newborn who died 4 hours after birth (Zemlickis *et al.* 1992b); this pregnancy was exposed in the first trimester to procarbazine, nitrogen mustard and vincristine. The apparent rate of major malformations following exposure to procarbazine during the first trimester was 27% (4/15 conceptuses based on 13 liveborn infants and examination of the fetuses of 2 induced abortions) (Table 64).

Table 64: Major malformations diagnosed at birth possibly attributable to in utero exposure to procarbazine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	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 -type atrial septal defect.	27% (4/15)
	Cleft lip and cleft palate	
	Small secundum atrial septal defect	
	Hydrocephalus	
2nd and/or 3rd only	None	0% (0/12)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Major malformations were observed in only one liveborn infant following exposure to procarbazine in the second and/or third trimester. Bilateral syndactyly of digits II and III was observed in one infant exposed during the second and third trimesters to procarbazine, nitrogen mustard, vincristine, doxorubicin, vinblastine and bleomycin as well as radiation therapy in the second trimesters (Van Calsteren *et al.* 2010a). Syndactylies are not likely caused by exposure to procarbazine in the second and/or third trimester only. Thus, the adjusted rate of major malformations in the second and/or third trimester was 0% (0/12 conceptuses based on 12 liveborn infants).

Minor Malformations

Minor malformations were observed in two liveborn infants gestationally exposed to procarbazine. Pectus excavatum was observed in an infant exposed in the second and third trimesters to procarbazine, nitrogen mustard, vincristine, doxorubicin, vinblastine and bleomycin (Van Calsteren *et al.* 2010a). Another infant had a hemangioma, a minor malformation, following exposure during the 1st trimester (through gestation day 38) (Wells *et al.* 1968). As mentioned above, the autopsies of two induced abortuses found no malformations, but did observe small, malpositioned kidneys (Mennuti *et al.* 1975) and toxic degenerative changes in the liver and kidneys (Peres *et al.* 2001).

Pregnancy Complications and Newborn Health

The only pregnancy complication reported following gestational exposure to procarbazine was one case of spontaneous preterm labor (Johnson and Filshie 1977).

A total of 25 liveborn infants were gestationally exposed to procarbazine. Early preterm delivery (<34 weeks) was reported for 2 infants, late preterm delivery (34 to <37 weeks) was reported for 2 infants and 14 infants were delivered at term. Data were insufficient to determine the gestational age at delivery for 7 infants. Of the preterm infants, 4 infants were delivered via spontaneous vaginal delivery. Small for gestational age was determined for 2 infants and 13 infants at normal body weight based on sex, gestational age and body weight at birth. Data were insufficient to determine small for gestational age for the remaining 10 infants.

A few health effects were observed in liveborn infants with gestational exposure to procarbazine. A large cerebral hemorrhage was reported in an infant born at gestation week 24 (Garrett 1974). Transient myelosuppression was reported in two infants (Johnson and Filshie 1977, Zuazu *et al.* 1991); both had anemia. One infant developed respiratory distress and died at age 2 days (Thomas and Peckham 1976). Placental changes were observed in one case at birth: villus degeneration and toxic vascular degeneration (Peres *et al.* 2001).

Infant Deaths

There were three deaths of infants gestationally exposed to procarbazine. One newborn developed respiratory distress and died at age 2 days (Thomas and Peckham 1976); autopsy revealed a small atrial septal defect. A newborn with hydrocephalus died 4 hours after birth (Zemlickis *et al.* 1992b). One infant died of gastroenteritis at age 3 months (Dilek *et al.* 2006).

Follow Up Evaluations

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 32 singleton pregnancies (32 conceptuses) (**Table 77**). Overall, the apparent rate of major malformations among all procarbazine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 19% (5/27 based on 25 liveborn infants and examination of the fetuses of 2 induced abortions). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations reported for 4 liveborn infants following exposure during the first trimester included cranial malformations (1 infant), hydrocephalus (1 infant), skeletal malformations of the distal limbs (1 infant) as well as a small atrial septal defect (1 infant). Similarly, developmental toxicity studies have also observed cranial and skeletal defects in rat fetuses exposed to procarbazine during organogenesis. Thus, the apparent rate of major malformations following exposure to procarbazine during the first trimester was 27% (4/15 conceptuses based on 13 liveborn infants and examination of the fetuses of 2 induced abortions). Distal limb syndactyly in one infant was the only major malformation reported following exposure to procarbazine in the second and/or third trimester only. However, it is unlikely that syndactyly would be induced by chemotherapy exposure outside of the

period of organogenesis. Thus, the adjusted apparent rate of major malformation following exposure to procarbazine in the second and/or third trimester only is 0% (0/25 conceptuses based on 25 liveborn infants).

5.29 RITUXIMAB

5.29.1 Mechanism of Action, Route of Administration, and Indications

Table 65: Pharmacology of rituximab in adult humans

Molecular weight:	**[Information not located]**
Protein binding:	**[Information not located]**
Metabolism:	**[Information not located]**
Half-life elimination:	CLL: Median terminal half-life: 32 days (range: 14-62 days); NHL: Median terminal half-life: 22 days (range: 6-52 days); RA: Mean terminal half-life: 18 days (range: 5-78 days); WG/MPA: 23 days (range: 9-49 days)
Distribution:	RA: 3.1 L; WG/MPA: 4.5 L
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system

Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CLL= chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; RA, rheumatoid arthritis; WG, Wegener granulomatosis; MPA, microscopic polyangiitis.

Rituximab is a genetically engineered chimeric murine/human IgG 1 monoclonal antibody that is directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The CD20 antigen (also called human B-lymphocyte-restricted differentiation antigen, Bp35) is involved in the activation process for cell cycle initiation and differentiation, and may also act as a calcium ion channel (Genentech 2011). Rituximab binds to the CD20 antigen and depletes the CD20-expressing cells by cell death. Rituximab is administered by intravenous injection. Additional information on the pharmacology of rituximab is located in **Table 65**.

Rituximab is indicated for treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia as well as non-cancer diseases, including adult rheumatoid arthritis, Wegner 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. Friedrichs et al. (2006) detected rituximab in maternal and cord blood serum at delivery **[timing of last dose not provided]**. In one case report, the cord blood level of rituximab (32.1 µg/mL) was three-times the level of rituximab in maternal serum (9.8 µg/mL) at birth **[timing of last dose not provided]** (Friedrichs *et al.* 2006). 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 (Friedrichs *et al.* 2006). In another report, comparable concentrations of rituximab were detected in maternal and infant serum at birth (0.2 versus 0.3 g/L, respectively) (Decker *et al.* 2006); 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, a non-cancerous health condition (Chakravarty *et al.* 2011).

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 (Telemo and Hanson 1996, Friedrichs *et al.* 2006, Pentsuk and van der Laan 2009). Rituximab has been

detected in the milk of lactating non-human primates administered rituximab in pregnancy and lactation. Vaidyanathan et al. (2011) reported that the levels of rituximab in breast milk were 0.2-0.3% of the levels in maternal serum on postnatal day 28, following daily administration of rituximab from gestation day 10 through postpartum day 28 in cynomolgus monkeys**.**

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). For the prenatal developmental toxicity study, pregnant cynomolgus monkeys were administered rituximab loading doses of 15, 37.5 and 75 mg/kg/day on gestation days 20, 21 and 22 and then weekly on gestation days 29, 36 43, and 50 at doses of 20, 50 or 100 mg/kg/week via intravenous injection. For the prenatal and postnatal developmental study, the design was the same, except that maternal dosing continued until postnatal day 28. No mortality, body weight changes or teratogenic effects were observed in monkey fetuses at any dose in the prenatal developmental toxicity study, 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 rituximab decreased B cell levels in the monkey offspring in the pre- and postnatal developmental toxicity study, 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

Number of Cases, Publications, and Types of Cancer Treated

Rituximab was administered to 26 female cancer patients (also called cases) during pregnancy identified from 8 case reports (8 cases), 1 registry survey (4 cases) and 2 retrospective surveys (14 cases) (Appendix C Table 28). Among these patients, rituximab was used to treat Hodgkin lymphoma (1 case), non-Hodgkin lymphoma (17 cases), Burkitt lymphoma (6 cases), B-cell lymphoma (1 case), and diffuse large B-cell lymphoma (1 case).

A total of 26 singleton pregnancies (26 conceptuses) were exposed to rituximab. Rituximab was administered in the first trimester in 6 singleton pregnancies (6 conceptuses) and in the second and/or third trimester only in 18 singleton pregnancies (18 conceptuses). Rituximab was administered as monotherapy in one case and as polytherapy in 17 cases. Data were not sufficient to determine whether rituximab was administered as mono- or polytherapy in 8 cases.

Termination of Pregnancy

No terminations of pregnancy were reported.

Spontaneous Fetal Death

Spontaneous fetal loss was reported in 3 singleton pregnancies exposed to rituximab. Spontaneous abortion occurred at gestation week 10 in one pregnancy exposed to rituximab during the first trimester (Chakravarty *et al.* 2011); no fetal data were provided. Stillbirth of a normal fetus occurred at 30 weeks gestation following second and third trimester exposure to rituximab and co-treatment with cyclophosphamide, vincristine and doxorubicin (Cardonick *et al.* 2010). A second stillbirth 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 second trimester and co-exposed to cyclophosphamide, vincristine, doxorubicin, cytarabine, etoposide, and ifosfamide and no examination of the fetus was reported (Peterson *et al.* 2010).

Rate of Occurrence of Congenital Malformations

Major Malformations

Table 66: Major malformations possibly attributable to in utero exposure to rituximab in humans

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Ventricular septal defect	20% (1/5)
2nd and/or 3rd only	None	0% (0/18)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

Major malformations were observed in 1 liveborn following gestational exposure to rituximab (Table 66). A ventricular septal defect was reported in an infant exposed during the first trimester through the first month of pregnancy (Chakravarty *et al.* 2011); no data were provided on co-exposure to other chemotherapy agents. Thus, the apparent rate of major malformations following exposure to rituximab during first trimester was 17% (1/5 conceptuses based on 5 liveborn infants).

No major malformations were reported in the 18 liveborn infants exposed to rituximab in the second and/or third trimester only. Thus, the apparent rate of major malformations following exposure to rituximab in the second and/or third trimester only was 0% (0/18 conceptuses based on 17 liveborn infants and examination of the fetus of 1 stillbirth).

Minor Malformations

A minor malformation was observed in one infant gestationally-exposed to rituximab. A patent foramen ovale was reported an infant born at term (Chakravarty *et al.* 2011); this infant also had a ventricular septal defect, a major malformation.

Pregnancy Complications and Newborn Health

A variety of pregnancy complications and health effects were reported in pregnancies exposed to rituximab. Pregnancy complications included preeclampsia (1 case) (Chakravarty *et al.* 2011), spontaneous preterm labor (2 cases) (Decker *et al.* 2006), including one case yielding a stillborn infant following reductions in amniotic fluid and intrauterine fetal growth restriction (Peterson *et al.* 2010).

There were 23 liveborn infants with in utero exposure to rituximab. Early preterm delivery (<34 weeks) was reported for 5 infants, late preterm delivery (34 to<37 weeks) was reported for 5 infants, and 7 infants were delivered at term. Data were insufficient to determine the gestational age at birth for 6 infants. Of the 10 preterm infants, 3 infants were delivered via spontaneous vaginal delivery and 3 infants were delivered via C-section; data were insufficient to determine the route of delivery for the remaining 4 infants. One newborn was identified as small for gestational age and 7 infants had normal body weight based on sex, gestational age and body weight at birth (Olsen *et al.* 2010). Data were insufficient to identify small for gestational age in the remaining 15 infants.

Transient myelosuppression was observed in four infants. A deficiency or absence of B-cells was reported for two newborns (Decker *et al.* 2006, Friedrichs *et al.* 2006). The B-cell levels recovered to a normal range by age 12 and 18 weeks, respectively (Decker *et al.* 2006, Friedrichs *et al.* 2006). One

infant had granulocytopenia and lymphopenia (also called lymphocytopenia) (Kimby *et al.* 2004), and another infant leukopenia and anemia (Chakravarty *et al.* 2011). Respiratory distress was reported in two infants accompanied by jaundice (Cardonick *et al.* 2010) or omphalitis (inflammation of the navel) (Cordeiro *et al.* 2009). One infant born at 38 weeks had a patent ductus arteriosus (Chakravarty *et al.* 2011); this infant also had a ventricular septal defect and a patent ovale foramen.

Infant Deaths

No infant deaths were reported.

Follow Up Evaluations

Follow up evaluations were reported for 7 infants ranging in age from 46 days to 5.3 years. Normal development was observed in all 7 children. Normal immunological function was reported for two infants who experienced myelosuppression as neonates (Kimby *et al.* 2004, Decker *et al.* 2006).

5.29.5 Summary of Pregnancy Outcomes for rituximab

In utero exposure to rituximab was documented for 24 singleton pregnancies (24 conceptuses) (**Table 81**). Overall, the apparent rate of major malformations among all rituximab-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 10% (1/24 conceptuses based on 23 liveborn infants and examination of the fetus of 1 stillbirth). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Only one major malformation was reported following treatment with rituximab polytherapy for cancer during the first trimester of pregnancy: a ventricular septal defect accompanied by a patent ovale foramen and patent ductus arteriosus in a term infant (Chakravarty *et al.* 2011). Malformations are not reported in animal developmental toxicity studies for rituximab. It is possible that this major malformation may have been induced by unspecified cytotoxic chemotherapy co-treatments; rituximab is often administered with cyclophosphamide, doxorubicin and vincristine (Chakravarty *et al.* 2011). Thus, the apparent rate of major malformations following exposure to rituximab during the first trimester was 20% (1/5 conceptuses based on 5 liveborn infants). No major malformations were observed following exposure to rituximab in the second and/or third trimester only (0/18 conceptuses based on 17 liveborn infants and examination of the fetus of 1 stillbirth).

Gestational exposure to rituximab was associated with a reduction in B-cells in two newborns (Decker *et al.* 2006, Friedrichs *et al.* 2006). This effect is consistent with decreases in B-cell levels in lymph tissue reported in developmental toxicity studies in cynomolgus monkeys (Vaidyanathan *et al.* 2011). Levels of B-cells were reported to return to normal levels several weeks following birth, with no adverse effect on the responsiveness of the infant's immune system (Decker *et al.* 2006, Friedrichs *et al.* 2006).

In a retrospective study of 90 liveborn infants following exposure to rituximab, only 2 infants had malformations possibly attributable to the drug (Chakravarty *et al.* 2011). The authors point out that this rate of major malformations was comparable to the prevalence of birth defects in the general population (Correa *et al.* 2007). This retrospective survey included cases treated for cancer and autoimmune diseases; however, draft NTP monograph included only the cases of cancer (i.e., Hodgkin or non-Hodgkin lymphoma patients) in the current NTP monograph (Chakravarty *et al.* 2011).

5.30 TAMOXIFEN

5.30.1 Mechanism of Action, Route of Administration, and Indications

Table 67: Pharmacology of tamoxifen in adult humans

Molecular weight:	371.521
Protein binding:	99%
Metabolism:	Hepatic: via CYP2D6 to 4-hydroxytamoxifen and via CYP3A4/5 to N-desmethyl-tamoxifen. Each is then further metabolized into endoxifen (4-hydroxy-tamoxifen via CYP3A4/5 and N-desmethyl-tamoxifen via CYP2D6); both 4-hydroxy-tamoxifen and endoxifen are 30-to 100-fold more potent than tamoxifen
Half-life elimination:	Tamoxifen: ~5-7 days; N-desmethyl tamoxifen: ~ 14 days
Distribution:	High concentrations found in uterus, endometrial and breast tissue
Time to peak, serum (C_{max}):	~ 5 hours
Excretion:	Feces (26% to 51%); urine (9% to 13%)

Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum

Tamoxifen is a non-steroidal selective estrogen receptor modulator that is 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 by binding to the estrogen receptor and blocking the stimulatory effects of estrogen on the cancer cells. Although tamoxifen blocks the effects of estrogen in breast tissue, it acts *like* an estrogen in other tissues, e.g., 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. Additional information on the pharmacology of tamoxifen is located in **Table 67**.

Tamoxifen is indicated for the treatment of estrogen receptor-positive breast cancer (Savient 2005).

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 in humans. Two placebo-controlled studies in over 150 women have shown that tamoxifen significantly inhibits early postpartum milk production for a range of 5 to 18 days when administered within 24 hours of delivery (Shaaban 1975, Masala *et al.* 1978). 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. Pregnant CD (SD) IGS rats treated orally with 0.12, 0.6 or 3 µg/kg bw/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 bw/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 tracts in female offspring, 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 bw/day (the maximum dose which did not terminate pregnancy) (reviewed in Furr and Jordan 1984). No fetal abnormalities were noted among the offspring of pregnant marmosets treated during the period of organogenesis with tamoxifen at 10 mg /kg bw/day (about 2-fold the daily maximum recommended human dose on a mg/m^2 basis) during organogenesis (Furr and Jordan 1984, Savient 2005) or in the last half of pregnancy (Savient 2005). Although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of malformations (Savient 2005).

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 bw/day 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 bw 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 tamoxifen/kg bw by oral gavage on gestation day 2 (Kaplan-Kraicer *et al.* 1996).

5.30.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Tamoxifen was administered to 14 female cancer patients (also called cases) during pregnancy identified from 12 case reports (12 cases) and 1 retrospective cohort study (2 cases) (Appendix C Table 29). Among these patients, tamoxifen was used to treat breast cancer (12 cases) and melanoma (2 cases).

A total of 14 pregnancies (15 conceptuses) were exposed to tamoxifen, including one set twins (Beale *et al.* 2009). Tamoxifen was administered during the 1st trimester of pregnancy in 11 cases (12 conceptuses) and in the 2nd and/or 3rd trimester only in 3 cases. Tamoxifen was administered as monotherapy in 7 cases (7 conceptuses), including one case also exposed to x-rays. Tamoxifen was administered as polytherapy in the remaining 7 cases (8 conceptuses).

Termination of Pregnancy

No terminations of pregnancy were reported.

Spontaneous Fetal Death

No spontaneous abortions or stillbirths were reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations occurred in 3 newborns with gestational exposure to tamoxifen.

Table 68: Major malformations diagnosed at birth possibly attributable to in utero exposure to tamoxifen

Trimester exposed	Major malformations observed[a]	Apparent rate (affected/total conceptuses[a])
During 1st	Microtia and hemifacial microsomia (Goldenhar syndrome); preauricular skin tags	25% (3/12)
	Cleft palate, glossoptosis and severe microretrognathia (Pierre Robin syndrome); clubfoot, acetabular and sacral dysplasia	
	Phallic-like clitoris, single perineal opening for both the vagina and urethra, and fused labioscrotal folds	
2nd and/or 3rd only	None	0% (0/3)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions and stillbirths

One infant had a combination of malformations consistent with Goldenhar syndrome, including right-sided microtia (underdevelopment of the exterior ear) and hemifacial microsomia (underdevelopment of the lower half of one side of the face) (Cullins *et al.* 1994). This infant, who also had preauricular skin tags, was exposed during the first and second trimesters. In addition, the infant was exposed to diagnostic x-rays and marijuana or cocaine at least once during the first 6 weeks of gestation (Cullins *et al.* 1994). Another infant exposed during the first trimester had multiple skeletal malformations diagnostic of Pierre Robin syndrome (i.e., cleft palate, hypoplastic mandibles and thin mandibular condyles, and glossoptosis) as well as clubfoot, and acetabular and sacral dysplasia (Berger and Clericuzio 2008); the infant had a family history of small mandibles, but no clefting. Ambiguous genitalia were reported in one female newborn exposed to tamoxifen during the first and second trimesters (Tewari *et al.* 1997). Specifically, this infant had an enlarged phallic-like clitoris , a single perineal opening representing both the urethra and the vagina, and fused labioscrotal folds (Tewari *et al.* 1997). Thus, the apparent rate of major malformations following exposure to tamoxifen during the first trimester was (3/11 conceptuses based on 11 liveborn infants) (**Table 68**).

No major malformations were observed in infants exposed to tamoxifen in the second and/or third trimester only (0/3 conceptuses based on 3 liveborn infants).

Minor Malformations

Minor malformations were observed in two newborns gestationally-exposed to tamoxifen. Preauricular skin tags were reported in an otherwise normal infant following exposure to tamoxifen during the entire pregnancy (Isaacs *et al.* 2001). Microphthalmos (abnormally small eyes) and severe hypermetropia (far-sightedness) were diagnosed in an infant at age 1 year (Li *et al.* 2007). This pregnancy was exposed in the first through second trimesters to tamoxifen and co-treatments carmustine, dacarbazine and cisplatin.

Pregnancy Complications and Newborn Health

Pregnancy complications occurred in 5 cases exposed to tamoxifen during pregnancy. Spontaneous preterm labor occurred in three cases (Andreadis *et al.* 2004), including one case with gestational diabetes and preeclampsia (Berger and Clericuzio 2008), and another case with chorioamniotis and abnormal lie of the fetus (Cullins *et al.* 1994). Preterm rupture of membranes occurred in one case (Beale *et al.* 2009). Oligohydramnios or anhydramnios complicated two pregnancies exposed to tamoxifen that were also co-exposed to trastuzumab during the second or second and third trimesters (Beale *et al.* 2009, Warraich and Smith 2009).

There were 15 liveborn infants with in utero exposure to tamoxifen. Early preterm delivery (<34 weeks) was reported 7 infants (including one set of twins)), late preterm deliveries (34 to <37 weeks) was reported for 2 infants, and 3 infants were delivered at term (≥37 weeks). Data were insufficient to identify the gestational age at birth for 3 infants. Of the 9 preterm infants, 2 infants were delivered via spontaneous vaginal birth and 7 infants (including 1 set of twins) were delivered via C-section. Fourteen infants had normal body weight based on data reported for sex, gestational age and body weight at birth of each infant, and the data were insufficient to identify small for gestational age in the remaining infant.

Respiratory issues were reported for five infants, including one set of twins. One infant who had moderate respiratory distress was also treated for enterocolitis (Isaacs *et al.* 2001). The infant with the glossoptosis required a tracheotomy due to airway obstruction (Berger and Clericuzio 2008). In a twin pregnancy complicated by oligohydramnios, the male twin had respiratory distress requiring intubation followed by oxygen as well as enlarged kidneys and a dilated ureter (Beale *et al.* 2009). By age 12 weeks, he developed chronic renal failure and died of respiratory arrest at age 13 weeks (Beale *et al.* 2009). His female twin was normal other than requiring oxygen at birth (Beale *et al.* 2009). In a pregnancy complicated by anhydramnios, the newborn was diagnosed with pulmonary hypoplasia and had atelectasis (partial or complete absence of lung expansion at birth) (Warraich and Smith 2009); the infant died 40 minutes following extubation on day 1.

Infant Deaths

Two infants died following gestational exposure to tamoxifen. Both infants, which had gestational exposure to trastuzumab during the second or second and third trimester, manifested symptoms of trastuzumab exposure. One term newborn with atelectasis (partial or complete absence of lung expansion at birth) had pulmonary hypoplasia, and she died 40 minutes following extubation on day 1 (Warraich and Smith 2009). One preterm infant from a twin pregnancy, who suffered from respiratory distress and enlarged kidneys and dilated ureter at birth, developed chronic renal failure and died of respiratory arrest at age 13 weeks (Beale *et al.* 2009).

Follow Up Evaluations

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).

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) (**Table 81**). Overall, the apparent rate of major malformations among all tamoxifen-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 2% (3/15 conceptuses based on 14 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in only three infants and all were exposed during the first trimester. One infant had reproductive tract malformations that were consistent with malformations reported in developmental toxicity in rat fetuses. Craniofacial malformations were observed in the other two infants. Similar craniofacial malformations have been observed in cases of retinoic acid embryopathy leading some researchers to hypothesize that tamoxifen may act in a similar way on early organogenesis as the retinoic acid drugs (reviewed in (Berger and Clericuzio 2008)). Thus, the apparent rate of major

malformations following exposure to tamoxifen during the first trimester is 25% (3/12 conceptuses based on 12 liveborn infants).

5.31 TRASTUZUMAB

5.31.1 Mechanism of Action, Route of Administration, and Indications

Table 69: Pharmacology of trastuzumab in adult humans	
Molecular weight:	145531.5
Protein binding:	**[Information not located]**
Metabolism:	**[Information not located]**
Half-life elimination:	Weekly dosing: Mean: 6 days (range: 1-32 days); every 3 week regimen: Mean: 16 days (range: 11-23 days)
Distribution:	Vd: 44 mL/kg; not likely to cross the (intact) blood-brain barrier (due to the large molecule size)
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	**[Information not located]**
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; Vd, volume of distribution.	

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. Additional information on the pharmacology of trastuzumab is located in **Table 69**.

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 bw/day (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 (Telemo and Hanson 1996, Pentsuk and van der Laan 2009) suggesting that lactational transfer of trastuzumab may also occur.

5.31.3 Laboratory Animal Developmental Toxicity

No embryolethal or fetotoxic effects have been reported in laboratory animal studies of trastuzumab. No fetal toxicity was observed in a reproductive study of cynomolgus monkeys administered trastuzumab at a dose 25 times higher than the recommended weekly human dose of 2 mg/kg bw (Genentech 2010). In contrast, an increased incidence of maternal cardiotoxicity has been observed when trastuzumab is co-administered with an anthracycline (Genentech 2010). In mice, erbB2 protein (mouse equivalent of the human HER2) has been detected in the fetal neural tissues and cardiac myocytes (Lee *et al.* 1995). Mice engineered without the erbB2 gene died during early gestation likely due to the absence of trabeculae in the myocardium, which is responsible for blood flow during early heart development (Lee *et al.* 1995). HER2 has also been detected in adult and fetal kidneys in humans (Press *et al.* 1990, Goodyer *et al.* 1993) 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).

5.31.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Trastuzumab was administered to 19 female patients (also called cases) treated for breast cancer during pregnancy identified from 17 case reports (17 cases) and 1 case series (2 cases) (Appendix C Table 29).

A total of 19 pregnancies yielded 20 conceptuses due to one twin pregnancy (Beale *et al.* 2009). Trastuzumab was administered during the first trimester in 13 pregnancies (14 conceptuses due to one set of twins (Beale *et al.* 2009)) and 6 pregnancies (6 conceptuses) were exposed in the second and/or third trimester only. Trastuzumab was administered as monotherapy to 12 cases. It was administered as polytherapy in 8 cases, including two cases in which it was administered with tamoxifen until the pregnancy was identified (Beale *et al.* 2009, Warraich and Smith 2009).

Termination of Pregnancy

An induced abortion was performed in the first trimester due to an ectopic pregnancy (Berveiller *et al.* 2008); the authors stated that no histological examination of the embryo performed.

Spontaneous Fetal Death

No spontaneous fetal deaths were reported with gestational exposure to trastuzumab.

Rate of Occurrence of Congenital Malformations

Major Malformations

No major malformations 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). However, at the time of completion of the NTP monograph, there were no published peer-reviewed journal articles documenting skeletal abnormalities with gestational exposure to trastuzumab. Thus, based on published peer-viewed reports, the apparent rate of major

malformations with gestational exposure to trastuzumab at any time during pregnancy was 0% (0/12 liveborn infants with first trimester exposure and 0/6 liveborn infants with second and/or third trimester only exposure).

Minor Malformations

No minor malformations were reported.

Pregnancy Complications and Newborn Health

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 second and/or third trimesters (13 of 15 conceptuses, including 1 set of twins). In particular, anhydramnios was documented in 5 pregnancies (Watson 2005, Sekar and Stone 2007, Warraich and Smith 2009). Oligohydramnios was documented in 8 pregnancies (9 conceptuses), including one twin pregnancy (Fanale *et al.* 2005, Bader *et al.* 2007b, Shrim *et al.* 2007, Pant *et al.* 2008, Weber-Schoendorfer and Schaefer 2008, Witzel *et al.* 2008, Beale *et al.* 2009, Mandrawa *et al.* 2011).

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) (Beale *et al.* 2009), premature detachment of the placenta (1 pregnancy) (Weber-Schoendorfer and Schaefer 2008), and maternal vaginal bleeding at 26 gestation weeks (1 pregnancy) (Witzel *et al.* 2008). A reduction in intrauterine growth was observed at the same time as a reduction in amniotic fluid for two infants (Bader *et al.* 2007b, Sekar and Stone 2007); placental function was only reported in one of these two studies, and it was normal (Bader *et al.* 2007b). Intrauterine growth restriction was observed in a third fetus, who had recovered from oligohydramnios following discontinuation of treatment with trastuzumab (Gottschalk *et al.* 2011).

There were 19 liveborn infants with in utero exposure to trastuzumab. Early preterm delivery (<34 weeks) was reported for 9 infants, late preterm delivery (34 to <37 weeks) was reported for 2 infants, and 8 infants were delivered at term (≥37 weeks). Of the 11 preterm infants, 2 infants were delivered via induced vaginal birth, and 9 infants were delivered via C-section (including 1 set of twins). Small for gestational age was determined for one newborn and 16 infants had normal body weight based on sex and gestational age at birth (Olsen *et al.* 2010). The data were insufficient to determine small for gestational age for the remaining two infants.

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.* 2007b); 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); his twin sibling had a normal renal ultrasound. The third infant had a dysmorphic/hypoplastic left kidney and kidney congestion, and died at 4 months due to decreased kidney function (Weber-Schoendorfer and Schaefer 2008).

Respiratory difficulties, which ranged from transient tachypnea to respiratory distress, were reported for 10 infants (Bader *et al.* 2007a, Shrim *et al.* 2007, Pant *et al.* 2008, Witzel *et al.* 2008, Beale *et al.* 2009, Goodyer *et al.* 2009, Roberts and Auld 2010, Mandrawa *et al.* 2011). One newborn with respiratory distress also had a very strong capillary leak, 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); however, normal kidneys were observed during fetal ultrasound. Other health effects included: bacterial sepsis and hypotension (Bader *et al.* 2007b), 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).

Infant Deaths

As mentioned above, four infant deaths were observed following gestational exposure to trastuzumab. All infants had experienced reduced amniotic fluid during gestation and all infants who died were born prematurely, except one. One male of fraternal twin infants died at 13 weeks from renal failure and respiratory distress (Beale *et al.* 2009). Another infant, who had a dysmorphic/hypoplastic left kidney and kidney congestion at birth, died at 4 months due to decreased kidney function (Weber-Schoendorfer and Schaefer 2008). One newborn, who had a very strong capillary leak at birth, ultimately died at 21 weeks due to multiple organ failure (Witzel *et al.* 2008). Finally, an infant that was born at term (37 weeks of gestation) had pulmonary hypoplasia and atelectasis (collapse of lung tissue), and died shortly after birth (Warraich and Smith 2009); normal kidneys were observed during fetal ultrasound.

Follow Up Evaluations

Follow up evaluations were reported for 11 infants at ages ranging from 2 months to 5 years; age at follow up evaluation was not specified for one child (El-Safadi *et al.* 2012). 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 was documented for 19 pregnancies and 20 conceptuses (**Table 81**). Overall, the apparent rate of major malformations among all docetaxel-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 0% (/19 conceptuses based on 19 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Thus, the apparent rate of major malformations following exposure to trastuzumab during the first trimester was 0% (0/12 liveborn infants) and in the second and/or third trimester only was 0% (0/6 liveborn infants).

However, exposure to trastuzumab appears to be associated with the absent or deficient amniotic fluid and, possibly, an effect on kidney development and function, when exposure occurs during the second and/or third trimester. For example, anhydramnios or oligohydramnios occurred in 13 of the 19 (68%) total pregnancies, including 13 of the 15 (87%) pregnancies exposed to trastuzumab during the second and/or third trimester. Renal failure or low renal function was reported in three infants who experienced deficient amniotic fluid in the womb (Bader *et al.* 2007b, Weber-Schoendorfer and Schaefer 2008, Beale *et al.* 2009). In addition, pulmonary hypoplasia was diagnosed in an infant who suffered from anhydramnios during gestation and atelectasis at birth; the infant died on day 1 of life (Warraich and Smith 2009). Pulmonary hypoplasia is known to be secondary to many health conditions in infants, including oligohydramnios (Nakamura *et al.* 1992).

Trastuzumab is designed to target the HER2 receptor in human breast cancer cell. However, fetal human kidneys also express HER2 and fetal rat kidneys express a similar receptor, epidermal growth

factor. Trastuzumab is also known to interact with VEGF, an epidermal growth factor that is expressed in the placenta in humans and is known to play a role in regulating amniotic fluid in laboratory animals. Thus, trastuzumab may be reducing amniotic fluid volume in humans via an inhibitory effect on VEGF (Pant *et al.* 2008). It has also been suggested that trastuzumab may be altering the function of aquaporins, a family of channel-forming proteins responsible for fluid regulation in various tissues, including fetal membranes (Sekar and Stone 2007, Liu *et al.* 2008). Finally, early heart development may be susceptible to trastuzumab as mice engineered without erbB2, a member of the epidermal growth receptor family, died in early gestation possibly due to the reduced blood flow in the heart tissue during development (Lee *et al.* 1995). However, there were no reports of abnormal cardiac development or function from the 19 cases reviewed in the draft NTP monograph.

5.32 VINBLASTINE

5.32.1 Mechanism of Action, Route of Administration, and Indications

Table 70: Pharmacology of vinblastine in adult humans	
Molecular weight:	810.983
Protein binding:	99%
Metabolism:	Hepatic to active metabolite
Half-life elimination:	Biphasic: Initial: 4 minutes; Terminal: 25 hours
Distribution:	Vd: 27.3 L/kg; binds extensively to tissues; does not penetrate CNS or other fatty tissues; distributes to liver
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (95%); urine (<1% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum; CSF, cerebral spinal fluid; Vd, volume of distribution	

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). Additional information on the pharmacology of vinblastine is located in **Table 70**.

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 transport of vinblastine in humans is not known. Placental transfer of vinblastine has been demonstrated in mice (Van Calsteren *et al.* 2010d) and baboons (Van Calsteren *et al.* 2010b). 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 bw 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.* 2010d). 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.* 2010b). Vinblastine was not detected in amniotic fluid or in cerebral spinal fluid of the maternal or fetal baboon (Van Calsteren *et al.* 2010b). 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. Administration of vinblastine (0.25 mg/kg bw) 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. (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 bw, 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 bw via subcutaneous injection to MT strain mouse dams on days 11-14 of gestation. Intraperitoneal injection of vinblastine (0.25 mg/kg bw/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 bw/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 vinblastine **[/kg bw]** 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

Number of Cases, Publications, and Types of Cancer Treated

Vinblastine was administered to 82 female cancer patients (also called cases) during pregnancy identified from 18 case reports (18 cases), 7 case series (22 cases), 1 retrospective case series (10 cases), 4 retrospective survey studies (10 cases), 1 retrospective cohort study (1 case), and 1 registry survey (21 cases) (Appendix C Table 30). Among these patients, vinblastine was used to treat Hodgkin lymphoma (75 cases), ovarian cancer (3 cases), Kaposi sarcoma (1 case), choriocarcinoma of the ovary (1 case) and cancer type was not specified in two cases.

A total of 84 pregnancies and 85 conceptuses were exposed to vinblastine with two cases having two singleton pregnancies (Dilek *et al.* 2006) (Nisce *et al.* 1986) and another case gave birth to twins (Cardonick *et al.* 2010). Vinblastine was administered during the first trimester in 18 pregnancies (18 conceptuses) and in the 2nd and/or 3rd trimester only in 58 pregnancies (59 conceptuses due to 1 set of twins); the timing of exposure was not specified for 8 pregnancies (8 conceptuses). Vinblastine was administered as monotherapy in 16 cases (yielding 16 conceptuses), including one case administered vinblastine monotherapy in the first through third trimester and radiation therapy in the eighth month of pregnancy. The drug was administered as polytherapy in 69 cases.

Termination of Pregnancy

Three singleton pregnancies were terminated by induced abortion following gestational exposure to vinblastine. Fetal examination of 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 first trimester to vinblastine, nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin, and dacarbazine. No examination of the fetus was report for two additional induced abortions following: first trimester exposure to vinblastine and procarbazine (Thomas and Peckham 1976), and second trimester exposure to vinblastine, doxorubicin, bleomycin and dacarbazine trimester (D'Incalci *et al.* 1983).

Spontaneous Fetal Death

Two singleton pregnancies ended in spontaneous fetal death following gestational exposure to vinblastine, including one spontaneous abortion and one stillbirth. A spontaneous abortion occurred at gestation week 6 following first trimester exposure vinblastine monotherapy (Mulvihill *et al.* 1987); no examination of the fetus was reported. One stillbirth occurred in the eighth month of gestation following second and third trimester exposure to vinblastine, doxorubicin, bleomycin and dacarbazine (Dilek *et al.* 2006); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major Malformations

Major malformations occurred in 8 liveborn infants gestationally exposed to vinblastine including 5 liveborn infants exposed during the first trimester (**Table 71**).

Table 71: Major malformations diagnosed at birth possibly attributable to in utero exposure to vinblastine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Floating thumb malformation involving the partial agenesis of a metacarpal bone and hypoplasia of two phalanges	
	Bilateral absence of one toe per foot, webbing between the 3rd and 4th toes of the right foot, an abnormal right pinna and bowing of the right tibia	
	Cleft lip and cleft palate	
	Small secundum atrial defect	
	Hydrocephalus	31% (5/16)
2nd and/or 3rd only	Clubfoot	2% (1/57)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Partial agenesis of metacarpal and hypoplasia of two phalanges on the left hand occurred in a newborn that was exposed in the first trimester to vinblastine, doxorubicin, bleomycin and dacarbazine (Dilek *et al.* 2006). Another infant had only 4 toes per foot with webbing on right foot, bowing of the right tibia, and an abnormal right pinna following exposure during the first trimester to vinblastine, procarbazine and nitrogen mustard (Garrett 1974) . One infant suffered from cleft lip and cleft palate following exposure in the first, second and third trimesters to vinblastine, lomustine, vincristine, and procarbazine (Mulvihill *et al.* 1987). Hydrocephalus occurred in an infant exposed during first trimester to vinblastine monotherapy (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 first trimester to vinblastine, vincristine and procarbazine. Thus, the apparent rate of major malformations following exposure to vinblastine during the first trimester was 31% (5/16 conceptuses based on 15 liveborn infants and examination of the fetus of 1 induced abortion).

Major malformations were observed in 3 liveborn infants exposed to vinblastine in the second and/or third trimester only. One infant had syndactyly of the 4th and 5th fingers, which required surgery following exposure in the second and third trimesters to vinblastine, doxorubicin, bleomycin and dacarbazine (Cardonick *et al.* 2010). Bilateral syndactyly of the 2nd and 3rd digits was reported in an infant exposed in the second and third trimesters to vinblastine, nitrogen mustard, vincristine, procarbazine, doxorubicin, bleomycin and dacarbazine (Van Calsteren *et al.* 2010a); this infant was also

exposed to radiation therapy in the second trimester. Clubfoot was reported in an infant following exposure in the third trimester to vinblastine, actinomycin D and methotrexate (Hutchison *et al.* 1968). However, it is unlikely that 2 infants with syndactylies were caused by exposure to vinblastine outside of the period of organogenesis in the first trimester. Thus, the adjusted apparent rate of major malformations following exposure to vinblastine in the second and/or third trimester only was 2% (1/57 conceptuses based on 57 liveborn infants). No malformations were observed in the 8 liveborn infants for whom timing of exposure was not reported.

Minor Malformations

Minor malformations were reported in 2 newborns with gestational exposure to vinblastine. Plagiocephaly was diagnosed in a newborn exposed in utero during the second and third trimesters to vinblastine, doxorubicin, bleomycin and dacarbazine (Cardonick *et al.* 2010). Pectus excavatum was reported in an infant with in utero exposure in the second and third trimesters to vinblastine, nitrogen mustard, vincristine, procarbazine, doxorubicin, and bleomycin (Van Calsteren *et al.* 2010a).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications were reported in pregnancies exposed to vinblastine. Pregnancy complications included one case each of preeclampsia (Anselmo *et al.* 1999), spontaneous preterm labor (Johnson and Filshie 1977), and septicemia, which was treated and resolved (Nordlund *et al.* 1968). Maternal hypertension was reported in a singleton pregnancy in which the fetus suffered from 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).

A total of 80 liveborn infants were gestationally exposed to vinblastine. Early preterm birth (<34 weeks) was reported for 7 infants, late preterm birth (34 to <37 weeks) was reported 11 infants, and 24 infants were born at term. Gestational age at birth was not specified for 38 infants. Of the preterm infants, 8 infants were born via spontaneous vaginal delivery, 9 infants were born via C-section and route of delivery was not specified for 1 infant. Small for gestational age was determined for 8 infants and normal body weights were determined for 46 infants based on sex, gestational age, and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for 26 infants.

Newborn health effects included respiratory difficulties in two infants, such as transient tachypnea (Malone *et al.* 1986) and, as mentioned above, respiratory distress (Thomas and Peckham 1976). Anemia was reported for two infants (Johnson and Filshie 1977, Zuazu *et al.* 1991) and hypoglycemia was reported in 3 infants (Cardonick *et al.* 2010). A large hemorrhage occurred in the right cerebral hemisphere in one infant (Garrett 1974). Another newborn had transitory focal seizures and a urinary tract infection (Hutchison *et al.* 1968).

Infant Deaths

One newborn developed respiratory distress and died at age 2 days following gestational exposure to vinblastine (Thomas and Peckham 1976). A small secundum atrial septal defect was observed at the autopsy of this infant with first trimester exposure to vinblastine monotherapy.

Follow Up Evaluations

Follow up evaluations were reported for 59 infants at ages ranging from 2 months to 17 years; age at follow-up was not specified for 3 children. All children demonstrated normal growth and development.

One child each had: chronic broncolitis, recurrent otis media, and asthma (Cardonick *et al.* 2010). One healthy child tested positive for human immunodeficiency virus (HIV) at age 2; her mother was HIV positive at the time of pregnancy (Okechukwu and Ross 1998).

5.32.5 Summary of Pregnancy Outcomes for vinblastine

Exposure to vinblastine was reported for 84 pregnancies (85 conceptuses) (**Table 79**). Overall, the apparent rate of major malformations among all vinblastine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 10% (8/81 conceptuses based on 80 liveborn infants and examination of the fetus of 1 induced abortion). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007).

Major malformations were reported in five liveborn infants following exposure to vinblastine in the first trimester. The craniofacial malformations observed in two of the infants exposed to vinblastine (Mulvihill *et al.* 1987) were consistent with malformations observed in developmental toxicity studies in animals. In addition, vinblastine induced twisted limbs in developmental toxicity studies in mice, which may be relevant to the bowed tibia reported in another infant (Garrett 1974). The incidence of skeletal malformations of the hands and feet as well as the secundum atrial defect may be due to vinblastine or the other agents used in the polytherapy (nitrogen mustard and procarbazine). Thus, the apparent rate of major malformations following exposure during the first trimester to vinblastine was 31% (5/16 conceptuses based on 15 liveborn infants and examination of the fetus of 1 stillbirth).

Major malformations were observed in 3 of 57 liveborn infants exposed to vinblastine in the second and/or third trimester only. However, the incidence of syndactylies in two infants was not likely caused by exposure to vinblastine polytherapy following the period of organogenesis in the first trimester. Thus, the adjusted apparent rate of major malformations following exposure to vinblastine in the second and/or third trimester only was 2% (1/57 conceptuses based on 57 liveborn infants).

5.33 VINCRISTINE

5.33.1 Mechanism of Action, Route of Administration, and Indications

Table 72: Pharmacology of vincristine in adult humans	
Molecular weight:	824.966
Protein binding:	**[Information not located]**
Metabolism:	Extensively hepatic, via CYP3A4
Half-life elimination:	Terminal: 85 hours (range: 19-155 hours)
Distribution:	**[Information not located]**
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (~80%); urine (10% to 20%; <1% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum	

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. Additional information on the pharmacology of vincristine is located in **Table 72**.

Vincristine is indicated for the treatment of acute leukemia (Hospira 2008b). It has also been used in combination with other chemotherapeutic agents for treatment of Hodgkin disease, rhabdomyosarcoma, neuroblastoma, Wilms tumor, and non-Hodgkin lymphomas (histocytic, lymphocytic, mixed cell, undifferentiated, nodular and diffuse types).

5.33.2 Evidence of Placental and Breast Milk Transport

Placental and breast milk transfer of vincristine in humans is not known. In vitro studies of human placental choriocarcinoma epithelial cell line (BeWo cells) demonstrated that the uptake of vincristine was increased by co-treatment 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 *et al.* 2010d) and baboons (Van Calsteren *et al.* 2010b).

5.33.3 Laboratory Animal Developmental Toxicity

Vincristine is reported to cause fetal loss and/or malformations in variety of laboratory animals (Hospira 2008b). Ferm et al. (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 bw via intravenous injection 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 (0.125, 0.15, or 0.2 mg/kg bw) on the 8th and 9th days of gestation (Tamaki *et al.* 1966). In the rat, fetal mortality was highest (48% to 94%) following exposure to gestation day 9 regardless of vincristine dose and fetal malformations were the most diverse following administration of 0.2 mg vincristine/kg bw on gestation day 8 (Tamaki *et al.* 1966). The most frequently occurring malformations were anophthalmos, microphthalmos, exencephaly, microtia, and talipomanus (clubhand) (Tamaki *et al.* 1966). Intramuscular administration of vincristine (0.5 to 0.7 mg/kg bw) to both Long Evans and Albino rat dams on gestation day 8.5 also induced micrognathia, anophthalmia or microphthalmia as well as cleft palate and jaw, among other malformations (DeMyer 1965).

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 Ungthavorn 1969). Another study in Swiss albino mice reported vincristine administered as a single intraperitoneal injection (0.2, 0.3 or 0.4 mg/kg bw) on gestation day 6, 7 or 8 induced primarily skeletal malformations (i.e., cleft palate, clubfoot, and malformations of digits), hydrocephalus, microtia, and ocular malformations (Sieber *et al.* 1978). Ocular malformations were reported in fetal Swiss-Webster mice exposed to 0.3 mg vincristine sulfate/kg bw via intraperitoneal injection to the dam on gestation day 10 as well as ex vivo incubation of the embryos (0.001 mg vincristine sulfate/mL at embryonic stage of 1-3 or 4-6 somites) (Svoboda and O'Shea 1984).

Vincristine was also reported to induce malformations in non-human primates. Five pregnant monkeys (Macaca mulatta) were administered 0.15 to 0.2 mg vincristine/kg intravenous injection 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). A subsequent developmental toxicity study in rhesus monkeys reported no teratogenic effects at doses ranging from a single dose of 0.2, 0.3 or 0.4 mg vincristine/kg bw on gestation day 27, 28, or 26, respectively (Wilson 1971); nor were teratogenic effects observed at higher doses of vincristine (up to 0.2 or 0.3 mg vincristine/kg bw administered two or four times daily on gestation days 27 and 28). Pregnancy loss was reported in rhesus monkeys at vincristine doses of 0.2 mg/kg bw administered twice a day on gestation day 27 and 28, which was five times higher than the daily dose that induced teratogenesis in rat fetuses (0.15 mg/kg bw administered to the rat dam for 9 days during organogenesis) (Wilson 1971).

5.33.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Vincristine was administered to 225 female cancer patients (also called cases) during pregnancy identified from 76 case reports (76 cases), 23 case series (44 cases), 4 retrospective case series (47 cases), 8 retrospective surveys (37 cases), 2 retrospective cohort studies (10 cases), and 1 registry survey (14 cases) (Appendix C Table 31). Among these patients, vincristine was predominantly used to treat leukemias and lymphomas, including acute leukemia (type not specified, 3 cases), acute lymphocytic leukemia (58 cases), acute myelogenous or granulocytic leukemia (27 cases), acute myelomonocytic leukemia (2 cases), acute promyelocytic leukemia (2 cases), chronic myelogenous leukemia (1 case), Hodgkin lymphoma (26 cases), non-Hodgkin lymphoma (56 cases), Burkitt lymphoma (7 cases), B-cell lymphoma (2 cases), diffuse large B-cell lymphoma (2 cases), T-cell lymphoma (2 cases), and adult T-cell leukemia/lymphoma (1 case). Vincristine was also used to treat the following non-blood-related cancers: breast (5 cases), cervix (7 cases), kidney (Wilms tumor, 2 cases), lung (1 case), melanoma (1 case), ovary (6 cases), choriocarcinoma of the uterus (1 case), vagina (neuroendocrine carcinoma; 1 case) as well as sarcoma (1 case), undifferentiated sarcoma (1 case), Ewing sarcoma (3 cases), rhabdomyosarcoma (3 cases) and soft tissue sarcoma (2 cases), and granulocytic sarcoma of the breast (1 case). The cancer type was not specified in 3 additional cases.

A total of 226 pregnancies with 228 conceptuses were exposed to vincristine, including one patient who had two pregnancies (Aviles and Niz 1988) and two twin pregnancies (Turchi and Villasis 1988, Nantel *et al.* 1990). Vincristine was administered during the first trimester in 58 pregnancies (58 conceptuses). It was administered in the second and/or third trimester only in 167 pregnancies (169 conceptuses),

including 2 singleton pregnancies presumed to have been exposed in the second and/or third trimester (Jameel and Jamil 2007). Specifically, the reported age of initiation of chemotherapy for all cases in this report was an age range from 12-33 weeks of gestation (mean = 24 weeks) (Jameel and Jamil 2007). Timing of exposure was not specified for 1 singleton pregnancy (1 embryo). Vincristine was predominantly administered as polytherapy (222 cases yielding 223 pregnancies and 225 conceptuses). Vincristine was used as monotherapy in only 6 cases (6 singleton pregnancies, 6 conceptuses).

Termination of Pregnancy

A total of 15 singleton pregnancies were terminated following gestational exposure to vincristine, including 11 induced abortions performed following exposure during the first trimester. Normal fetuses were reported for two induced abortions. 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 first trimester to vincristine, nitrogen mustard, procarbazine, doxorubicin, bleomycin, vinblastine, and dacarabazine. Examination revealed a normal fetus with small, malpositioned kidneys from a second induced abortion following first trimester exposure to vincristine, procarbazine and nitrogen mustard (Mennuti *et al.* 1975). No examination of the fetus was reported for the remaining 9 induced abortuses exposed to vincristine polytherapy during the first trimester (Blatt *et al.* 1980, Fassas *et al.* 1984, Zuazu *et al.* 1991, Zemlickis *et al.* 1992b, Chelghoum *et al.* 2005, Molkenboer *et al.* 2005).

Four singleton pregnancies were terminated by induced abortion following exposure to vincristine in the second and/or third trimester only. A normal fetus was reported for an induced abortion following exposure in the second trimester to vincristine, hydroxyurea, daunorubicin, cytarabine, and 6-thioguanine (Doney *et al.* 1979); the fetus had normal organ weights with the exception of an enlarged spleen. Another normal fetus from an induced abortion was exposed in the second trimester to vincristine, daunorubicin, cytarabine, and 6-thioguanine (Lilleyman *et al.* 1977). No examination of the fetus was reported for the remaining 2 induced abortions following exposure to vincristine in the second trimester (Zuazu *et al.* 1991, Zemlickis *et al.* 1992b).

Spontaneous Fetal Death

Spontaneous fetal death was reported for 15 singleton pregnancies exposed to vincristine, including 7 spontaneous abortions and 8 stillbirths. Spontaneous abortion was reported for 7 singleton pregnancies exposed to vincristine during the first trimester and no examination of the fetuses reported. The spontaneous abortions occurred following exposure in the first trimester to vincristine and the following co-treatments: cyclophosphamide (Zuazu *et al.* 1991); daunorubicin, cytarabine and 6-thioguanine (Zuazu *et al.* 1991); doxorubicin (Peres *et al.* 2001); doxorubicin and cytarabine (Awidi *et al.* 1983); epirubicin and methotrexate (Giacalone *et al.* 1999); methotrexate and 6-mercaptopurine (Bergstrom and Altman 1998); and nitrogen mustard and procarbazine (Zemlickis *et al.* 1992b).

Stillbirth was reported for 8 singleton pregnancies following exposure to vincristine in the second and/or third trimester only. Normal fetuses at autopsies were reported for 3 stillbirths. These 3 normal fetuses were exposed to: vincristine, doxorubicin, cyclophosphamide, and rituximab exposed in the second and third trimesters (Cardonick *et al.* 2010); vincristine, doxorubicin and radiation therapy in the third trimester (Karp *et al.* 1983); and vincristine, daunorubicin, cytarabine and 6-thioguanine in the third trimester (Zuazu *et al.* 1991). No examination of the fetus was reported for the remaining 5 stillbirths that occurred following exposure to vincristine in the second and/or third trimester only. The stillbirths without fetal data were exposed to the following vincristine polytherapy: vincristine and epirubicin in the second trimester (Peres *et al.* 2001), daunorubicin, intrathecal methotrexate, cytarabine and

asparaginase in the second trimester (Molkenboer *et al.* 2005); and cyclophosphamide, doxorubicin and dacarbazine in the second trimester (Jameel and Jamil 2007) or vincristine and daunorubicin in the second and third trimesters (Jameel and Jamil 2007). The remaining stillbirth without reported examination of the fetus was exposed to cyclophosphamide, vincristine, doxorubicin, ifosfamide, etoposide, cytarabine, and rituximab in the second trimester (Peterson *et al.* 2010); this fetus experienced oligohydramnios and intrauterine fetal growth restriction prior to death.

Two additional singleton fetal deaths were the result of maternal death. Examination revealed a normal fetus from one maternal and fetal death at gestation week 23 following in utero exposure during the first and second trimester to vincristine, 6-mercaptopurine, daunorubicin and cytarabine (Feliu *et al.* 1988). The second maternal and fetal death occurred in the second trimester [in ~gestation week 24] following exposure during the second trimester to vincristine, daunorubicin and cytarabine (Greenlund *et al.* 2001); no examination of the fetus was reported.

Rate of Occurrence of Congenital Malformations

Major malformations

Table 73: Major malformations diagnosed at birth following in utero exposure to vincristine

Trimester exposed	Major malformations observed	Apparent rate of major malformations
During 1st	Bilateral loss of the radius and the 5th digit and an atrial septal defect	10% (4/41)
	Cleft lip and cleft palate	
	Small secundum atrial septal defect	
	Hydrocephalus	
2nd and/or 3rd only	None	0% (0/163)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

Major malformations were reported in 4 liveborn infants exposed to vincristine during the first trimester (Table 73). One newborn had bilateral loss of the radius and the 5th digit as well as an atrial septal defect following exposure in the first trimester to vincristine, 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 first trimester to vincristine, vinblastine and procarbazine. Cleft lip and cleft palate were observed in an infant following first trimester exposure to vincristine, lomustine, procarbazine, and vinblastine (Mulvihill *et al.* 1987). Hydrocephalus was reported in a newborn exposed during the first trimester to vincristine, nitrogen mustard and procarbazine (Zemlickis *et al.* 1992b); this infant died 4 hours after birth. Thus, the apparent rate of major malformations following exposure to vincristine during the first trimester was 10% (4/41 conceptuses based on 38 liveborn infants and examination of the fetuses of 2 induced abortions and 1 maternal/fetal death).

One major malformation occurred in one infant following exposure to vincristine in the second and/or third trimester only. Bilateral syndactyly of digits II and III occurred in an infant exposed during the second and third trimester to vincristine, nitrogen mustard, procarbazine, doxorubicin, bleomycin, vinblastine (Van Calsteren *et al.* 2010a); this infant was also exposed to radiotherapy in the second trimester. However, it is not likely that syndactyly was induced by exposure to vincristine polytherapy beginning at gestation week 26 because skeletal development occurs during organogenesis during the

first trimester. Thus, the adjusted apparent rate of major malformations following exposure to vincristine to the second and/or third trimester only was 0% (0/163 conceptuses based on 158 liveborn infants and examination of the fetuses of 2 induced abortions and 3 stillbirths). No major malformations were reported in the one liveborn infant for which timing of exposure was not specified (Sears and Reid 1976).

Minor Malformations

Two liveborn infants had minor malformations following exposure in the second and third trimesters. Pectus excavatum was reported in one liveborn infant following exposure during the second and third trimesters to vincristine, nitrogen mustard, procarbazine, doxorubicin, bleomycin, and vinblastine (Van Calsteren *et al.* 2010a). A hemangioma was reported in another infant following exposure in the second and third trimesters to vincristine, methotrexate, daunorubicin, cyclophosphamide, asparaginase, and 6-mercaptopurine (Van Calsteren *et al.* 2010a).

In addition, some chromosomal breakage and a ring chromosome were observed in an otherwise normal newborn exposed to vincristine polytherapy in the second trimester (Schleuning and Clemm 1987).

Pregnancy Complications and Newborn Health

A variety of pregnancy complications and infant health issues were reported following in utero exposure to vincristine. Pregnancy complications included preeclampsia (4 pregnancies) (Coopland *et al.* 1969, Bartsch *et al.* 1988, Lambert *et al.* 1991, Bergstrom and Altman 1998, Chakravarty *et al.* 2011), one case of preeclampsia was treated and subsided (Bartsch *et al.* 1988), and premature rupture of membranes (7 pregnancies) (Doney *et al.* 1979, Okun *et al.* 1979, Webb 1980, Karp *et al.* 1983, Meador *et al.* 1987, Ali *et al.* 2009a, Udink ten Cate *et al.* 2009). Spontaneous preterm labor occurred in 17 pregnancies (Wells *et al.* 1968, Doney *et al.* 1979, Tobias and Bloom 1980, Berrebi *et al.* 1983, Karp *et al.* 1983, Fassas *et al.* 1984, Reynoso *et al.* 1987, Kim and Park 1989, Nantel *et al.* 1990, Willemse *et al.* 1990, Moore and Taslimi 1991, Martin *et al.* 1997, Decker *et al.* 2006, Brudie *et al.* 2011) (Weed *et al.* 1979, Webb 1980, Avasthi and Agarwal 1993). Transient preterm labor occurred in 1 pregnancy (Ortega 1977, Hansen *et al.* 2001). Placenta previa was reported in 1 singleton pregnancy (Cardonick *et al.* 2010). A reduction in amniotic fluid was observed in 2 singleton pregnancies yielding liveborn infants (transient oligohydramnios (Hansen *et al.* 2001) and anhydramnios (Fernandez *et al.* 1989). Intrauterine growth restriction was reported in three singleton pregnancies yielding liveborn infants (Lambert *et al.* 1991, Matsouka *et al.* 2008), including one pregnancy with a reduction in amniotic fluid (Fernandez *et al.* 1989, Peterson *et al.* 2010). In addition, intrauterine growth restriction and a reduction in amniotic fluid preceded a stillbirth (Peterson *et al.* 2010). Fetal distress was reported in three cases (Veneri *et al.* 1996, Mavrommatis *et al.* 1998, Ali *et al.* 2009a).

A total of 196 liveborn infants were gestationally exposed to vincristine. Early preterm delivery (<34 weeks) was reported for 42 infants, late preterm delivery (34 to <37 weeks) was reported for 36 infants and 79 infants were delivered at term. Data were insufficient to determine the gestational age at delivery for 39 liveborn infants. Of the preterm infants, 25 infants were born via spontaneous vaginal delivery, 8 infants were born via induced vaginal delivery, and 37 infants were born via C-section. Route of delivery was not specified for 8 infants. Small for gestational age was determined for 18 infants and 123 infants had normal body weights based on sex, gestational age, and body weight at birth (Olsen *et al.* 2010). Data were insufficient to determine small for gestational age for the remaining 55 infants.

Chelghoum et al. (2005) reported two infants were premature**; [age at delivery and the definition of premature were not specified so they are not included in the tally.]**

Respiratory difficulties were reported for 15 newborns. Respiratory distress was most frequently reported (Thomas and Peckham 1976, Haerr and Pratt 1985, Willemse *et al.* 1990, Veneri *et al.* 1996, Mavrommatis *et al.* 1998, Achtari and Hohlfeld 2000, Corapcioglu *et al.* 2004, Lam 2006, Bader *et al.* 2007a, Matsouka *et al.* 2008, Papantoniou *et al.* 2008, Ali *et al.* 2009a, Cordeiro *et al.* 2009, Cardonick *et al.* 2010), including one infant with tachypnea that developed into respiratory distress requiring intubation and surfactant treatment (Bartsch *et al.* 1988). One infant had transient tachypnea (Cardonick *et al.* 2010) and another infant required oxygen treatment after meconium aspiration (Hansen *et al.* 2001). Transient myelosuppression was observed in 13 infants, including anemia (5 infants) (Doney *et al.* 1979, Aviles and Niz 1988, Cardonick *et al.* 2010, Gambino *et al.* 2011), absent or low levels of B-cells (4 infants) (Decker *et al.* 2006, Friedrichs *et al.* 2006, Chakravarty *et al.* 2011), leukopenia (Khurshid and Saleem 1978, Garcia *et al.* 1999), 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 hypoglycemic, and had electrolyte abnormalities (Doney *et al.* 1979). Polycythemia (Dara *et al.* 1981) and low hemoglobin (Gulati *et al.* 1986) were observed in one infant each. Several other health effects were observed in newborns gestationally exposed to vincristine. One newborn required intravenous calcium (Haerr and Pratt 1985). Jaundice was observed in 7 infants (Dara *et al.* 1981, Hansen *et al.* 2001, Peres *et al.* 2001, Matsouka *et al.* 2008, Papantoniou *et al.* 2008, Cardonick *et al.* 2010). Cerebral hemorrhages were observed in three early preterm infants (Fernandez *et al.* 1989, Veneri *et al.* 1996, Achtari and Hohlfeld 2000). Cardiac effects were observed in two infants, including acute cardiac failure on day 1, which resolved in three days with treatment (Achtari and Hohlfeld 2000) and asystole (in addition to apnea, then respiratory distress) on day of birth (Willemse *et al.* 1990). Several infants suffered from infections, such as necrotizing enterocolitis (1 infant) (Achtari and Hohlfeld 2000), omphalitis (1 infant) (Cordeiro *et al.* 2009), septicemia resulting in death at 21 days (1 infant) (Aviles and Niz 1988), gastroenteritis resulting in the death of two infants at age 90 days (Aviles and Niz 1988, Dilek *et al.* 2006), and sepsis (1 infant) (Willemse *et al.* 1990). 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); the female twin was also hypotonic.

Adverse placenta findings were reported for a few singleton pregnancies yielding liveborn infants without major malformations. One placenta had multiple tumor deposits (Ateser *et al.* 2007). Two placentas had areas of infarction (Lambert *et al.* 1991, Cardonick *et al.* 2010). One placenta had large areas of ischemic necrosis without chorioamniotis (Fernandez *et al.* 1989). Another placenta was reported to be small (350 g); the full term infant weighed 2860 g (Toki *et al.* 1990).

Infant Deaths

Five infant deaths were reported following gestational exposure to vincristine. One preterm infant with bilateral intraventricular hemorrhages died at age 7 days and autopsy revealed a meningeal hematoma (Fernandez *et al.* 1989); this infant had anuria for 7 days prior to death and experienced anhydramnios during pregnancy. One preterm infant suffered from septicemia resulting in death at age 21 days (Aviles and Niz 1988). Gastroenteritis resulted in the death of two infants at age 90 days (Aviles and Niz 1988, Dilek *et al.* 2006). Another infant died on day 2 after developing respiratory distress (Thomas and Peckham 1976); autopsy revealed a small secundum atrial septal defect.

Follow Up Evaluations

Follow up evaluations were reported for 143 children ranging in age from 8 weeks to 19 years; age at follow up was not specified for 5 children (Khurshid and Saleem 1978, Willemse *et al.* 1990, Bergstrom and Altman 1998, Seamon *et al.* 2009). 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 delays at 18 months (Achtari and Hohlfeld 2000) or at 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. In addition, 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 226 pregnancies and 228 conceptuses, including one case with two singleton pregnancies and two sets of twins (**Table 79**). Overall, the apparent rate of major malformations among all vincristine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 2% (5/204 conceptuses based on 196 liveborn infants and examination of the fetuses of 4 induced abortions, 3 stillbirths, and 1 maternal/fetal death). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in four liveborn infants with exposure to vincristine during the first trimester. The cranial and skeletal malformations, and hydrocephalus observed in 3 infants gestationally exposed to vincristine polytherapy were also observed in developmental toxicity studies of vincristine administered during organogenesis to rats and mice. Thus, the apparent rate of major malformations following exposure to vincristine during the first trimester was 10% (4/41 conceptuses based on 38 liveborn infants and examination of the fetuses of 2 induced abortions and 1 maternal/fetal death). Major malformations were observed in one liveborn infant exposed to vincristine in the second and third trimesters: bilateral syndactyly of digits II and III (Van Calsteren *et al.* 2010a). However, syndactyly in this infant was not likely caused by vincristine polytherapy because it was administered on gestation week 26, after the active period of skeletal development in the first trimester. Thus, the adjusted rate of major malformations following exposure to vincristine in the second and/or third trimester only was 0% (0/163 conceptuses based on 158 liveborn infants and examination of the fetuses of 2 induced abortions and 3 stillbirths). No major malformations were reported in one liveborn infant for which timing of exposure was not specified.

5.34 VINORELBINE

5.34.1 Mechanisms of action, route of administration, and indications

Table 74: Pharmacology of vinorelbine in adult humans	
Molecular weight:	778.942
Protein binding:	80% to 91%
Metabolism:	Extensively hepatic, via CYP3A4, to two metabolites, deacetylvinorelbine (active) and vinorelbine N-oxide
Half-life elimination:	Triphasic: Terminal: 28-44 hours
Distribution:	Vd: 25-40 L/kg; binds extensively to human platelets and lymphocytes (80% to 91%)
Time to peak, serum (C_{max}):	**[Information not located]**
Excretion:	Feces (46%); urine (18%, 10% to 12% as unchanged drug)
Data from Brunton et al. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum, Vd, volume of distribution	

Vinorelbine is a semi-synthetic vinca alkaloid, which interferes with microtubule assembly (GlaxoSmithKline 2002). Vinorelbine is administered intravenously. Additional information on the pharmacology of vinorelbine is located in **Table 74**.

Vinorelbine is indicated for the treatment of advanced non-small cell lung cancer (GlaxoSmithKline 2002) and breast cancer (PPC 2009).

5.34.2 Evidence of Placental and Breast Milk Transport

Placental 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 radiolabelled vinorelbine/kg bw to pregnant rats on gestation day 19.

Maternal transfer of vinorelbine to the infant in humans via breast milk is not known.

5.34.3 Laboratory Animal Developmental Toxicity

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

5.34.4 Human Gestational Exposure and Effects

Number of Cases, Publications, and Types of Cancer Treated

Vinorelbine was administered to 15 female cancer patients (also called cases) during pregnancy identified from 5 case reports (5 cases), 2 case series (4 cases), 1 retrospective survey (4 cases), and 1

registry survey (2 cases) (Appendix C Table 32). Among these cases, vinorelbine was used to treat cancer of the breast (11 cases), lung (3 cases) as well as one case with rhabdomyosarcoma.

A total of 15 singleton pregnancies (15 conceptuses) were exposed to vinorelbine. Vinorelbine was administered during first trimester in one pregnancy (1 embryo) and in the second and/or third trimester only in the remaining 14 pregnancies (14 conceptuses). The agent was administered as monotherapy in one case and as polytherapy in 14 cases.

Termination of Pregnancy

No terminations of pregnancy were reported following gestational exposure to vinorelbine.

Spontaneous Fetal Death

No spontaneous abortions or stillbirths were reported following gestational exposure to vinorelbine.

Rate of Occurrence of Congenital Malformations

Major malformations

Table 75. Major malformations diagnosed at birth possibly attributable to in utero exposure to vinorelbine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Cleft palate, tracheoesophageal fistula and esophageal atresia	(1/1)
2nd and/or 3rd only	None	0% (0/14)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths

One liveborn infant had major congenital malformations following gestational exposure to vinorelbine. Cleft lip, cleft palate, tracheoesophageal fistula, and esophageal atresia were reported in an infant exposed during the first through third trimesters to vinorelbine, oxaliplatin and irinotecan (Abellar *et al.* 2009) (Table 75).

Minor Malformations

No minor malformations were reported following gestational exposure to vinorelbine.

Pregnancy Complications and Newborn Health

A few pregnancy complications were reported following in utero exposure to vinorelbine. Reductions in amniotic fluid were observed in two pregnancies that were exposed to vinorelbine polytherapy in the third (El-Safadi *et al.* 2012) or second and third trimesters (Fanale *et al.* 2005). Specifically, one fetus experienced anhydramnios (El-Safadi *et al.* 2012) and oligohydramnios, occasional fetal cardiac decelerations, and decreased fetal movements were reported for a second fetus(Fanale *et al.* 2005). Maternal respiratory difficulties due to the progression of lung cancer lead to an emergency C-section (Janne *et al.* 2001).

A total of 15 liveborn infants were gestationally exposed to vinorelbine. Early preterm delivery (<34 weeks) occurred for 4 infants, late preterm delivery (34 to <37 weeks) occurred for 5 infants, and 5 infants were delivered at term. Data were insufficient to determine gestational age at delivery for 1 infant. Of the preterm infants, one infant was delivered via induced vaginal delivery, 6 infants were born via C-section; route of delivery was not specified for 2 infants. Normal body weight was

determined for 14 infants and data were insufficient to determine small for gestational age for 1 infant based on sex, gestational age, and body weight at birth (Olsen *et al.* 2010).

Transient myelosuppression was observed in 3 newborns (Cuvier *et al.* 1997, Giacalone *et al.* 1999), including two infants with anemia and one infant with a decrease in white blood cells and neutrophils at 10 days of age, which resolved 3 weeks later (Janne *et al.* 2001). Adverse placenta observations were reported in two births of normal infants. One placenta had vacuolization and nuclear pleomorphism, extravillous trophoblasts of the chorion laueve villous hypermaturity, and multifocal edema (Abellar *et al.* 2009). Another placenta had areas of infarction (Cardonick *et al.* 2010)

Infant Deaths

No infant deaths were reported following gestational exposure to vinorelbine.

Follow Up Evaluations

Follow up evaluations were available for 12 offspring ranging in age from 4 to 80 months. Normal development was reported in all children.

5.34.5 Summary of Pregnancy Outcomes for vinorelbine

In utero exposure to vinorelbine was documented for 15 singleton pregnancies (15 conceptuses) (**Table 79**). Overall, the apparent rate of major malformations among all vinorelbine-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 7% (1/15 conceptuses based on 15 liveborn infants). As a point of reference, the prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Major malformations were observed in the only one liveborn infant exposed to vinorelbine polytherapy during the first trimester of pregnancy, including cleft lip, cleft palate, tracheoesophageal fistula and esophageal atresia (Abellar *et al.* 2009). It was not possible to determine if the major malformations observed were consistent with the developmental toxicity studies of vinorelbine in animals due to the relatively few details provided in the product label (GlaxoSmithKline 2002). The malformations may also have been due to co-treatments with irinotecan and oxaliplatin or the combination therapy. Irinotecan is reported to cause visceral and skeletal malformations when administered to rats and rabbits during organogenesis at doses less than the recommended human dose (per surface area) (Sagent 2012). It was not possible to calculate an apparent rate of major malformations following exposure to vinorelbine during the first trimester because there was only one singleton pregnancy exposed (1 /1 conceptus based on 1 liveborn infant exposed). No malformations were observed in the 14 infants exposed in utero to vinorelbine during the second and/or third trimester only. Thus, the apparent rate of major malformations following exposure to vinorelbine in the second and/or third trimester only was 0% (0/14 conceptuses based on 14 liveborn infants). Reductions in amniotic fluid reported in two fetuses exposed to vinorelbine polytherapy in the second or second and third trimesters were likely due to co-treatment with trastuzumab.

Table 76: Summary table of pregnancy outcomes in humans following gestational exposure to anti-metabolites

Agent	Spontaneous abortions[a] (No. of affected/total conceptuses)			Stillbirths[b] (No. of affected/total conceptuses)			Major malformations[c] (No. of affected/total conceptuses)		
	During 1st[d]	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified
5-Fluorouracil	27% (4/15)	(0/161)	--	9% (1/11)	(0/161)	--	31% (4/13)	1% (2/161)	--
6-Mercaptopurine	13% (5/39)	(0/42)	(0/4)	3% (1/34)	2% (1/42)	25% (1/4)	6% (2/35)	(0/41)	(0/3)
6-Thioguanine	20% (1/5)	(0/42)	--	(0/4)	12% (5/42)	--	33% (2/6)	(0/44)	--
Cytarabine	17% (4/24)	4% (4/114)	(0/13)	20% (4/20)	8% (9/110)	8% (1/13)	19% (4/21)	(0/109)	(0/13)
Hydroxyurea	(0/13)	(0/20)	--	8% (1/13)	5% (1/20)	--	8% (1/13)	5% (1/21)	--
Methotrexate	14% (4/28)	(0/57)	--	4% (1/24)	2% (1/57)	--	4% (1/24)	(0/58)	--

[a] Spontaneous fetal death at <22 weeks of gestation; denominator excludes termination of pregnancy and maternal and fetal deaths
[b] Spontaneous fetal death at ≥22 weeks of gestation; denominator excludes termination of pregnancy, spontaneous abortions, and maternal and fetal deaths
[c] Excludes any induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths without examination of the fetus
[d] Includes exposures in the 1st trimester only and exposure in the 1st trimester and subsequent trimesters

Agent	Timing of birth[f] (No. of affected/total liveborn infants)				Spontaneous preterm birth[g]	Body weight at birth[h] (No. of affected/total liveborn infants)			Adverse health effects at follow up[i]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/total liveborn infants)	SGA	Normal	Not specified	(No. of affected/total offspring)
5-Fluorouracil	6% (11/171)	16% (27/171)	9% (15/171)	68% (117/171)	4% (6/171)	6% (11/171)	54% (93/171)	39% (67/171)	3% (4/129)
6-Mercaptopurine	18% (13/74)	27% (20/74)	36% (27/74)	19% (14/74)	23% (17/74)	11% (8/74)	53% (39/74)	36% (27/74)	2% (1/52)
6-Thioguanine	27% (11/41)	22% (9/41)	44% (18/41)	7% (3/41)	22% (9/41)	15% (6/41)	66% (27/41)	20% (8/41)	6% (2/33)
Cytarabine	21% (28/119)	20% (26/119)	37% (49/131)	21% (28/131)	13% (17/131)	13% (17/131)	59% (77/131)	28% (37/131)	5% (4/88)
Hydroxyurea	10% (3/31)	23% (7/31)	52% (16/31)	16% (5/31)	7% (2/31)	3% (1/31)	68% (21/31)	29% (9/31)	5% (1/22)
Methotrexate	20% (16/79)	14% (11/79)	35% (28/79)	30% (24/79)	15% (12/79)	13% (10/79)	62% (49/79)	25% (20/79)	4% (2/53)

[f] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[g] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation
[h] Small for gestational age newborns were determined by comparing the sex, gestational age at birth and birth weight to the 10th percentile body weight per sex (Olsen *et al.* 2010) or as reported by the authors when clearly defined
[i] Denominator includes only the gestationally-exposed offspring with follow up evaluations

Table 77: Summary table of pregnancy outcomes in humans following gestational exposure to DNA alkylating agents

Agent	Spontaneous abortions[a] (No. of affected/total conceptuses)			Stillbirths[b] (No. of affected/total conceptuses)			Major malformations[c] (No. of affected/total conceptuses)		
	During 1st [d]	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified
Busulfan	5% (1/19)	(0/6)	0% (0/5)	(0/18)	(0/6)	0% (0/5)	16% (3/19)	(0/6)	0% (0/5)
Carboplatin	--	6% (1/17)	--	--	(0/17)	--	--	(0/17)	--
Cisplatin	(0/3)	1% (1/99)	--	(0/3)	1% (1/98)	--	(0/5)	1% (1/99)	--
Cyclophosphamide	10% (4/41)	0.3% (1/369)	--	5% (2/37)	1% (3/368)	--	18% (7/39)	1% (3/367)	--
Dacarbazine	(0/8)	(0/47)	--	(0/8)	4% (2/47)	--	11% (1/9)	(0/45)	--
Ifosfamide	(0/1)	(0/10)	--	(0/1)	10% (1/10)	--	(0/1)	(0/9)	--
Nitrogen mustard	14% (2/14)	(0/13)	--	(0/12)	(0/13)	--	13% (2/15)	(0/13)	--
Procarbazine	7% (1/14)	(0/12)	--	(0/13)	(0/12)	--	27% (4/15)	(0/12)	--

[a] Spontaneous fetal death at <22 weeks of gestation; denominator excludes termination of pregnancy
[b] Spontaneous fetal death at ≥22weeks of gestation; denominator excludes termination of pregnancy and spontaneous abortions
[c] Excludes any termination of pregnancy, spontaneous abortions and stillbirths without examination of the fetus
[d] Includes exposures in the 1st trimester only and exposure in the 1st trimester and subsequent trimesters

Agent	Timing of birth[f] (No. of affected/total liveborn infants)				Spontaneous preterm birth[g]	Body weight at birth[h] (No. of affected/total liveborn infants)			Adverse health effects at follow up[i]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/total liveborn infants)	SGA	Normal	Not specified	(No. of affected/total offspring)
Busulfan	3% (1/29)	17% (5/29)	59% (17/29)	21% (6/29)	10% (3/29)	28% (8/29)	28% (8/29)	45% (13/29)	5% (1/22)
Carboplatin	38% (6/16)	38% (6/16)	6% (1/16)	19% (3/16)	6% (1/16)	13% (2/16)	81% (13/16)	6% (1/16)	7% (1/14)
Cisplatin	33% (34/102)	29% (30/102)	17% (17/102)	21% (20/102)	4% (4/102)	13% (13/102)	60% (61/102)	27% (28/102)	4% (3/68)
Cyclophosphamide	9% (37/400)	14% (56/400)	19% (74/400)	58% (233/400)	7% (27/400)	7% (28/400)	66% (263/400)	27% (109/400)	3% (8/284)
Dacarbazine	9% (5/53)	17% (9/53)	26% (14/53)	47% (25/53)	11% (6/53)	13% (7/53)	75% (40/53)	11% (6/53)	(0/39)
Ifosfamide	4% (4/10)	50% (5/10)	1% (1/10)	(0/10)	40% (4/10)	30% (3/10)	7% (7/10)	(0/10)	13% (1/8)
Nitrogen Mustard	16% (4/25)	8% (2/25)	52% (13/25)	24% (6/25)	20% (5/25)	4% (1/25)	48% (12/25)	48% (12/25)	(0/15)

Procarbazine	8% (2/25)	8% (2/25)	56% (14/25)	28% (7/25)	16% (4/25)	8% (2/25)	52% (13/25)	40% (10/25)	(0/13)

[f] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.

[g] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation

[h] Small for gestational age newborns were determined by comparing the sex, gestational age at birth and birth weight to the 10th percentile body weight per sex (Olsen *et al.* 2010) or as reported by the authors when clearly defined

[i] Denominator includes only the gestationally-exposed offspring with follow up evaluations

Table 78: Summary table of pregnancy outcomes in humans following gestational exposure to DNA intercalating agents

Agent	Spontaneous abortions[a] (No. of affected/total conceptuses)			Stillbirths[b] (No. of affected/total conceptuses)			Major malformations[c] (No. of affected/total conceptuses)		
	During 1st [d]	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified
Actinomycin D	--	(0/16)	--	--	(0/16)	--	--	(0/16)	--
Daunorubicin	50% (4/8)	3% (2/78)	(0/5)	(0/4)	11% (8/76)	(0/5)	20% (1/5)	(0/75)	(0/5)
Doxorubicin	3% (1/39)	0.3% (1/387)	--	(0/38)	2% (6/385)	--	13% (5/39)	1% (2/383)	--
Epirubicin	33% (2/6)	(0/62)	--	(0/4)	3% (2/62)	--	20% (1/5)	3% (2/58)	--
Idarubicin	--	(0/15)	(0/5)	--	13% (2/15)	20% (1/5)	--	(0/14)	(0/5)
Mitoxantrone	100% (1/1)	(0/12)	(0/3)	--	8% (1/12)	(0/3)	--	(0/12)	(0/3)

[a] Spontaneous fetal death at <22 weeks of gestation; denominator excludes termination of pregnancy (induced abortions) and maternal/fetal deaths
[b] Spontaneous fetal death at ≥22weeks of gestation; denominator excludes termination of pregnancy, spontaneous abortions, and maternal/fetal deaths
[c] Excludes any termination of pregnancy, spontaneous abortions and stillbirths without examination of the fetus
[d] Includes exposures in the 1st trimester only and exposure in the 1st trimester and subsequent trimesters

Agent	Timing of birth[f] (No. of affected/total liveborn infants)				Spontaneous preterm birth[g]	Body weight at birth[h] (No. of affected/total liveborn infants)			Adverse health effects at follow up[i]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/total liveborn infants)	SGA	Normal	Not specified	(No. of affected/total offspring)
Actinomycin D	44% (7/16)	19% (3/16)	25% (4/16)	13% (2/16)	19% (3/16)	6% (1/16)	81% (13/16)	13% (2/16)	(0/16)
Daunorubicin	32% (25/77)	22% (17/77)	27% (21/77)	18% (14/77)	16% (12/77)	10% (8/77)	61% (47/77)	29% (22/77)	4% (2/52)
Doxorubicin	8% (35/417)	15% (64/417)	17% (71/417)	59% (247/417)	8% (32/417)	6% (26/417)	66% (274/417)	28% (117/417)	2% (7/323)
Epirubicin	3% (2/62)	29% (18/62)	11% (7/62)	56% (35/62)	6% (4/62)	5% (3/62)	53% (33/62)	42% (26/62)	(0/48)
Idarubicin	41 % (7/17)	29% (5/17)	6% (1/17)	24% (4/17)	(0/17)	18% (3/17)	53% (9/17)	29% (5/17)	8% (1/12)
Mitoxantrone	36% (5/14)	43% (6/14)	(0/14)	21% (3/14)	(0/14)	29% (4/14)	50% (7/14)	21% (3/14)	8% (1/13)

[f] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[g] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation
[h] Small for gestational age newborns were determined by comparing the sex, gestational age at birth and birth weight to the 10th percentile body weight per sex (Olsen *et al.* 2010) or as reported by the authors when clearly defined
[i] Denominator includes only the gestationally-exposed offspring with follow up evaluations

Table 79: Summary table of pregnancy outcomes in humans following gestational exposure to microtubule function inhibitors

Agent	Spontaneous abortions[a] (No. of affected/total conceptuses)			Stillbirths[b] (No. of affected/total conceptuses)			Major malformations[c] (No. of affected/total conceptuses)		
	During 1st [d]	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified
Docetaxel	(0/2)	(0/19)	--	(0/2)	(0/19)	--	(0/2)	5% (1/19)	--
Paclitaxel	--	(0/38)	--	--	(0/38)	--	--	3% (1/38)	--
Vinblastine	6% (1/16)	(0/58)	(0/8)	(0/15)	2% (1/58)	(0/8)	31% (5/16)	2% (1/57)	(0/8)
Vincristine	19% (9/47)	(0/165)	(0/1)	(0/38)	4% (6/165)	(0/1)	10% (4/40)	(0/163)	(0/1)
Vinorelbine	(0/1)	(0/14)	--	(0/1)	(0/14)	--	(1/1)	(0/14)	--

[a] Spontaneous fetal death at <22 weeks of gestation; denominator excludes termination of pregnancy (induced abortions) and maternal/fetal deaths
[b] Spontaneous fetal death at ≥22 weeks of gestation; denominator excludes termination of pregnancy, spontaneous abortions and maternal/fetal deaths
[c] Excludes any termination of pregnancy, spontaneous abortions and stillbirths without examination of the fetus
[d] Includes exposures in the 1st trimester only and exposure in the 1st trimester and subsequent trimesters

Agent	Timing of birth[f] (No. of affected/total liveborn infants)				Spontaneous preterm birth[g]	Body weight at birth[h] (No. of affected/total liveborn infants)			Adverse health effects at follow up[i]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/total liveborn infants)	SGA	Normal	Not specified	(No. of affected/total offspring)
Docetaxel	19% (4/21)	33% (7/21)	19% (4/21)	29% (6/21)	10% (2/21)	19% (4/21)	67% (14/21)	14% (3/21)	(0/13)
Paclitaxel	13% (5/38)	34% (13/38)	16% (6/38)	37% (14/38)	(0/38)	13% (5/38)	74% (28/38)	13% (5/38)	(0/34)
Vinblastine	9% (7/80)	14% (11/80)	30% (24/80)	48% (38/80)	10% (8/80)	10% (8/80)	58% (46/80)	33% (26/80)	(0/59)
Vincristine	21% (42/199)	18% (36/199)	40% (79/199)	20% (39/199)	13% (25/199)	9% (18/199)	62% (123/199)	28% (55/199)	3% (5/143)
Vinorelbine	27% (4/15)	33% (5/15)	33% (5/15)	7% (1/15)	(0/15)	(0/15)	93% (14/15)	7% (1/15)	(0/12)

[f] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[g] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation
[h] Small for gestational age newborns were determined by comparing the sex, gestational age at birth and birth weight to the 10th percentile body weight per sex (Olsen *et al.* 2010) or as reported by the authors when clearly defined
[i] Denominator includes only the gestationally-exposed offspring with follow up evaluations

Table 80: Summary table of pregnancy outcomes in humans following gestational exposure to topoisomerase II inhibitors and oxygen radical generators

Agent	Spontaneous abortions[a] (No. of affected/total conceptuses)			Stillbirths[b] (No. of affected/total conceptuses)			Major malformations[c] (No. of affected/total conceptuses)		
	During 1st [d]	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified
Oxygen radical generator									
Bleomycin	(0/14)	(0/81)	--	(0/14)	1% (1/81)	--	7% (1/15)	1% (1/80)	--
Topoisomerase II inhibitor									
Etoposide	(0/4)	(0/40)	--	(0/4)	5% (2/40)	--	(0/4)	3% (1/39)	--

[a] Spontaneous fetal death at <22 weeks of gestation; denominator excludes termination of pregnancy (induced abortions)
[b] Spontaneous fetal death at ≥22weeks of gestation; denominator excludes termination of pregnancy and spontaneous abortions
[c] Excludes any termination of pregnancy, spontaneous abortions and stillbirths without examination of the fetus
[d] Includes exposures in the 1st trimester only and exposure in the 1st trimester and subsequent trimesters

Agent	Timing of birth[f] (No. of affected/total liveborn infants)				Spontaneous preterm birth[g]	Body weight at birth[h] (No. of affected/total liveborn infants)			Adverse health effects at follow up[i]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/total liveborn infants)	SGA	Normal	Not specified	(No. of affected/total offspring)
Oxygen radical generator									
Bleomycin	12% (11/94)	17% (16/94)	39% (37/94)	32% (30/94)	10% (9/94)	13% (12/94)	69% (5/94)	18% (17/94)	3% (2/76)
Topoisomerase II inhibitor									
Etoposide	17% (7/42)	29% (12/42)	38% (16/42)	17% (7/42)	10% (4/42)	24% (10/42)	57% (24/42)	19% (8/42)	14% (4/28)

[f] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[g] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation
[h] Small for gestational age newborns were determined by comparing the sex, gestational age at birth and birth weight to the 10th percentile body weight per sex (Olsen *et al.* 2010) or as reported by the authors when clearly defined
[i] Denominator includes only the gestationally-exposed offspring with follow up evaluations

Table 81: Summary table of pregnancy outcomes in humans following gestational exposure to targeted therapies

Agent	Spontaneous abortions[a] (No. of affected/total conceptuses)			Stillbirths[b] (No. of affected/total conceptuses)			Major malformations[c] (No. of affected/total conceptuses)		
	During 1st d	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified	During 1st	2nd and/or 3rd only	Not specified
ATRA	33% (1/3)	(0/24)	--	50% (1/2)	(0/24)	--	(0/2)	(0/24)	--
Imatinib	17% (19/115)	(0/6)	--	1% (1/96)	(0/6)	--	11% (11/100)	(0/6)	--
Interferon alpha	(0/20)	(0/21)	(0/2)	(0/20)	(0/21)	(0/2)	(0/20)	(0/21)	(0/2)
Rituximab	17% (1/6)	(0/20)	--	(0/5)	10% (2/20)	--	20% (1/5)	(0/18)	--
Tamoxifen	(0/12)	(0/3)	--	(0/12)	(0/3)	--	25% (3/12)	(0/3)	--
Trastuzumab	(0/12)	(0/6)	--	(0/12)	(0/6)	--	(0/12)	(0/6)	--

[a] Spontaneous fetal death at <22 weeks of gestation; denominator excludes termination of pregnancy (induced abortions) and maternal/fetal deaths
[b] Spontaneous fetal death at ≥22 weeks of gestation; denominator excludes termination of pregnancy, spontaneous abortions and maternal/fetal deaths
[c] Excludes any termination of pregnancy, spontaneous abortions and stillbirths without examination of the fetus

Agent	Timing of birth[f] (No. of affected/total liveborn infants)				Spontaneous preterm birth[g]	Body weight at birth[h] (No. of affected/total liveborn infants)			Adverse health effects at follow up[i]
	Early preterm	Late preterm	Term	Not specified	(No. of affected/total liveborn infants)	SGA	Normal	Not specified	(No. of affected/total offspring)
ATRA	58% (15/26)	31% (8/26)	12% (3/26)	--	27% (7/26)	(0/26)	88% (23/26)	12% (3/26)	5% (1/19)
Imatinib	3% (3/101)	6% (6/101)	25% (25/101)	66% (67/101)	4% (4/101)	2% (2/101)	23% (23/101)	75% (76/101)	(0/26)
Interferon alpha	7% (3/43)	18% (8/43)	70% (30/43)	5% (2/43)	5% (2/43)	9% (4/43)	51% (22/43)	40% (17/43)	(0/25)
Rituximab	22% (5/23)	22% (5/23)	30% (7/23)	17% (4/23)	13% (3/23)	5% (1/23)	30% (7/23)	8% (15/23)	(0/7)
Tamoxifen	47% (7/15)	13% (2/15)	20% (3/15)	20% (3/15)	13% (2/15)	(0/15)	93% (14/15)	7% (1/15)	(0/8)
Trastuzumab	47% (9/19)	11% (2/19)	42% (8/19)	--	(0/19)	5% (1/19)	84% (16/19)	11% (2/19)	(0/11)

[f] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[g] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation
[h] Small for gestational age newborns were determined by comparing the sex, gestational age at birth and birth weight to the 10th percentile body weight per sex (Olsen *et al.* 2010) or as reported by the authors when clearly defined
[i] Denominator includes only the gestationally-exposed offspring with follow up evaluations

6.0 DISCUSSION

Incidence of major congenital malformations

Chemotherapy for treatment of cancer in the first trimester represents a higher apparent risk of major malformation than treatment only in the second or third trimesters. Among the reports reviewed in the NTP monograph, the apparent rate of major malformations was 14% (41/303 conceptuses) following exposure to any cancer chemotherapy during the first trimester compared to the apparent rate of 3% (21/826 conceptuses) of major malformations following exposure during the second and/or third trimester only; timing of exposure was not specified for 28 conceptuses and none of them were malformed. These data are consistent with the current medical practice 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.* 2010a). Exposure during the second and/or third trimester poses less risk of major malformations at birth, but may result in more functional deficits (Moore and Persaud 2003). The overall apparent rate of major malformations associated with treatment with chemotherapy for cancer at any time during pregnancy was 5% (62/1157 conceptuses based on 1119 liveborn infants and examination of 38 fetuses of induced abortions, spontaneous fetal deaths and maternal/fetal deaths). 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). Two larger case series reviewed in the NTP monograph reported a similar percentage of major malformations among live infants exposed gestationally to cancer chemotherapy: 3% (2/66 liveborn infants) reported in a survey retrospective (Van Calsteren *et al.* 2010a) and 3.8% (6/157 liveborn infants) in a registry survey (Cardonick *et al.* 2010).

Some of the major congenital malformations included in this review of the literature were not likely to be associated with cancer chemotherapy use during pregnancy. For example, cancer chemotherapy exposures could not be associated with malformations diagnosed prior to chemotherapy treatment (Sham 1996, Rouzi *et al.* 2009) or inherited conditions, e.g., familial polydactyly (Volkenandt *et al.* 1987)). In addition, the following major malformations were not likely caused by exposure to cancer chemotherapy in the second and/or third trimester only because they occur in structures or organs that are formed during the first trimester of pregnancy: agenesis (absence) of the right kidney and ureter, Down syndrome, gastroschisis, hypospadias, meningocele, neurofibromatosis (spontaneous mutation), pulmonary artery fistula, rectal atresia, syndactyly of fingers or toes, and ventricular septal defect (Moore and Persaud 2003). In another singleton pregnancy, major malformations were clearly attributed to co-exposure to warfarin based on the constellation of malformations observed in the liveborn infant (Pye *et al.* 2008); thus, the cancer chemotherapy was not associated with major malformations in this infant. All subsequent calculations of the apparent rate of major malformations based on timing of exposure are adjusted to remove the malformations not likely caused by cancer chemotherapy during gestation. 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 or heritable malformations, malformations due to non-cancer chemotherapy co-treatments (e.g., Warfarin embryopathy), or malformations not likely caused by exposure in the second and/or third trimester only did not appreciably change the rate of malformations in the first trimester and it decreased the rate of malformations in the second and/or third trimester.

When reviewing the data by individual chemotherapeutic agent, the apparent rates of major malformations attributed to some agents were higher than others in the first trimester (**Figure 1**). As mentioned above, the apparent rates for the individual agents were adjusted for malformations not likely caused the agent. For example, the apparent rate of major malformations were higher following exposure to cyclophosphamide (18%; 7/39 conceptuses) and 5-fluorouracil (31%; 4/13 conceptuses) compared to interferon alpha (0/20 conceptuses). However, these data are challenging to interpret due to differences in the timing of exposure relate to the period of organogenesis, the small sample size, and the fact that combination therapies employ agent of various mechanisms of action. Generally, there were no increased rates of major malformations when comparing the data by classes of agents working via similar mechanisms of action (see **Table 76** to **Table 81**). Specific combinations of major malformations may be related to exposure to certain agents (e.g., imatinib (Pye *et al.* 2008, Vandyke *et al.* 2010)). For example, a pattern of craniofacial and skeletal malformations has been observed in a small number of infants following exposure to cyclophosphamide, methotrexate or cytarabine during the period of organogenesis (Vaux *et al.* 2003) and are similar to the type of malformations observed in animal studies (Hyoun *et al.* 2012). Similarly, a combination of exomphalos (umbilical hernia), skeletal malformations and/or urogenital malformations (i.e., kidney agenesis) have been observed in a few infants gestationally exposed to imatinib (Pye *et al.* 2008, Vandyke *et al.* 2010).

Of interest, a lack of teratogenic effects was observed in animal developmental toxicity studies for trastuzumab and rituximab. Trastuzumab and rituximab are targeted therapies that target specific proteins in an effort to increase efficacy and reducing side effects in cancer patients. Similar to the animal data, there no major malformations observed in liveborn infants gestationally exposed to trastuzumab reviewed in the NTP monograph. For rituximab, one major malformation was reported among 4 infants gestationally exposed; however, a retrospective survey of 90 patients reported the major malformation rate (2%; 2/90) (Chakravarty *et al.* 2011) was similar to the prevalence of major malformations in the general population (Correa *et al.* 2007). While these two agents do not appear to increase the rate of major malformations following gestational exposure, they lead to Pregnancy Complications and Newborn Health issues (e.g., trastuzumab induced reductions in amniotic fluid and rituximab caused decreases in B-cell populations in newborns).

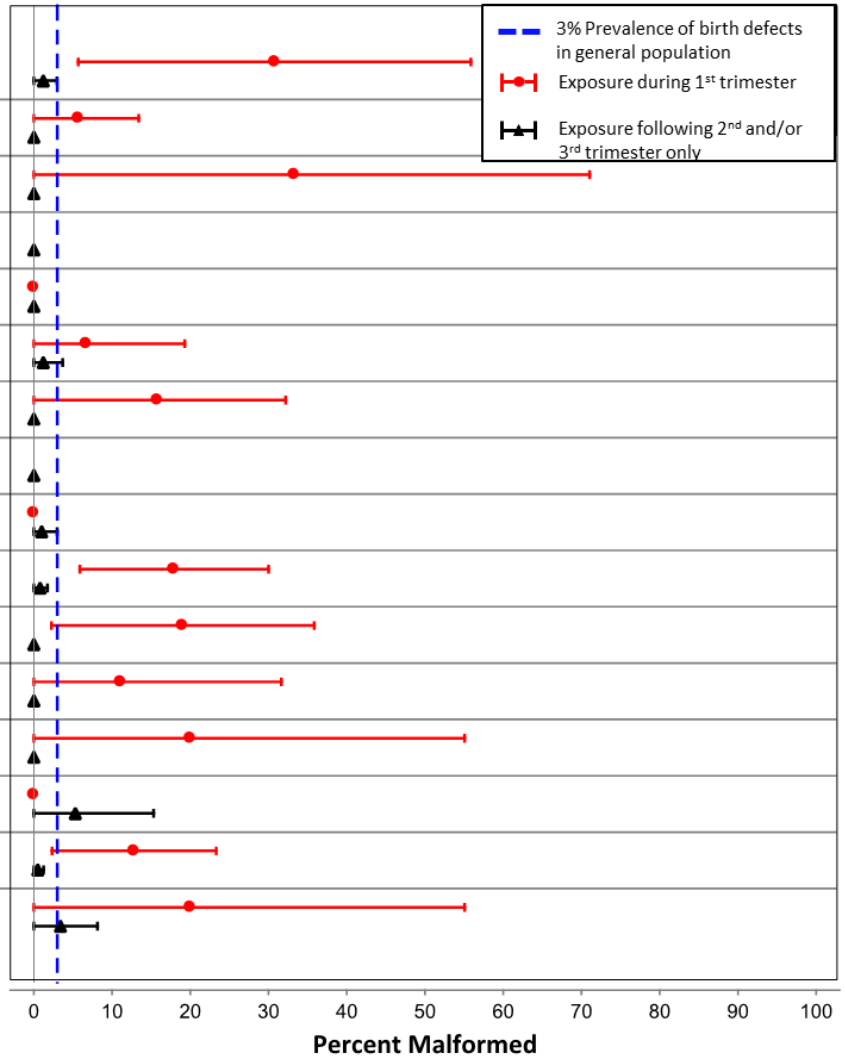
Spontaneous fetal death

The apparent rate of spontaneous abortion (spontaneous fetal loss at <22 weeks of gestation) was 13% (42/327 conceptuses, not including induced abortions) following exposure to any cancer chemotherapy in the first trimester. This apparent rate was similar to a pooled estimate of spontaneous abortion in healthy women of 13% (95% CI = 10% to 16%) (Wilcox 2010). However, the reported information in human studies is insufficient to determine whether chemotherapy for treatment of cancer in the first trimester affects early spontaneous fetal loss (also called spontaneous abortion, <22 weeks of gestation).

In contrast, the apparent rate of stillbirths (late spontaneous fetal death, ≥22 weeks of gestation) following exposure to any cancer chemotherapy during the second and/or third trimester only (2%; 20/836 conceptuses, not including induced abortions or spontaneous abortions) 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 chemotherapeutic agent (administered either singly or in combination therapy), the apparent rates of stillbirth were highest with gestational exposure to chemotherapeutic agents used primarily to treat hematological cancers. For example, the apparent rate of stillbirth following second and/or third trimester only

Figure 1: Apparent rates of occurrence of major malformations (±95% confidence interval) reported following cancer chemotherapy use during pregnancy. Data are presented by individual agent, combining mono- and polytherapy exposure.

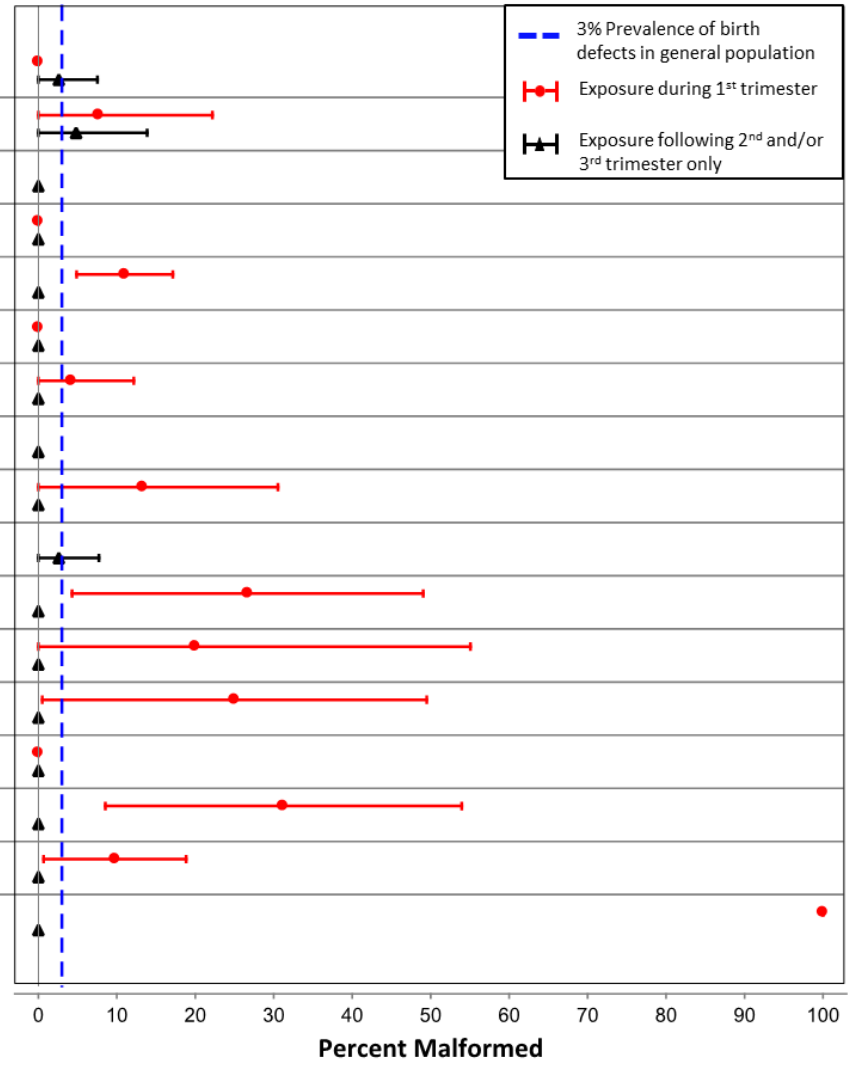
Agent	Trimester Exposed	% Malformed ±CI[b]
5-Fluorouracil	During 1st [a]	30.8 ± 25.1 (4/13)
	2nd and/or 3rd Only [c]	1.2 ± 1.7 (2/161)
6-Mercaptopurine	During 1st	5.7 ± 7.7 (2/35)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/41)
6-Thioguanine	During 1st	33.3 ± 37.7 (2/6)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/44)
Actinomycin D	During 1st	No Data
	2nd and/or 3rd Only	0.0 ± 0.0 (0/16)
All-trans retinoic acid	During 1st	0.0 ± 0.0 (0/2)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/24)
Bleomycin	During 1st	6.7 ± 12.6 (1/15)
	2nd and/or 3rd Only	1.3 ± 2.4 (1/80)
Busulfan	During 1st	15.8 ± 16.4 (3/19)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/6)
Carboplatin	During 1st	No Data
	2nd and/or 3rd Only	0.0 ± 0.0 (0/17)
Cisplatin	During 1st	0.0 ± 0.0 (0/5)
	2nd and/or 3rd Only	1.0 ± 2.0 (1/99)
Cyclophosphamide	During 1st	17.9 ± 12.0 (7/39)
	2nd and/or 3rd Only	0.8 ± 0.9 (3/367)
Cytarabine	During 1st	19.0 ± 16.8 (4/21)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/109)
Dacarbazine	During 1st	11.1 ± 20.5 (1/9)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/45)
Daunorubicin	During 1st	20.0 ± 35.1 (1/5)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/75)
Docetaxel	During 1st	0.0 ± 0.0 (0/2)
	2nd and/or 3rd Only	5.3 ± 10.0 (1/19)
Doxorubicin	During 1st	12.8 ± 10.5 (5/39)
	2nd and/or 3rd Only	0.5 ± 0.7 (2/383)
Epirubicin	During 1st	20.0 ± 35.1 (1/5)
	2nd and/or 3rd Only	3.4 ± 4.7 (2/58)



Includes conceptuses exposed during the first trimester only, and first trimester and subsequent trimesters. [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 Sections 5.2.4 to 5.34.4).

Figure 1: Continued

Agent	Trimester Exposed	% Malformed ±CI[b]
Etoposide	During 1st [a] 2nd and/or 3rd Only [c]	0.0 ± 0.0 (0/4) 2.6 ± 5.0 (1/39)
Hydroxyurea	During 1st 2nd and/or 3rd Only	7.7 ± 14.5 (1/13) 4.8 ± 9.1 (1/21)
Idarubicin	During 1st 2nd and/or 3rd Only	No Data 0.0 ± 0.0 (0/14)
Ifosfamide	During 1st 2nd and/or 3rd Only	0.0 ± 0.0 (0/1) 0.0 ± 0.0 (0/9)
Imatinib	During 1st 2nd and/or 3rd Only	11.0 ± 6.1 (11/100) 0.0 ± 0.0 (0/6)
Interferon alpha	During 1st 2nd and/or 3rd Only	0.0 ± 0.0 (0/20) 0.0 ± 0.0 (0/21)
Methotrexate	During 1st 2nd and/or 3rd Only	4.2 ± 8.0 (1/24) 0.0 ± 0.0 (0/58)
Mitoxantrone	During 1st 2nd and/or 3rd Only	No Data 0.0 ± 0.0 (0/12)
Nitrogen mustard	During 1st 2nd and/or 3rd Only	13.3 ± 17.2 (2/15) 0.0 ± 0.0 (0/13)
Paclitaxel	During 1st 2nd and/or 3rd Only	No Data 2.6 ± 5.1 (1/38)
Procarbazine	During 1st 2nd and/or 3rd Only	26.7 ± 22.4 (4/15) 0.0 ± 0.0 (0/12)
Rituximab	During 1st 2nd and/or 3rd Only	20.0 ± 35.1 (1/5) 0.0 ± 0.0 (0/18)
Tamoxifen	During 1st 2nd and/or 3rd Only	25.0 ± 24.5 (3/12) 0.0 ± 0.0 (0/3)
Trastuzumab	During 1st 2nd and/or 3rd Only	0.0 ± 0.0 (0/12) 0.0 ± 0.0 (0/6)
Vinblastine	During 1st 2nd and/or 3rd Only	31.3 ± 22.7 (5/16) 0.0 ± 0.0 (0/57)
Vincristine	During 1st 2nd and/or 3rd Only	9.8 ± 9.1 (4/41) 0.0 ± 0.0 (0/163)
Vinorelbine	During 1st 2nd and/or 3rd Only	100.0 ± 0.0 (1/1) 0.0 ± 0.0 (0/14)



Includes conceptuses exposed during the first trimester only, and first trimester and subsequent trimesters. [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 Sections 5.2.4 to 5.34.4).

exposure to cytarabine, an agent used primarily to treat acute leukemia, was 8% (9/110 conceptuses) compared to an apparent rate of 1% (3/368 conceptuses) for cyclophosphamide, an agent used primarily to treat solid cancers. It is possible that the mother's disease may influence the rate of spontaneous abortion or stillbirth. For example, leukemia and other myeloproliferative neoplasias pose an increased risk of thrombosis, which can lead to spontaneous fetal death or intrauterine growth restriction (Brenner *et al.* 2012).

Abnormally low levels of amniotic fluid

Abnormally low levels of amniotic fluid (i.e., oligohydramnios and anhydramnios) during development can lead to several adverse effects on the fetus, including pulmonary hypoplasia (Nakamura *et al.* 1992) and limb anomalies (Christianson *et al.* 1999). The apparent rate of abnormally low levels of amniotic fluid during pregnancy was 2.9% (33/1118 conceptuses based on liveborn infants) following gestational exposure to any cancer chemotherapy; this calculation included all cases reporting oligohydramnios, anhydramnios and any progressive reduction in amniotic fluid. This apparent rate of abnormally low 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 note, the majority of cases reporting abnormally low levels of amniotic fluid were exposed to trastuzumab (42%; 14/33 liveborn infants). Among the liveborn infants gestationally exposed to trastuzumab, the apparent rate of abnormally low levels of amniotic fluid was 74% (14/19 liveborn infants). 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.* 2009a). Abnormally low levels of amniotic fluid were not reported in pregnancies exposed to trastuzumab in the first trimester only or in pregnancies that occurred with 3 months of completing treatment with the drug (Azim *et al.* 2012). Thus, based on the available data, treatment with chemotherapy for cancer can result in abnormally low amniotic fluid levels that are primarily attributable to trastuzumab. There are potential mechanisms by which trastuzumab may be decreasing amniotic fluid levels. While trastuzumab is engineered to block the human epidermal growth factor receptor 2 (HER2) in cancer cell, HER2 is also expressed in the fetal kidney tissues of humans (Press *et al.* 1990, Goodyer *et al.* 1993). Trastuzumab is also reported to inhibit vascular epidermal growth factor (VEGF) in tumor cells (Petit *et al.* 1997), and it is hypothesized that trastuzumab may inhibit the normal action of VEGF in regulating fluid balance across the fetal membranes (Pant *et al.* 2008).

Spontaneous preterm birth

Chemotherapy for the treatment of cancer does not appear to be associated with spontaneous preterm birth. Preterm birth is defined as <37 weeks of gestation and is associated with number of medical issues in the newborn and later in life ((Institute of Medicine 2007) (described the paragraph below). The apparent rate of spontaneous preterm birth following gestational exposure to chemotherapy for the treatment of cancer was 9% (97/1118 liveborn infants). When reviewing the individual agent exposure, higher apparent rates of spontaneous preterm birth were observed following exposure to 6-mercaptopurine (23%, 17/74 infants) and 6-thioguanine (22%; 9/41 infants). A similar rate of spontaneous preterm delivery (26% of 19 cases) was reported following gestational exposure to 6-mercaptopurine in a retrospective survey of pregnancy outcomes of patients with inflammatory bowel disease (IBD; a non-cancerous disease) compared to 13.5% in IBD patients not administered the drug (n=74 cases included) (Shim *et al.* 2011); however, these results were not statistically significant. Thus, the reason for the higher rates of spontaneous preterm labor with 6-mercaptopurine and 6-thioguanine

is not known. In many cases, infants exposed in utero to cancer chemotherapy were delivered preterm via induced delivery (i.e., induced vaginal delivery or C-section). It is also possible that the high rate of induced preterm birth may mask any possible effect of chemotherapy on initiating spontaneous preterm birth.

Many of the other health effects that 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 C-section) 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 monograph. Thus, in many cases, the complications may have been due to prematurity rather than to gestational exposure to cancer chemotherapeutic agents.

Newborn health issues

Small for gestational age infants

Body weight at birth (corrected for age and gestational age) was used to assess effects of cancer chemotherapy during pregnancy on fetal growth. Data were compared to a standardized intrauterine growth curve (Olsen *et al.* 2010), which provided a common basis for determining small for gestational age infants (<10^{th} percentile body weight for gestational age). The data were insufficient, but suggestive, of effects of chemotherapy for the treatment of cancer during pregnancy to impair fetal growth. The apparent rate of small for gestational age newborns following gestational exposure to chemotherapy was 8% (90/1118 liveborn infants); small for gestational age was identified as body weights that were <10^{th} percentile of the normal population based on sex and gestational age at birth (Olsen *et al.* 2010). However, the apparent rate data on small for gestational age are challenging to compare to a common intrauterine growth curve because the data include variations in fetal growth rates due to the international nature of the literature (e.g., differences in geographical location and ethnicity) as well as temporal differences (e.g., the data were collected from reports published from 1950 to 2012) as well as for the lack of information on body weight provided by many studies (e.g., no body weight data or body weight and gestational age data were provided for 395 of 1118 conceptuses in the NTP monograph). Small for gestational infants was reported at rates comparable to control population in several large case series of breast cancer patients treated with chemotherapy during pregnancy: 8% (Cardonick *et al.* 2010), 9% (Loibl *et al.* 2012), 4% (1/24 infants) (Berry *et al.* 1999) and 0 of 17 infants (Ring *et al.* 2005b). However, in one large prospective series, small for gestational age were reported more frequently in specific subgroups of patients treated with chemotherapy during pregnancy; specifically, of the 14 of 70 infants that were small for gestational age, 8 infants were born to mothers treated for hematological cancer (4 acute leukemia, 4 lymphoma) (Van Calsteren *et al.* 2010a). In contrast, another large case series without individual data reported no significant differences in body weight at birth between chemotherapy-exposed and control children (born to healthy mothers)

matched for gestational age (Abdel-Hady el *et al.* 2012); the patients were treated for breast cancer (32%), lymphoma (16%) or leukemia (13%).

When observing individual agent data, several agents had high apparent rates of small for gestational age when compared to the 10th percentile for body weight by sex and gestational age. For example, the apparent rates for small for gestational age were higher for busulfan (28%; 8/29 liveborn infants) and docetaxel (19%, 4/21 liveborn infants). While these apparent rates are based on small sample sizes, reduced fetal growth was observed in developmental toxicity studies in animal administered these agents (see Sections 5.8 Busulfan and 5.15 Docetaxel). While it is possible that cancer chemotherapy during pregnancy may negatively affect fetal growth, more research on cancer subtypes and treatment regimens are needed to clarify this issue. As mentioned before, the increased risk of thrombosis observed with myeloproliferative neoplasias, including hematological cancers, has been reported to be associated with intrauterine growth restriction (Brenner *et al.* 2012).

Transient myelosuppression

Many antineoplastic chemotherapy drugs induce myelosuppression in patients directly administered these drugs (Perry and Mckinney 2008). The data are suggestive, but insufficient, that chemotherapy for the treatment of cancer may lead to transient myelosuppression in the newborn. Transient myelosuppression was reported in 46 of 1118 liveborn infants gestationally exposed to cancer chemotherapy evaluated in this monograph; however, an apparent rate of transient myelosuppression was not calculated because it was not always clear whether a newborn's blood count had been evaluated. 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). However, the data that were provided in the published reports were often insufficient to determine if complete blood counts of the newborn were conducted. The duration of time between cessation of treatment and birth was frequently not reported for the infants with transient myelosuppression. Furthermore, it is difficult to provide a point of reference to provide context for the transient myelosuppression findings because 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).

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)). All-*trans* retinoic acid chemotherapy has also been reported to cause cardiotoxicity in cancer patient directly administered the drug (Roche 2008). Of a total of 1118 liveborn infants reviewed in the NTP monograph, only 10 infants were reported to have any symptoms of fetal or neonatal cardiotoxicity (e.g., arrhythmia, cardiomyopathy, tachycardia and heart failure) following gestational exposure to any cancer chemotherapy. These cases of cardiotoxicity did not appear to limited to one class of chemotherapeutic agents: 6 singleton pregnancies were exposed to anthracyclines in polytherapy including: idarubicin (3 cases) (Achtari and Hohlfeld 2000, Siu *et al.* 2002, Niedermeier *et al.* 2005), idarubicin and mitoxtantrone (1 case) (Baumgartner *et al.* 2009), daunorubicin polytherapy (1 case) (Okun *et al.* 1979), and daunorubicin and mitoxantrone (1 case) (Garcia *et al.* 1999). Three singleton pregnancies were exposed to all-*trans* retinoic acid (Harrison *et al.* 1994, Leong *et al.* 2000, Takitani *et al.* 2005), including one singleton pregnancy exposed to idarubicin and all-trans retinoic acid (Siu *et al.* 2002). The remaining pregnancy was exposed to cyclophosphamide

and cisplatin (King *et al.* 1991). 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 10 infants. For 3 of these infants (Okun *et al.* 1979, Garcia *et al.* 1999, Baumgartner *et al.* 2009), anemia was reported and it may have been the cause of the cardiotoxicity (Strauss 1986). Anemia may have contributed to fetal and neonatal cardiac malfunction in one liveborn infant gestationally exposed to cyclophosphamide and docetaxel in the first and second trimester (Massey Skatulla *et al.* 2012); other pregnancy complications included preeclampsia and the HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count).

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.

Of the studies reviewed in the NTP monograph, follow up data were available for 60% of the infants (670/1118 liveborn children) gestationally exposed to cancer chemotherapy. Normal growth and development were reported for a majority of the children with follow up examinations. For example, 97% 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=276 of 282 children) (Section **5.11**, Appendix C Table 10). Some of the commonly observed adverse effects observed in children gestationally exposed to cancer chemotherapy were growth, speech and developmental delays. There was only one report of a child developing cancer following gestational exposure to cancer chemotherapy (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). His mother was administered cyclophosphamide monotherapy during the entire pregnancy, and his female twin had normal growth and development (Zemlickis *et al.* 1993).

The total number of children with follow up evaluation following gestational exposure to chemotherapy did not include the 25 infants who died. Of the infants who died, 15 infants were born preterm, 2 infants were born at term; data were insufficient to determine the gestational age at delivery for 4 infants. Four infants died of complications related to their malformations (Zemlickis *et al.* 1992b, Pye *et al.* 2008), including 2 infants with malformations observed prior to chemotherapy (Sham 1996, Rouzi *et al.* 2009). Other deaths were caused by prematurity-related health effects such as intercranial hemorrhaging (1 infant) (Dilek *et al.* 2006), and respiratory distress (5 infants) (Merskey and Rigal 1956, Rothberg *et al.* 1959, Thomas and Peckham 1976, Dilek *et al.* 2006). Infections were the cause of death for four infants (Ruiz Reyes and Tamayo Perez 1961, Aviles *et al.* 1991, Dilek *et al.* 2006); the cause of death of 4 early preterm infants was not identified (Boland 1951, O'Leary and Bepko 1963, Giacalone *et al.* 1999, Meera *et al.* 2008). Four infants died following decreasing kidney function and pulmonary issues, likely associated with experiencing oligo- or anhydramnios following gestational exposure to chemotherapy (Fernandez *et al.* 1989, Weber-Schoendorfer and Schaefer 2008, Witzel *et al.* 2008, Beale *et al.* 2009, Warraich and Smith 2009). The remaining malformed infant died at 10 weeks following a respiratory infection, and autopsy revealed multiple internal malformations (Diamond *et al.* 1960). One infant died at 13 weeks due to a severe autoimmune disease (Cardonick *et al.* 2010).

The age at follow up examination for most of these children with gestational exposure to chemotherapy was limited to the first few months or years of life. Based on the 438 offspring with individual data at follow up examination, the percentage of children with follow up examinations at ages ranging from birth to 2 years was 56% (246/438 children based on published reports with individual biometric data). Fewer of the children gestationally exposed to cancer chemotherapy had follow up examinations at later than 2 years of age (based on published reports with individual biometric data): 114 children (26%) at >2- 5 years of age, 59 children (13%) at >5-12 years of age, 16 children (4%) at >12-17 years of age, and 3 children (1%) at >17-22 years of age. 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 or growth and development, and no increase in auditory, neurological or cardiac morbidity (Amant *et al.* 2012, Aviles *et al.* 2012). However, the authors of one study reported subtle changes in cardiac function and neurological outcome, which merit further follow-up evaluation (Amant *et al.* 2012). Thus, it is important to recognize that the data are limited and adverse effects may not be apparent until later in life (e.g., effects on reproduction and other reproductive function).

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 (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 and colleagues reported follow up information on 6 children born to mothers who were treated with chemotherapy for acute leukemia while pregnant (Reynoso *et al.* 1987). 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).
- 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.
- 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 and Niz 1988, Aviles *et al.* 1991, Aviles and Neri 2001, Aviles *et al.* 2006, 2012). In their 2001 paper, the authors reported on 84 offspring that ranged in age from 6 to 29 years at the time of follow up examination (Aviles and Neri 2001). 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. In their 2012 report, Avilés et al. (2012) provided continued long term examination of 143 offspring gestationally exposed to cancer chemotherapy of patients treated for hematological cancers at their institution. They report similar observations of normal growth and development, and normal results of functional testing of the offspring at ages ranging from birth to 32 years. In addition, no malformations have been observed in the 12 infants born to the offspring who were gestationally exposed.

- Avilés et al. (2006) also conducted cardiologic assessments in 81 children of women who received cancer chemotherapy with anthracyclines (doxorubicin, daunorubicin, mitoxantrone, or idarubicin) while pregnant. Baseline echocardiogram data were collected when the children were 5 years old and were repeated at 5-year intervals until age 20 years or until the last follow up. They evaluated left ventricular internal dimensions, septal wall thickness, and posterior wall thickness, and fractional shortening (FS) of the left ventricle, and selected an FS value of <28% to define the presence of cardiac toxicity. The authors report that echocardiograms provided no evidence of cardiac disease and that FS values were normal in the baseline study and all subsequent determinations. These results appear to be consistent with the findings reported by Van Calsteren et al. (2006).
- 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.
- 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 (often less than 2 years of age), and involving a limited number of health endpoints in each individual. In addition, the quality and comprehensiveness of follow up examinations vary greatly among reports. Current data available on growth and development of offspring gestationally exposed to cancer chemotherapy is often based on a phone call or a questionnaire completed by the child's parents or teachers, or a general physical examination. Another challenge to interpreting the data on growth and development of children gestationally exposed to cancer chemotherapy are the lack of international standardized long-term follow up testing guidelines, which would facilitate the accurate comparison of observations made by researchers around the world. Furthermore, the high rate of preterm infants with gestational exposure to cancer chemotherapy complicates the assessment of whether observed adverse effects are due to the cancer chemotherapy or the preterm birth. Therefore, 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 (1989) and Partridge (2000).

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 reported for most chemotherapeutic regimens.** In most instances, the number of cases treated with an individual agent as monotherapy or in specific combination therapies (polytherapy) was small. Furthermore, differences in maternal disease, treatment regimen, doses, and timing of exposure complicate the interpretation of the pooled analysis of the NTP monograph. In addition, over 110 cancer chemotherapeutic agents are currently in use (Perry and Mckinney 2008); however, published data on use during pregnancy were only identified for 56 agents.
- **Small numbers conceptuses reported with specific types of major malformations.** The prevalence of the individual types of major malformations in the general population is infrequent (Correa *et al.* 2007). Given the limited number of conceptuses reported to be exposed to cancer chemotherapy, it is difficult to conduct a robust analysis for the effects of individual cancer chemotherapy exposure on the rate of occurrence of any specific malformation.
- **Reports with no information on the condition of the abortus or fetus.** Numerous reports of pregnancy outcomes involving induced abortions, spontaneous fetal deaths or stillbirths provide no information on the presence or absence of malformations in the conceptus. If the conceptus was carefully examined and its condition reported, it would provide additional information of value to analyses such are the present one.

- **Reports lacking information on individual cases.** Some larger case series reported data for the group as opposed to the individual case. Data for individual cases were often not reported for normal pregnancy outcomes (Mulvihill *et al.* 1987, Van Calsteren *et al.* 2010a). In contrast, individual data on timing of exposure and agents administered were provided for cases with malformed infants from these studies.
- **Lack of follow up examination and variable quality of the assessments**. The period of follow up examinations of offspring exposed in utero to cancer chemotherapy is very short in most cases (<2 years). In addition, the quality and comprehensiveness of follow up examinations vary greatly among reports, and there is a lack of international standardized follow up assessments making it difficult to accurately compare data from different research groups around the world.
- **High rate of premature birth.** The high rate of preterm birth in infants with gestational exposure to cancer chemotherapy complicates the assessment of whether adverse effects observed at birth or in follow up examinations are due to the cancer chemotherapy or the preterm birth.
- **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 *et al.* 2010b, Azim *et al.* 2010c). 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 in Appendix C Table 1, there were 109 pregnant patients treated for breast cancer with 5-fluorouracil, doxorubicin, and cyclophosphamide, and there were 20 pregnant patient treated for breast cancer with 5-fluorouracil, epirubucin, and cyclophosphamide.

Broader participation in registries of cancer during pregnancy, prospective studies of the pregnancy outcomes of women receiving chemotherapy for cancer treatment, and studies evaluating the likelihood of late onset adverse health outcomes of the children exposed in utero to cancer chemotherapy are needed to more thoroughly assess the risks of gestational exposure to cancer chemotherapy. There are at least two registries of patients with cancer during pregnancy in the United States: Cooper University Hospital in Camden, New Jersey coordinated by Dr. Elyce Cardonick (www.cancerandpregnancy.com) and University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma coordinated by Dr. John Mulvihill. In addition, there are at least two registries for such patients outside of the United States: the Toronto Hospital of Sick Children in Ontario, Canada (www.MotherRisk.com) and the University of Frankfurt and German Breast Group (http://www.germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft/english-summary-.html). There are also several ongoing clinical trials including prospective studies of pregnancy outcomes at institutions in the United States and internationally; some of the clinical trials are listed in Appendix E.

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. Exposure to cancer chemotherapy agents may occur in an important group of people who do not have cancer (i.e., 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, cleaning personnel, and other hospital and clinic staff. 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 non-pregnant women of reproductive age and pregnant women. Although the levels of such exposures are likely 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 (2006). In addition, information regarding pregnancy outcomes and long-term health effects of cancer chemotherapeutic agents may be gained by evaluating the pregnancy outcomes of pregnant patients treated with these drugs for other non-cancer medical conditions. Examples of non-cancerous medical conditions frequently treated with cancer chemotherapeutics include blood diseases, e.g., sickle cell anemia, essential thrombocythemia (Thauvin-Robinet *et al.* 2001) and autoimmune disorders, e.g., rheumatoid arthritis and systemic lupus erythematosus (Ebert *et al.* 1997, Lloyd *et al.* 1999). For concerns regarding possible adverse developmental effects of drugs or environmental chemical exposures during pregnancy, the Organization of Teratogen Information Specialists (OTIS; www.mothertobaby.org) is a free and confidential counseling service that is available to the public.

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), 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.

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