NTP Monograph

**Developmental Effects
and Pregnancy Outcomes
Associated With Cancer
Chemotherapy Use
During Pregnancy**

May 2013

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

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Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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NTP Monograph on Cancer Chemotherapy during Pregnancy

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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PEER REVIEW OF THE DRAFT NTP MONOGRAPH

Peer review of the Draft NTP Monograph was conducted by a 9-member ad hoc expert panel at a public meeting held October 1-2, 2012, at the National Institute of Environmental Health Sciences, Research Triangle Park, NC (see *http://ntp.niehs.nih.gov/go/37090* for materials, public comments, minutes, and panel recommendations from the peer review meeting). The selection of panel members and conduct of the peer review were in accordance with NTP practice, the Federal Advisory Committee Act, and Federal policies and regulations. The panel members served as independent scientists, not as represetatives of any institution, company, or government agency. In this capacity, panel members had 2 major responsibilities in peer-reviewing the draft NTP Monograph: (1) to determine whether the scientific information cited in the draft monograph was technically correct, clearly stated, and objectively presented and (2) to determine whether the scientific evidence presented in the draft monograph supported the NTP's interpretation of the developmental effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy.

The panel agreed with the draft NTP overall interpretations except for 3 instances:

- The panel stated that human studies data were insufficient to conclude that chemotherapy for treatment of cancer in the first trimester affects spontaneous abortion; whereas, the original draft NTP interpretation was that chemotherapy use in the first trimester does not appear to increase the apparent risk of early spontenous fetal loss.
- The panel stated that the data are insufficient, but suggestive, of effects of impaired fetal growth and myelosuppression; whereas, the original draft NTP interpretation states that it is not possible to evaluate apparent risk of small for gestational age based on current reports.
- (3) The panel stated that chemotherapy for treatment of cancer during pregnancy does not appear to be associated with spontaneous preterm birth; the original draft NTP interpretation was focused on spontaneous preterm labor.

Comments from the peer reviewers and written public comments received on the draft monograph were considered during finalization of the monograph. The NTP concurred with the peer review panel on all of its recommendations on the conclusions regarding developmental effects and pregnancy outcomes associated with treatment with chemotherapy for cancer during pregnancy in this final document.

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ABBREVIATIONS

6-MMP	6-methylmercaptopurine
AGL	acute granulocytic leukemia
ALL	acute lymphocytic leukemia
AML	acute myelogenous leukemia (also called acute myeloid leukemia)
AMML	acute myelomonocytic leukemia
AMSA	amsacrine
APL	acute promyelocytic leukemia
ara-CTP	cytarabine-5'-triphosphate
ara-U	uracil arabinoside
Arg	abl-related gene
ATP	adenosine triphosphate
ATRA	all-*trans* retinoic acid
AUC	area under the curve
Behenoyl-araC	behenoyl cytosine arabinoside
bFGF	basic fibroblast growth factor
bw	body weight
CanQues	Cancer Query Systems
CDC	Center for Disease Control and Prevention
CGL	chronic granulocytic leukemia
Clcr	creatinine clearance
CLL	chronic lymphocytic leukemia
cm	centimeter
Cmax	time to reach maximal concentration in serum
CML	chronic myelogenous leukemia (also called chronic myeloid leukemia)
CNS	central nervous system
C-section	Cesarean-section
CSF	cerebral spinal fluid
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration (United States)
HELLP syndrome	hemolysis, elevated liver enzymes, and low platelet count
HER2	human epidermal growth factor receptor 2
HPV	human papilloma virus
HR	hazard ratio
IARC	International Agency for Research on Cancer
IBD	inflammatory bowel disease
IgA	immunoglobulin A
IgG	immunoglobulin G
IQ	intelligence quotient
IM	intramuscular
IT	intrathecal
IU	international units
IUGR	intrauterine growth retardation
IV	intravenous
kg	kilogram
L	liter
MeSH	medical subject headings
µg	microgram

mg	milligram
m^2	meter squared
mL	milliliter
M	mole
µM	micromole
mm^3	millimeter cubed
MPA	microscopic polyangiitis
NCCN	National Comprehensive Cancer Network
NIEHS	National Institute of Environmental Health Sciences
ng	nanogram
NHL	non-Hodgkin lymphoma
NS	not specified
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
OTIS	Organization of Teratogen Information Specialists
PDGFR	platelet-derived growth factor receptor
pg	picogram
pt	patient
RA	rheumatoid arthritis
RNA	ribonucleic acid
RoC	Report on Carcinogens
SC	subcutaneous
SEER	Surveillance, Epidemiology, and End Results Program, National Cancer Institute
SERM	selective estrogen receptor modulator
SLL	small lymphocytic lymphoma
ULN	upper limit of normal
US	United States of America
VATER	vertebral defects, anal atresia, trachea-esophageal fistula with esophageal atresia, renal defects and/or radial limb dysplasia
Vd	volume of distribution
Vdss	volume of distribution at steady state
VEGF	vascular endothelial growth factor
WG	Wegener granulomatosis

PREFACE

The National Toxicology Program (NTP) established the Office of Health Assessment and Translation (OHAT) in 2011 to serve as an environmental health resource to the public and to regulatory and health agencies. The purpose of OHAT is to conduct technical assessments focused on understanding the potential for adverse effects on human health by agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances"). These evaluations can lead to NTP opinions on whether these substances may be of concern given what is known about current human exposure levels. OHAT organizes workshops or state-of-the-science evaluations to address other issues of importance in environmental health sciences. OHAT assessments are published as NTP Monographs.

OHAT broadly solicits nominations of chemicals for evaluation from the public and private sectors. Chemicals are selected for evaluation based on several factors including the following:

- Potential for human exposure from use and occurrence in the environment
- Extent of public concern
- Production volume
- Extent of database on reproductive and developmental toxicity studies

OHAT follows a formal process for review and evaluation of nominated chemicals that includes opportunities for public comment. Briefly, OHAT develops the draft monograph and utilizes technical advisors to provide feedback on development of the monograph. OHAT convenes a scientific expert panel that meets in a public forum to peer review the draft monograph. Public comment is invited prior to and during the meeting. Next, OHAT revises the NTP monograph based upon the peer review and public comments, and presents it to the NTP Board of Scientific Counselors at a public meeting. The final monograph is made publicly available on the OHAT website and in hardcopy or CD from OHAT.

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NTP Monograph on Cancer Chemotherapy during Pregnancy

ABSTRACT

The National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) conducted an evaluation of the developmental effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy in humans. The final NTP monograph was completed in May 2013 (available at *http://ntp.niehs.nih.gov/go/36495*). The incidence of cancer during pregnancy has been reported to occur from 17 to 100 per 100,000 pregnant women. Chemotherapy is a common treatment for cancer; however, most chemotherapy agents are classified as known or suspected human teratogens. Cancer chemotherapy use during pregnancy was selected for evaluation by the NTP because of the: (1) paucity of comprehensive reviews on the pregnancy outcomes following cancer chemotherapy use during pregnancy in humans, including the integration of the developmental animal toxicology literature with the observational studies in humans, and (2) growing public interest in the developmental effects of chemotherapy on offspring exposed to cancer chemotherapy during gestation due to the expected incidence of cancer diagnosed during pregnancy as women delay pregnancy to later ages.

Of the approximately 110 cancer chemotherapeutic agents currently in use, the NTP monograph includes data on 56 agents used during 1,261 pregnancies for which pregnancy outcomes were documented. Overall, the NTP evaluation found that treatment with chemotherapy for cancer appeared to be associated with: (1) a higher rate of major malformations following exposure during the first trimester compared to exposure in the second and/or third trimester; (2) an increase the rate of stillbirth following exposure in the second and/or third trimester; abnormally low levels of amniotic fluid (primarily attributable to Trastuzumab); and (3), also data are insufficient, impaired fetal growth and myelosuppression. Treatment with chemotherapy for cancer during pregnancy did not appear to increase spontaneous preterm birth, or impair normal growth and development of offspring during early life. In addition, the NTP monograph provides background materials on individual cancer chemotherapeutic agents (e.g., evidence for placenta and breast milk transport, developmental toxicity in animals), and a brief review of the prevalence and prognosis of seven frequently diagnosed cancers in women during pregnancy. Finally, the NTP monograph identifies challenges in interpreting the health outcomes from this observational literature base and discussed possible actions to improve the understanding of the developmental effects of chemotherapy treatment for cancer administered during pregnancy.

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NTP Monograph on Cancer Chemotherapy during Pregnancy

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. The evidence of the risk that chemotherapeutic agents pose to the fetus is 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 have been documented.

The NTP monograph focuses on the following health outcomes:

- Major congenital malformations[1] associated with treatment during the first trimester versus the second and/or third trimester only
- Early and late spontaneous fetal loss
- Pregnancy complications (e.g., abnormally low levels of amniotic fluid and spontaneous preterm birth)
- Newborn weight and health (e.g., small for gestational size, cardiotoxicity, and transient myelosuppression)
- Growth and development of gestationally exposed children

In an effort to put these effects in context, this NTP monograph also provides background information on the individual cancer chemotherapeutic agents and a brief review of the prevalence and prognosis of 7 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 that 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 7 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 4 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 pregnancy outcome data on 1 or more female cancer patients treated with cancer chemotherapeutic agents during the pregnancy. 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 1,247 female cancer patients with 1,261 pregnancies

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

and 1,276 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 Section **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 agents for which more 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,

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[2] A total of 1,247 female cancer patients were identified from the 457 reports. Fifteen patients gave birth to twins and 14 patients received treatment with chemotherapy for cancer during 2 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 of conceptuses for reported twin births; most reports of twin births did not specify if they were monozygotic).

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, as the majority of these publications were case reports (75%, n=342/457 publications) and case series (20%, n=90/457 publications). These 2 types of reports comprised 57% of the total conceptuses exposed to chemotherapy (i.e., of 1,276 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 7 of the cancer types frequently diagnosed during pregnancy as identified by population studies (Haas 1984, Smith *et al.* 2003). This section on the 7 tumor types reviews the definition and occurrence of each cancer type as well as the impact of pregnancy on the prognosis of each cancer type, and it provides a summary table of the number of reported cases treated with each chemotherapeutic agent. The background information on the chemotherapy agents and 7 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 the use of cancer chemotherapy during pregnancy, but it is not intended to be an exhaustive review of these topics.

1.3 Findings

1.3.1 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 because of 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% (62/1,156 conceptuses, based on 1,118 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).

A review of the data by individual chemotherapeutic agent shows that 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 was higher following exposure to cyclophosphamide (18%, 7/40 conceptuses) and 5-fluorouracil (31%, 4/13 conceptuses) compared to interferon alpha (5%, 1/20 conceptuses). However, these data are challenging to interpret because of differences in the timing of exposure in relation 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 differences in rates of major malformations in comparisons of the data by classes of agents working via similar mechanisms of action (see **Table 81** to **Table 86**). 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 is similar to the type of malformations observed in animal studies (Hyoun et al. 2012).

1.3.2 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% confidence interval, 10%-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%-0.4%) (MacDorman and Kirmeyer 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).

1.3.3 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 1 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 a 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% (97/1,118 liveborn infants). As a point of comparison, the rate of preterm births in the United States population in the year 2009 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.

1.3.4 Is treatment with chemotherapy for cancer during pregnancy associated with adverse effects on newborn weight and health?

Small for gestational age infants: The data are suggestive, but not definitive, concerning the effects of chemotherapy for the treatment of cancer during pregnancy with respect to impaired fetal growth. The apparent rate of small for gestational age newborns following gestational exposure to chemotherapy was 8% (89/1,118 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), and because many studies do not provide information on body weight (e.g., no body weight data or body weight and gestational age data were provided for 395 of 1,118 conceptuses in the NTP monograph). Small for gestational age infants were 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 1 large prospective series, small for gestational age infants 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%).

As concerns 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 animals that were administered these agents (see Section **5.8** and Section **5.15**). 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 1,118 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 3 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 determine 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, given that 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 1,118 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 was routinely performed or consistently reported. The chemotherapy treatments used in the cases resulting in fetal/neonatal cardiotoxicity did not appear to be limited to 1 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 1 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 the 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). 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.

1.3.5 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 (670/1,118 liveborn 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, Avilés *et al.* 2012); however, the authors observed subtle changes 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.)

1.4 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 of 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 as 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.

1.5 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 2 population-based studies and an institution-based study (Haas 1984, Smith *et al.* 2003). Approximately 4 million births occurred in 2009 in the US (Martin 2011); therefore, this range of rates of occurrence means that between 670 and 4,000 pregnant women will be diagnosed with cancer each year in the US alone. Over the past 20 to 30 years, there has been a trend for women in the US 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 because of 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 to 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 2 registries of patients with cancer during pregnancy in the US: at Cooper University Hospital in Camden, New Jersey coordinated by Dr. Elyce Cardonick (*www.cancerandpregnancy.com*) and at the University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma coordinated by Dr. John Mulvihill. In addition, there are at least 2 registries for such patients outside of the US: at the Toronto Hospital of Sick Children in Ontario, Canada (*www.MotherRisk.com*) and at 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 US 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:

- Major congenital malformations[3] associated with treatment during the first trimester versus the second and/or third trimester only
- Early and late spontaneous fetal loss
- Pregnancy complications (e.g., abnormally low levels of amniotic fluid and spontaneous preterm birth)
- Newborn weight and health (e.g., small for gestational size, cardiotoxicity, and transient myelosuppression)
- 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 7 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 7 cancers frequently diagnosed in patients during pregnancy reviewed in the monograph are breast cancer, cervical cancer,

Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, ovarian cancer, and melanoma. These summaries include a definition of the tumor type, its rate of occurrence during pregnancy, the impact of pregnancy on its prognosis, and the chemotherapy agents used to treat the tumor 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.

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

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 4 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 4 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 2 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 4 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 Institutes 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 1,425 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 1 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); 57% of the pregnancy outcomes were reported in case reports (357/1,276 conceptuses, 28%) and case series (371/1,276 conceptuses, 29%) (Table 1). The NTP monograph categorized the publications reporting on more than 1 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.

Supplementary Literature

Although not the main focus of the evaluation, the NTP monograph also reviewed primary and secondary literature on 7 of the cancer types frequently diagnosed during pregnancy. This section on the 7 tumor types reviewed the definition and occurrence of each cancer type as well as the impact of pregnancy on the prognosis of each cancer, and it 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 7 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 the topic of pregnancy outcomes following cancer chemotherapy during pregnancy, but it 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, 11 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 1 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

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	1,276

(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, Avilés *et al.* 2012, Loibl *et al.* 2012), including 2 studies that were long-term follow-up examinations of gestationally exposed offspring (Amant *et al.* 2012, Avilés *et al.* 2012). In addition, a retrospective cohort study by Lishner *et al*. (1992) was not included because it provided individual patient data for only 1 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 1 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 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, Avilés *et al.* 1990, Halaska *et al.* 2009, Peccatori *et al.* 2009) were subsequently reported in other case series or retrospective case series, and 1 retrospective survey (Hensley and Ford 2003) was 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 a 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, 4 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., because of 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 (**Table 2**). A table was created for each agent, which reported the cases (pregnant patients with cancer) exposed to the single agent as well as combination chemotherapy that included 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 1 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 A.

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.

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
Lapatinib	1	Appendix D Table 12

Methods

Table 2 (continued)

Chemotherapeutic agent	Number of reported conceptuses	Location in the NTP monograph
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

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 Measured

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 the 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:

Methods

- 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 as 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 US (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 be due, in part, to the fact that the literature covers a period of approximately 60 years, and to the fact that many of the studies originated outside of the US. 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 1 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 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: (1) an amniotic fluid index <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 of the 2 amniotic fluid index determinations 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 2 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 "seventh month" of gestation or earlier are considered early preterm births (~ 31 weeks of gestation or earlier), while births reported in the "ninth month" of gestation or "at term" are considered term. Births reported in the "eighth 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 2 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 1 case study by the authors' report of intrauterine growth arrest in an infant born at approximately 8 months of gestation with a birth weight of 1,077 g (Diamond *et al.* 1960). In another example, normal body weight for gestational age was 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 2,020 g and who was reported as "full term" (Norhaya *et al.* 1994) or for a male infant with a birth weight of 2,183 g and who 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 2 of the primary adverse health effects suspected to occur in newborns following exposure to chemotherapy agents *in utero*, 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 third 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, 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). 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 exposure during the 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

Methods

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 underdetect 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 7 of the types of cancer most frequently diagnosed during pregnancy: cancer of the breast, cervix, and ovary; Hodgkin lymphoma; non-Hodgkin lymphoma; leukemia; and melanoma (Section **4.1** to Section **4.7**). While there is disagreement in the literature on which specific cancer types are most frequently diagnosed during pregnancy, these 7 cancers were selected from 2 large population-based studies of California (Smith *et al.* 2001) and Germany (Haas 1984). Breast cancer was identified as the 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 7 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 US National Cancer Institute website (*http://www.cancer.gov/cancertopics/ types/breast*, accessed November 15, 2012) (**Table 3**).

"**[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."

4.1.2 Occurrence Rate in Reproductive-Aged Women
In 2009, the age-adjusted rate of breast cancer among all women of reproductive age (15-44 years) in the US 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 US population and were calculated using the SEER Cancer Query System (CanQues, *www.seer.cancer.gov/canques*). Rates were standardized using the US population data from the year 2000, included all races, and were restricted to females between the ages of 15 and 44 years.

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 1 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 to 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 1 year

Table 3: Estimated new cases and deaths from breast cancer in the US 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).

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, were diagnosed during pregnancy.

The estimated frequencies of occurrence for these 3 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 (US, 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 1/1,500 pregnancies. Ranges of rates of occurrence are often cited in the literature, such as 1/1,000 to 1/5,000 (Pereg et al. 2008) and 1/3,000 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, to 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 (1 case had 2 pregnancies). Fourteen cases were diagnosed before conception, 42 while pregnant, and 55 after delivery or termination, while 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 2 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 rates 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.

NTP Monograph on Cancer Chemotherapy during Pregnancy

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 3 non-pregnant patients for age, tumor stage, and year of diagnosis. They concluded that there was no significant difference in survival between the 2 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), those diagnosed during lactation (n=102), and those who gave birth more than 9 months after diagnosis (diagnosed before pregnancy; n=51). They report that survival was significantly lower in the women diagnosed during pregnancy and lactation than in those women diagnosed prior to pregnancy. 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 aged 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 comparing this group 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 1 year following delivery (n=16) were identified from medical records (1995-2007) of 2 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 1 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% confidence interval, 0.83-1.81) 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 (40-44 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 1,000 person years) than in the non-pregnant cases (37.6 per 1,000 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% confidence interval, 1.83-3.29). For cases diagnosed during pregnancy, the adjusted hazard ratio for mortality rates was 1.85 (95% confidence interval, 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 2 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 4 years, the authors report that pregnancy-associated breast cancer cases had a worse disease-free survival than controls (HR 2.3; 95% confidence interval, 1.0-6.5). 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 1 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 3 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 those limited to cases 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 2012a). The NCCN guidelines note that in pregnant patients, considerations and selection of optimal local and systemic therapy are similar to those 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**.

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 US National Cancer Institute

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

Agent	Number of published reports[a]	Number of cases[a]	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

[a]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.

website (*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 US in 2013

New cases	12,340
Deaths	4,030

Source: *http://www.cancer.gov/cancertopics/types/cervical* (accessed March 12, 2013).

4.2.2   Occurrence Rate in Reproductive-Aged Women

In 2009, the age-adjusted rate of cervical cancer among all women of reproductive age (15-44 years) in the US 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 US population and were calculated using the SEER Cancer Query System (CanQues, *www.seer.cancer.gov/canques*). Rates were standardized using the US population data from the year 2000, included all races, and were restricted to females between the ages of 15 and 44 years.

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 1 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 to 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 1/2,205 pregnancies. Combining both *in situ* and invasive cancer types, the rate was 80.7/100,000, or approximately 1/1,240 pregnancies, based on 800 cases in 991,536 pregnancies. Duggan *et al*. (1993) report a rate of invasive cervical cancer diagnosed and/or treated during pregnancy of 12/100,000, or approximately 1/8,000 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 1/4,348 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 6 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 4 universities in Germany. At 1-year follow-up, they found no significant difference in the survival rates of the 2 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

(1958-1984), report no statistically significant difference in 30-year survivals in a group of 34 cases compared to 89 matched controls.

Hopkins and Morley (1992) reviewed the records of the University of Michigan Medical Center (1960-1989) 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 2 groups.

Sood *et al*. (1997), using records from the University of Iowa Hospitals and Clinics (1960-1994), 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 (5,865 cases) patients. For cervical cancer, they reported no elevation in the risk of cause-specific death (hazard ratio, 0.89; 95% confidence interval, 0.52-1.53) 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 2 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 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 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[a]	Number of cases[a]	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

[a]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 US National Cancer Institute website (*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 2 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 US in 2013

New cases	9,290
Deaths	1,180

Source: *http://www.cancer.gov/cancertopics/types/hodgkin* (accessed March 12, 2013).

4.3.2 Occurrence Rate in Reproductive-Aged Women

In 2009, the age-adjusted rate of Hodgkin lymphoma among all women of reproductive age (15-44 years) in the US 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 US population and were calculated using the SEER Cancer Query System (CanQues, *www.seer.cancer.gov/canques*). Rates were standardized using the US population data from the year 2000, included all races, and were restricted to females between the ages of 15 and 44 years.

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 1 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 to 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, 18 gave birth during the course of their disease. They concluded that "**[i]**n 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 1 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 2 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 3 combination therapies for the treatment of classical Hodgkin lymphoma (NCCN 2012b).

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**.

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 US National Cancer Institute website (*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 lymphomas 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,

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

Agent	Number of published reports[a]	Number of cases[a]	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

[a]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.

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 US in 2013

New cases	69,740
Deaths	19,020

Source: *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 2012c):
- 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-Aged Women

In 2009, the age-adjusted rate of non-Hodgkin lymphoma among all women of reproductive age (15-44 years) in the US 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 US population and were calculated using the SEER Cancer Query System (CanQues, *www.seer.cancer.gov/canques*). Rates were standardized using the US population data from the year 2000, included all races, and were restricted to females between the ages of 15 and 44 years.

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 1 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 to 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 4 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.

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

Agent	Number of published reports[a]	Number of cases[a]	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

[a]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.

4.4.5 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 2012c). 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**.

4.5 Leukemia and Pregnancy

4.5.1 Definition of Leukemia

The definition and estimated new cases and deaths are taken directly from the US National Cancer Institute website (*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 US in 2013

New Cases	48,610
Deaths	23,720

Source: *http://www.cancer.gov/cancertopics/types/leukemia* (accessed March 12, 2013).

4.5.2 Occurrence Rate in Reproductive-Aged Women

In 2009, the age-adjusted rate of leukemia among all women of reproductive age (15-44 years) in the US 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 US population and were calculated using the SEER Cancer Query System (CanQues, *www.seer.cancer.gov/canques*). Rates were standardized using the US population data from the year 2000, included all races, and were restricted to females between the ages of 15 and 44 years.

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 1 obstetric delivery. Leukemia was the seventh most common cancer diagnosed during pregnancy, following cancer of the breast, cervix, thyroid, skin (melanoma), and 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 cancer of the cervix, breast, and ovary, lymphoma, melanoma, and cancer of the 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 US National Cancer Institute website (*http://seer.cancer.gov/statfacts/html/leuks.html,* accessed April 18, 2011) lists 4 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 are 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 (1959-1965), 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 (1972-1982) 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 (1975-1988) 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 2012d), and chronic myelogenous leukemia (NCCN 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.

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 US National Cancer Institute

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

Agent	Number of published reports[a]	Number of cases[a]	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

[a]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.

website (*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 US in 2013

New cases	22,240
Deaths	14,030

Source: *http://www.cancer.gov/cancertopics/types/ovarian* (accessed March 12, 2013).

4.6.2 Occurrence Rate in Reproductive-Aged Women

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

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 1 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 3 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 4 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; 2 cases were diagnosed 4 weeks postpartum, 1 case was an ectopic pregnancy, and 1 was diagnosed 2 weeks following an abortion. Machado *et al*. (2007), using records from a hospital in Murcia, Spain (1987-2005), 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 2 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), using records

from the University of Garyounis in Benghazi, Libya, and the King Faisal University College of Medicine in Dammam, Saudi Arabia (1976-2000), 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 1/1,700. Finally, Munnell (1963) reported 3 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 1 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 (2,688 cases) patients. For ovarian cancer, they reported no elevation in risk of cause-specific death (hazard ratio, 0.46; 95% confidence interval, 0.17-1.23) 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 2012a).

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[a]	Number of cases[a]	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

[a]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 US National Cancer Institute website (*http://www.cancer.gov/cancertopics/types/melanoma*, accessed November 15, 2012) (**Table 15**).

Table 15: Estimated new cases and deaths from melanoma in the US in 2013

New cases	76,690
Deaths	9,480

Source: *http://www.cancer.gov/cancertopics/types/melanoma* (accessed March 12, 2013).

"**[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."

4.7.2 Occurrence Rate in Reproductive-Aged Women

In 2009, the age-adjusted rate of melanoma among all women of reproductive age (15-44 years) in the US 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 US population and were calculated using the SEER Cancer Query System (CanQues, *www.seer.cancer.gov/canques*). Rates were standardized using the US population data from the year 2000, included all races, and were restricted to females between the ages of 15 and 44 years.

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 1 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 to 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, fifth in descending rank order following cancer of the cervix, breast, and 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 (1970-1996), cited a figure of 260/100,000 deliveries. Smith and Randall (1969) presented figures from 2 hospitals, 1 in New York and 1 in Tennessee. At the hospital in New York, 4 cases were observed among 1,400 deliveries over a 3-year period (1964-1967) for an occurrence of 280/100,000. At the hospital in Tennessee, 3 cases were observed in 9,400 deliveries over a 7-year period (1960-1967) 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 at which melanoma occurs during pregnancy are not unexpected, considering the differences in melanoma occurrence rates 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- to 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, aged 19 to 40, diagnosed with melanoma during pregnancy and compared them to a group of 86 age-matched women who were not pregnant when diagnosed. These cases were patients at the Duke University Medical Center, Durham, North Carolina. **[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 I 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 results similar to those of Slingluff *et al.* (1990): 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 (4,460 cases) patients. For melanoma, they reported a slightly elevated risk of cause-specific death (hazard ratio, 1.52; 95% confidence interval, 1.01-2.31) 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 1 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 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[a]	Number of cases[a]	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

[a]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.

Background

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 (Section **5.2** to Sectio **5.34**) (**Table 17**). These agents can be classified into 7 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). It is important to note that some agents have multiple mechanisms 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 1,247 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 (percentage of total cases) was as follows: 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 cases (7%); ovarian cancer, 62 cases (5%); cervical

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

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

Note: Many of these agents have more than 1 mechanism of action.

cancer, 42 cases (3%); and melanoma, 12 cases (1%). Additional types of cancers receiving treatment with chemotherapy during pregnancy included the following: 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 1 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 (Section **5.2** to Section **5.34;** Appendix C) and in the Appendix Table D for agents with 10 or fewer cases reported.

Of the 1,247 cases, there were a total of 1,261 pregnancies and 1,276 conceptuses exposed to chemotherapy for treatment of cancer. Fourteen cases had 2 pregnancies each, and 15 pregnancies yielded twin infants. Of the 1,276 conceptuses, 397 conceptuses were exposed to chemotherapy during the first trimester, 851 conceptuses were exposed in the second and/or third trimester, and 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

because of 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% (62/1,156 conceptuses, based on 1,118 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 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 death) 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. The reported major malformations observed in conceptuses that were observed following *in utero* exposure to chemotherapy for treatment of cancer during pregnancy are identified in tables within each individual agent chapter (see Section **5.2** to Section **5.34**).

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 the following: 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. Exclusion of pre-existing 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. Specifically, the adjusted 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 death) following exposure during the second and/or third trimester only.

Minor Malformations

Minor malformations were reported in 25 liveborn infants and 1 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 the following (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)); and 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 the following: 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 Section **5.2** to Section **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 the following: 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% (33/1,118 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 1 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 1 set of twins). Intrauterine growth restriction (based on measurements of the fetus) was reported for 29 of 1,118 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 the following: spontaneous preterm labor (63 pregnancies), preeclampsia (28 pregnancies, including 2 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 (366/1,118 liveborn infants). Specifically, early preterm birth (<34 weeks of gestation) was reported for 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% (97/1,118 liveborn infants), while the majority of the preterm infants were delivered via C-section (19%, 207/1,118 liveborn infants). The remaining 6% of preterm infants (62/1,118 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% (90/1,118 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 of 1,118 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 1 case of non-hemolytic anemia that was not included in the total liveborn infants with myelosuppression (Peres *et al.* 2001). Of a total of 1,118 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 was routinely performed or consistently reported. Six singleton pregnancies were exposed to anthracyclines in polytherapy including the following: 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 1 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). 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 1 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 1,118 liveborn infants exposed to chemotherapy for treatment of cancer died; all but 1 infant died within the first 4 months of life. Fifteen infants were born preterm, 2 infants were born at term, and 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 1 infant with a small secundum atrial septal defect identified at autopsy (Thomas and Peckham 1976). Two newborns with hydrocephalus died within 4 hours of birth (Zemlickis *et al.* 1992b), including 1 infant with communicating hydrocephalus and several cardiac anomalies (Pye *et al.* 2008). Infections were the cause of death for 4 infants: 1 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 (Avilés *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 (Avilés *et al.* 1991). Four infants who died had experienced oligo- or anhydramnios following gestational exposure to trastuzumab. Of the trastuzumab-exposed infants, 1 preterm infant suffered from prematurity-related problems and died following decreasing kidney function at age 4 months (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 1 day (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 because of 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 1,118 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 to 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 1 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 1 infant at age 9 months with 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 biometric data, the percentage of children with follow-up examinations at ages ranging from birth to 2 years was 56% (246 children). 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 to 5 years of age, 59 children (13%) at >5 to 12 years of age, 16 children (4%) at >12 to 17 years of age, and 3 children (1%) at >17 to 22 years of age.

5.2 5-Fluorouracil

5.2.1 *Mechanism of Action, Route of Administration, and Indications*

5-Fluorouracil is a pyrimidine analogue that belongs to a class of chemotherapy drugs known as antimetabolites. 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**.

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).

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; 2 metabolites, fluoro-dexouridine 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 (Cmax):	**[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.

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 2 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 1 case each of cancers of the cervix, ovary, bowel, rectum, and pancreas. Type of cancer was not specified for 2 cases.

5-Fluorouracil was administered during 178 pregnancies for a total of 179 exposed conceptuses, because of 1 twin pregnancy (Jeppesen and Osterlind 2011). 5-Fluorouracil was administered during the first trimester in 17 pregnancies (18 conceptuses because of 1 twin pregnancy). The drug was administered to 161 singleton pregnancies (161 conceptuses) in the second and/or third trimester only, including 2 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 2 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 to 34 weeks (median, 23 weeks (Hahn *et al.* 2006)) or 12 to 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 upon examination of 2 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 the following: 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 1 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 4 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

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 7.5-28.5) 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 2 fetuses from induced abortions with first-trimester exposure to 5-fluorouracil. Skeletal malformations and

Table 19: Major malformations observed following *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	2% (3/161)
	Clubfoot	
	Down syndrome	

[a] Data based on liveborn infants as well as examination of fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

micrognathia were observed in 1 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 the following: shortened second and third fingers, clinodactyly of the fifth finger, skin syndactyly of the first and second fingers, a short first toe, and osseous syndactyly of the fourth and fifth 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, and 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 gestation week 11 and was co-exposed to diagnostic X-rays in the first trimester (Stephens *et al.* 1980). The authors stated that 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 3 infants exposed in the second and/or third trimester only. Hemi-hypertrophy of the lower extremity was observed in 1 infant following exposure to 5-fluorouracil monotherapy in the second and third trimester only (Cardonick *et al.* 2010). One case series reported 1 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 with 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, 1 infant had a hemangioma on its abdomen, which the authors deemed was not due to chemotherapy (Ring *et al.* 2005b); the infant was exposed in the 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 2 pregnancies (Cordoba *et al.* 2010), including 1 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 2 pregnancies (Berry *et al.* 1999, Kuerer *et al.* 2002), eclamptic seizures in 1 pregnancy (Muller *et al.* 1996), maternal hypertension in 1 pregnancy (Turchi and Villasis 1988), and premature rupture of the membranes in 1 pregnancy (Jeppesen and Osterlind 2011), while 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 16 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: anemia (2 infants) (Cuvier *et al.* 1997, Giacalone *et al.* 1999), leukopenia (2 infants) (Berry *et al.* 1999, Giacalone *et al.* 1999), and 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 3 infants, including 1 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 1 child (Stadler and Knowles 1971). Normal growth and development were reported for all but 4 children. At 8.5 years, 1 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 1 twin pregnancy (179 conceptuses) (**Table 81**). 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 1 stillbirth) (**Table 19**). 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 2 liveborn infants and 2 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 1 stillbirth). Major malformations were observed in 3 liveborn infants following second- and/or third-trimester only exposure to 5-fluorouracil. However, 1 major malformation (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 81**). 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

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**.

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 (Cmax):	~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 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 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%-25% of maternal dose) and 6-mercaptopurine (5%-13% of maternal dose) were detected in fetal blood at 2.5 to 6 hours following administration of radiolabelled-azathioprine to 3 women in gestation weeks 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 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 2 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 2 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 1 of 31 breast milk samples from 10 women treated with azathioprine for lupus, Crohn disease, or renal transplant; levels were 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 (2002). Exposure to a single injection of 6-mercaptopurine (37.5-156 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 <1-6.25 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 the following types: 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 3 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 because of 2 patients having 2 pregnancies each (Diamond *et al.* 1960, Avilés and Niz 1988) and 1 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 because of 1 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 1 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 1 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 2 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 3 spontaneous abortions: 1 pregnancy exposed in the first and second trimesters (Boggs *et al.* 1962), 1 pregnancy exposed in the first trimester (Zemlickis *et al.* 1992b), and 1 fetus exposed during the first trimester and co-exposed to methotrexate and vincristine (Bergstrom and Altman 1998). Polydactyly was reported in 1 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 1 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, 3 singleton pregnancies ended in maternal/fetal death following gestational exposure to 6-mercaptopurine. A normal fetus was reported from 1 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**). 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 through 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

Table 21: Major malformations observed following *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)
Not specified	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. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

abnormalities (Diamond *et al.* 1960). As mentioned above, polydactyly was reported in 1 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 1 infant following gestational exposure to 6-mercaptopurine. An asymptomatic cardiac murmur was reported in 1 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 1 pregnancy (Hansen *et al.* 2001), and 1 fetus had intrauterine growth restriction (Morishita *et al.* 1994). Other pregnancy complications included the following: 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 1 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; 3 of these infants died shortly after birth (see **Infant Deaths** section below). Transient myelosuppression was reported in 5 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, Avilés 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 3 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 (Avilés and Niz 1988). The remaining 4 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); 3 of these infants had respiratory distress.

Follow-Up Evaluations

Follow-up examinations were available on 51 infants (including 1 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 1 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 1 set of twins (86 conceptuses) (**Table 81**). 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) (**Table 21**). 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 81**). 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

6-Thioguanine is a purine analogue that belongs to a class of chemotherapy drugs known as anti-metabolites. It is a metabolite of azathioprine 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**.

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-methylthio-guanine (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 (Cmax):	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 indicated for acute non-lympho-blastic 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 one-twelfth of the levels detected in maternal blood (41 versus 494 picomoles/$8x10^8$ red blood cells, respectively). At 1 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 4 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 were observed following intravenous injection of pregnant rats treated with **[6-]**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, and 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 leukemia (also called acute granulocytic leukemia, 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 1 patient with both acute myelogenous and acute lymphocytic leukemia and 2 cases of chronic myelogenous leukemia (also called chronic granulocytic).

A total of 53 singleton pregnancies (53 conceptuses) were exposed to 6-thioguanine because of 3 patients having 2 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

Six 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 2 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, and 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 2 normal male spreads, 2 spreads with trisomy C, and 1 very abnormal chromosome.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 6 singleton pregnancies (6 conceptuses), including 2 spontaneous abortions and 4 stillbirths. No examination of the fetus was reported for 1 spontaneous abortion, which occurred 20 days following first-trimester exposure to 6-thioguanine and co-treatments with 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 in any of the 4 stillbirths occurring following second-trimester exposure to 6-thioguanine and co-exposure to the following: 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
Major malformations following *in utero* exposure to 6-thioguanine were observed in 4 liveborn infants . Major malformations occurred in 2 infants exposed during the first trimester (**Table 23**). One infant was born with multiple skeletal defects and a small ostium

Table 23: Major malformations observed following *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.	50% (2/4)
	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	Down syndrome	05% (2/44)
	Polydactyly	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 2 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 50% (2/4, based on 3 liveborn infants and examinations of the fetuses of 1 induced abortus).

Major malformations were observed in 2 infants with exposure to 6-thioguanine in the second and/or third trimester only. An infant was born with 6 toes on his right foot, which was likely because of his family's history of polydactyly (Volkenandt *et al.* 1987); this infant was exposed in the third trimester and co-treated with cytarabine and daunorubicin. Down syndrome was diagnosed in 1 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 incidences 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 38 liveborn infants and examinations of the fetus of 4 stillbirths and 2 induced abortions).

Minor Malformations
Minor malformations were observed in 1 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 1 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 5 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 2 newborns (Au-Yong *et al.* 1972), including 1 infant with thrombocytopenia (Taylor and Blom 1980). Low hemoglobin was reported in 1 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 were observed in all but 2 children. At age 13.5 months, 1 child was below the third 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 81**). 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% (4/48 conceptuses, based on 41 liveborn infants and examination of the fetuses of 3 induced abortions and 4 stillbirths) (**Table 23**). 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 2 infants with exposure to 6-thioguanine during the first trimester. 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 50% (2/4 conceptuses, based on 3 liveborn infants and the examination of 1 induced abortus). The major malformations observed in 2 infants with exposure to 6-thioguanine in the second and/or third trimester

only were 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 38 liveborn infants and examination of the fetus of 2 induced abortions and 4 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 (10%) than the frequency of stillbirths in the general population of the US (0.3%-0.6%) (MacDorman and Kirmeyer 2005) (**Table 81**). 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

Actinomycin D is a cytotoxic antibiotic produced by *Streptomyces parvulus*. 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**.

Table 24: Pharmacology of actinomycin D in adult humans

Molecular weight:	1,255.4294
Protein binding:	**[Information not located]**
Metabolism:	Minimal
Half-life elimination:	~36 hours
Distribution:	Does not penetrate blood-brain barrier
Time to peak, serum (Cmax):	**[Information not located]**
Excretion:	~30% in urine and feces within 1 week

Data from Brunton *et al.* (2011). Abbreviations: Cmax, time to reach maximal concentration in serum.

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 (0.0625-0.25 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 the ovary (1 case), uterus (1 case), and vagina (1 case).

A total of 15 pregnancies were exposed to actinomycin D (16 conceptuses because of 1 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

Major malformations were reported in one infant gestationally exposed to actinomycin D (**Table 25**). Major malformations were observed in 1 liveborn infant exposed to actinomycin D in the second and/or third trimester only. Clubfoot was reported in an infant following exposure in the third trimester to actinomycin D, methotrexate, and vinblastine (Hutchison *et al.* 1968). Thus, the apparent rate of major malformations following exposure to actinomycin D in the second and/or third trimester only was 6% (1/16 conceptuses, based on 16 liveborn infants). No conceptuses were exposed during the first trimester.

Table 25: Major malformations observed following *in utero* exposure to actinomycin D

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	No data	(0/0)
2nd and/or 3rd only	Clubfoot	6% (1/16)

[a] Data based on liveborn infants as well as examination of fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 4 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 2 infants with respiratory distress (Corapcioglu *et al.* 2004), including 1 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 hemorrhage 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 were 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 1 twin pregnancy (Table 83). 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 6% (1/16 conceptuses, based on 16 liveborn infants) (Table 25). 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 6% (1/16 conceptuses, based on 16 liveborn infants).

5.6 All-*Trans* Retinoic Acid

5.6.1 Mechanism of Action, Route of Administration, and Indications

All-*trans* retinoic acid (ATRA, tretinoin) is a chemical related to retinol (vitamin A). 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 26**.

Table 26: 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 (Cmax):	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 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 1 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 3 patients, Taikitani *et al*. (2005) reported that all-*trans* retinoic acid administered to 1 mother prior to delivery was detected in maternal blood (26 ng/mL) at 6 hours, and in umbilical cord blood (8 ng/mL) at 9 hours post-treatment. In the remaining 2 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 to 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 one-twentieth, one-fourth, and one-half 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 to 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 to 24 (Hendrickx and Hummler

1992). No malformations were reported at 5 mg/kg bw/day; however, 1 fetus out of 7 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 monkeys 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 1 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 1 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 because of a twin pregnancy). All-*trans* retinoic acid was administered as monotherapy in 15 pregnancies (16 conceptuses because of 1 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 one infant gestationally exposed to all-*trans* retinoic acid (**Table 27**). No major malformations were observed following exposure to all-*trans* retinoic acid during the first trimester. Thus, the apparent rate of malformations following exposure to all-*trans* retinoic acid during the first trimester was 0% (0/2 conceptuses, based on 2 liveborn infants). One infant was diagnosed *in utero* with Potter syndrome (bilateral renal agenesis

Table 27: Major malformations observed following *in utero* exposure to all-*trans* retinoic acid

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	None	(0/2)
2nd and/or 3rd only	Potter syndrome (diagnosed prior to treatment)	4% (1/24)

[a] Data based on liveborn infants as well as examination of fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 adjusted apparent rate of malformations following exposure to all-*trans* retinoic acid in the second and/or third trimester only was 0% (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 had a small patent ductus arteriosus accompanied by 2 small secundum atrial septal defects (Siu *et al.* 2002). The 2 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 because they did not significantly impact blood flow in the heart. The remaining 2 infants with patent ductus arteriosus were born prior to 34 weeks of gestation: 1 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 3 cases, this condition resolved with further growth of the infant and, in 1 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. Pregnancy complications included the following: 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, and intrauterine growth restriction due to placental insufficiency occurred in 1 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, 1 pregnancy had oligohydramnios associated with bilateral renal agenesis diagnosed prior to treatment with all-*trans* retinoic acid (Sham 1996). Fetal distress occurred in 1 pregnancy (Nakamura *et al.* 1995). Fetal arrhythmia occurred in 2 fetuses (Leong *et al.* 2000), including 1 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 3 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 were insufficient to determine the route of delivery for 1 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 1 preterm infant with small bilateral subependymal hemorrhages (Incerpi *et al.* 1997).

Health issues related to cardiac function occurred in 3 infants gestationally exposed to all-*trans* retinoic acid. Cardiac arrhythmia led to cardiac arrest in 1 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 1 day. Moderate dilation of the right atrium and right ventricle was reported in an infant with a small patent ductus arteriosus and 2 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 to all-*trans* retinoic acid 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 1 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 2 small secundum atrial septal defects 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 1 set of twins (**Table 86**). 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 4% (1/26 conceptuses, based on 26 liveborn infants) (**Table 27**). 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 (0/2 conceptuses, based on 2 liveborn infants). One infant was diagnosed *in utero* a major malformation (Potter syndrome) prior to the administration of all-*trans* retinoic acid in the third trimester (Sham 1996); thus, the adjusted apparent rate of malformations possibly attributed to exposure to all-*trans* retinoic acid in the second and/or third trimester only was 0% (0/24 conceptuses, based on 24 liveborn infants). Abnormal cardiac function was reported for 3 infants with *in utero* exposure to all-*trans* retinoic acid; all 3 infants were exposed in the second and third trimesters. Specifically, arrhythmia was reported for 2 newborns (Harrison *et al.* 1994, Terada *et al.* 1997, Takitani *et al.* 2005), and 1 infant experienced dilation of the right atrium and ventricle. Further investigation of possible effects of all-*trans* retinoic acid on heart development and function is 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 the following: 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); and 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

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 28**.

Table 28: Pharmacology of bleomycin in adult humans

Molecular weight:	1,415.56
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 (Cmax):	IM: Within 30 minutes
Excretion:	Urine (50%-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 indicated for Hodgkin and non-Hodgkin lymphomas, squamous cell carcinomas, testicular cancer, and malignant pleural effusion (Bristol-Myers Squibb 2010c).

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 2010c).

5.7.3 Laboratory Animal Developmental Toxicity

Bleomycin is reported to induce teratogenic effects in rats, but not in rabbits (Bristol-Myers Squibb 2010c). 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 and 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 to 1 mg/kg or 3 to 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 1 case each of Ewing sarcoma, Kaposi sarcoma, adenocarcinoma (primary cancer not identified), and cervical cancer. Cancer type was not specified in 2 cases.

There were a total of 95 pregnancies with 97 conceptuses exposed to bleomycin because of 1 patient having 2 pregnancies (Dilek *et al.* 2006) and 2 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 because of 2 sets of twins), including 2 singleton pregnancies for which individual timing of exposure was not provided but which 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 to 34 weeks (median, 23 weeks (Hahn *et al.* 2006)) or 12 to 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 1 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 2 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 1 induced abortion) (**Table 29**).

Major malformations occurred in 4 liveborn infants exposed to bleomycin in the second and/or third trimester only. Syndactyly of the fourth and fifth fingers was reported in 1 infant with second- and third-trimester exposure to bleomycin, doxorubicin, vinblastine, and dacarbazine (Cardonick *et al.* 2010). Another infant had bilateral syndactyly of digits 2 and 3 following exposure in the second and third trimesters to bleomycin, doxorubicin, and 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

Table 29: Major malformations observed following *in utero* exposure to bleomycin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Floating thumb malformation on the left hand (i.e., partial agenesis of a metacarpal and hypoplasia of 2 phalanges)	7% (1/15)
2nd and/or 3rd only	Cerebral atrophy and ventriculomegaly	5% (4/80)
	Neurofibromatosis and genetic hearing loss	
	Syndactylies of fingers (2 infants)	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

trimester to bleomycin, etoposide, and cisplatin (Elit *et al.* 1999); mild-to-moderate ventriculomegaly occurred prenatally 3 weeks following exposure in the second trimester.

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 3 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 6 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 2 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 1 singleton pregnancy (Ghaemmaghami and Hasanzadeh 2006). Spontaneous preterm labor was reported in 3 pregnancies, including 1 twin pregnancy (Raffles *et al.* 1989, Nantel *et al.* 1990, Moore and Taslimi 1991), and 1 singleton pregnancy experienced transient spontaneous preterm labor (Ortega 1977). Fetal distress occurred in 1 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 3 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 2 infants, including anemia (1 infant) (Horbelt *et al.* 1994) and leukopenia with neutropenia, anemia, and thrombocytopenia (Raffles *et al.* 1989); 1 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 2 children. Motor/language delays were observed in 1 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 2 twin pregnancies, for a total of 97 conceptuses (**Table 85**). 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) (**Table 29**). 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 1 newborn had a major malformation (i.e., partial agenesis of a metacarpal and hypoplasia of 2 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 4 newborns exposed to bleomycin in the second and/or third trimester only. However, only 1 malformation was likely caused by bleomycin polytherapy: ventriculomegaly and cerebral atrophy in a newborn (Elit *et al.* 1999); mild ventriculomegaly was first observed prenatally 1 week after 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 30**.

Table 30: 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 (Cmax):	Oral: ~1 hour; IV: within 5 minutes
Excretion:	Urine: 25%-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/day on gestation days 12 to 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 to 34 mg of 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 2 types of leukemia: chronic myelogenous (also called chronic granulocytic, 30 cases) and acute granulocytic (1 case).

Of these 31 cases, a total of 32 singleton pregnancies (32 conceptuses) were exposed to busulfan, including 1 case having 2 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 third 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 (**Table 31**). Two of the liveborn infants and 1 induced abortus with major

Table 31: Major malformations observed following *in utero* exposure to busulfan

Trimester exposed	Major malformations observed	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	Congenital absence of right kidney and right ureter	17% (1/6)
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. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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, was co-treated with radiation therapy prior to conception, and was 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).

Major malformations were observed in 1 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 was observed in an infant exposed in the second and third trimester to busulfan monotherapy beginning in 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 weeks 5-15) (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 6 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 4 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 1 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 2 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 because of 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 1 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 2 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 82**). 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) (**Table 31**). 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 1 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 (i.e., 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). No malformations were observed in the 5 infants with *in utero* exposure to busulfan with exact timing not specified.

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 82**).

5.9   Carboplatin

5.9.1   Mechanism of Action, Route of Administration, and Indications
Carboplatin is an organoplatinum compound in the class of alkylating agents that possess anti-neoplastic activity. Carboplatin binds to DNA, producing predominately interstrand versus intrastrand cross-links that lead to DNA breakage, and it 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 32**.

Carboplatin is indicated for ovarian cancer (Bedford 2004).

Table 32: 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/m²); into liver, kidney, skin, and tumor tissue
Time to peak, serum (Cmax):	**[Information not specified]**
Excretion:	Urine (~70% as carboplatin within 24 hours; 3%-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.

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/m² every 4 weeks); the first dose was administered at gestation week 22 and the last dose was administered 9 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).

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 the percentage 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 1 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 1 major malformation reported following gestational exposure to carboplatin (**Table 33**). 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 because of the 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 to 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 were observed in 1 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 1 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

Table 33: Major malformations observed following *in utero* exposure to carboplatin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	No data	(0/0)
2nd and/or 3rd only	Gastroschisis	6% (1/17)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 2 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); this newborn 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 1 child. Normal growth and development were reported for all the children, except 1 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 82**). 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) (**Table 33**). 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

Cisplatin, an inorganic compound, is a *cis*-isomer of diammine dichloroplatinum. Cisplatin is a DNA-alkylating agent, and it also induces interstrand and intrastrand cross-links 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 34**.

Table 34: 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 (Cmax):	**[Information not located]**
Excretion:	Urine (>90%); feces (minimal)

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

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 1,148.8 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, 3 days post-administration of cisplatin to the mother **[this value is 1,000-fold higher than 2 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% of the levels 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 (Köpf-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 LD50s were 1.0 to 2.9 mg cisplatin/kg bw/day in the rat and 5.2 mg cisplatin/kg bw/day in the mouse during the period of organogenesis; these doses are below the estimated human dose of 6 mg/kg bw/day. Other studies also reported dose-dependent increases in fetal resorptions during organogenesis, but not after organogenesis, in the mouse (Köpf-Maier *et al.* 1985), rat (Muranaka *et al.* 1995), and rabbit. High rates of fetal mortality were reported for rabbits exposed *in utero* to ≥0.125 mg cisplatin/kg bw/day 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, Köpf-Maier *et al.* 1985, Muranaka *et al.* 1995). While Muranaka *et*

al. (1995) reported that 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 (Köpf-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 (Köpf-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, Köpf-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/day (Shepard and Lemire 2004). Fetal malformations that occurred following in utero exposure to cisplatin included the following: 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)), and hydrocephaly in rats (Köpf-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 was 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 (Köpf-Maier and Merker 1983, Köpf-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 2 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 because of 2 sets of twins). Cisplatin was administered as monotherapy in 33 cases (34 conceptuses because of 1 set of twins) and as polytherapy in 71 cases (72 conceptuses because of 1 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 in 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 2 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 (**Table 35**).

Table 35: Major malformations observed following *in utero* exposure to cisplatin

Trimester exposed	Major malformations observed	Apparent rate (affected/ total conceptuses[a])
During 1st	Blepharophimosis, microcephaly, and hydrocephalus	20% (1/5)
2nd and/or 3rd only	Ventriculomegaly and cerebral atrophy	4% (4/99)
	Ventriculomegaly (diagnosed prior to chemotherapy)	
	Hereditary spherocytosis	
	Neurofibromatosis and genetic hearing loss	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

One major malformation 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 (Kim *et al.* 1996). Blepharophimosis is characterized by bilateral ptosis (drooping eyelids) with reduced lid size, and a flat nasal bridge with a small orbital rim. Thus, the apparent rate of major malformations following exposure during the first trimester was 20% (1/5 conceptuses, based on 4 liveborn infants and examination of the fetus of 1 induced abortion).

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 1 newborn who had been diagnosed with ventriculomegaly at gestation week 26 and 5 days, 1 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 from congenital malformations detected prior to chemotherapy exposure. Hereditary spherocytosis was diagnosed at 1 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 1 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, Tseng and ChangChien 2004, Han *et al.* 2005, Gottschalk *et al.* 2009, Benjapibal *et al.* 2010), 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 1 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 1 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 2 cases that also had spontaneous preterm labor (King *et al.* 1991, Huang *et al.* 2004). Spontaneous preterm labor occurred in 4 additional pregnancies (Raffles *et al.* 1989, Kim *et al.* 1996), including 2 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 because of 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 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 (Buller *et al.* 1992, Arango *et al.* 1994, Tseng and ChangChien 2004, Han *et al.* 2005, Caluwaerts *et al.* 2006, Raghunath and Shashi 2006, Motegi *et al.* 2007, Kim *et al.* 2008, Abellar *et al.* 2009, Ghaemmaghami *et al.* 2009, Gottschalk *et al.* 2009, Benjapibal *et al.* 2010, Cardonick *et al.* 2010), 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 1 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 3 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 3 children. Hearing loss was reported for 2 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 2 sets of twins (**Table 82**). 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) (**Table 35**). 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 1 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 3 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% (1/99 conceptuses, based on 98 liveborn infants and examination of the fetus of 1 stillbirth).

Microphthalmia, a minor malformation, was reported in 1 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 82**).

5.11 Cyclophosphamide

5.11.1 Mechanism of Action, Route of Administration, and Indications

Cyclophosphamide is an anti-neoplastic alkylating agent that is chemically similar to the nitrogen mustards (Baxter 2009). It is biotransformed in the liver to metabolites that cross-link 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 36**.

Table 36: Pharmacology of cyclophosphamide in adult humans

Molecular weight:	261.0875
Protein binding:	10%-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 (Cmax):	Oral: ~1 hour; IV ~ 1 hour; metabolites: 2-3 hours
Excretion:	Urine (<30% as unchanged drug, 85%-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 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 1 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 2 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 2 infants whose mothers continued breastfeeding while being treated with cyclophosphamide. A patient with Burkitt lymphoma would not stop breastfeeding 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 third dose), and no follow-up data were available for the infant. Transient neutropenia occurred in an infant who was breastfed 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 day 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, while 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, was 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 the 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, 1 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 to 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), cancer of the 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 cases), B-cell lymphoma (2 cases), 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 on account of 3 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 because of 1 set of twins (Reynoso et al. 1987)). The drug was administered in the second and/or third trimester only in 368 cases (370 conceptuses because of 2 sets of twins (Nantel et al. 1990, Lycette et al. 2006)), including 47 singleton pregnancies from 2 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 2 studies ranged from 11 to 34 weeks (median, 23 weeks) for 40 cases (Hahn et al. 2006) and 12 to 33 weeks (mean=24 weeks) for 7 cases (Jameel and Jamil 2007). Cyclophosphamide was most commonly administered as polytherapy (413 cases, 415 conceptuses because of 2 sets of twins). Only 6 cases (7 conceptuses because of 1 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 2 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 fifth finger, and syndactyly of the fourth and the fifth metatarsal bones of both feet among other skeletal malformations following exposure to cyclophosphamide, 5-fluorouracil, and epirubicin as well as 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 that 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 following 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 1 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 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 2 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 (**Table 37**). Skeletal malformations were reported in 1 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 1 toe, first and fourth toes that were larger than the middle toes, and feet that 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 first and second fingers, and a cleft between the second and third). A male infant from a twin pregnancy was born with Madelung deformity of the right arm (i.e., an absent thumb, clubhand, 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

Table 37: Major malformations observed following *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 1 toe, first and fourth 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	18% (7/40)
	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 first and second fingers, and a cleft between the second and third	
	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 first and second fingers, clinodactyly of the fifth finger, and bilateral syndactyly of the fourth and fifth metatarsal bones, among other skeletal malformations	
	Missing phalanges in both feet and only a single left coronary artery	
	Polydactyly	
2nd and/or 3rd only	Pyloric stenosis	1% (5/366)
	Clubfoot (2 infants)	
	Down syndrome	
	Pulmonary fistula	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

of the digits were reported in 2 induced abortuses (Toledo *et al.* 1971, Leyder *et al.* 2010) and 1 stillborn fetus (Mulvihill *et al.* 1987). Thus, the apparent rate of major malformations following exposure to cyclophosphamide during the first trimester was 18% (7/40 conceptuses, based on 36 liveborn infants and examination of the fetuses of 2 stillbirths and 2 induced abortions).

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 1 infant and clubfoot in another infant following second- and/or third-trimester exposure to

Chemotherapeutic Agents

cyclophosphamide, 5-fluorouracil, and doxorubicin (Hahn *et al.* 2006). Of these malformations, the incidence of Down syndrome and the incidence of 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% (3/366 conceptuses, based on 364 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

3 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 1 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 1 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 1 singleton pregnancy that ended in stillbirth (Peterson 2008). Intrauterine growth retardation was observed in 3 additional pregnancies (Lambert *et al.* 1991, Cordoba *et al.* 2010), including 1 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 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 (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, Andreadis *et al.* 2004, Huang *et al.* 2004, Ring *et al.* 2005b, Decker *et al.* 2006, Sharma *et al.* 2009, Brudie *et al.* 2011), and 4 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 1 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 1 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 follows: anemia (5 infants) (Avilés 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 2 newborns were treated for acute cardiac failure (Achtari and Hohlfeld 2000), including 1 infant who was hydropic and also had slight cardiomegaly, an enlarged spleen, and a petechial rash (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 3 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 (Avilés and Niz 1988). One infant, who had thrombocytopenia at birth, died at 13 months because of 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 1 with Down syndrome (Hahn *et al.* 2006), 2 with developmental delay (Lam 2006, Cardonick *et al.* 2010), 1 with motor development delay (Paskulin *et al.* 2005), and 1 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 he had a ruptured neuroblastoma in his adrenal gland at age 14 years, as well as metastatic thyroid cancer at age 16 years; he also had severe anemia at ages 2 to 4 years. At age 17 years, he was free of thyroid cancer (Reynoso *et al.* 1987, Zemlickis *et al.* 1993). His twin sister had normal growth and development. She had surgery to correct strabismus (cross-eye) 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 2 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), and selective IgA deficiency not requiring treatment, while 1 child had 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 3 sets of twins (**Table 82**). 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) (**Table 37**). 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 on account of 1 set of twins) exposed to cyclophosphamide during the first trimester, major malformations were observed in 4 liveborn infants, 2 induced abortuses, and 1 stillborn fetus. Skeletal malformations were common to 6 singleton pregnancies exposed during the first trimester, including the following: 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% (7/40 conceptuses, based on 36 liveborn infants and examination of the fetuses of 2 stillbirths and 2 induced abortions). In contrast, the adjusted apparent rate of major malformations following exposure to cyclophosphamide in the second and/or third trimester only was 1% (3/366 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 38: 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%-96% of dose is metabolized to inactive uracil arabinoside (ARA-U); intrathecal administration results in little conversion to ARA-U because of 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%-50% of plasma level
Time to peak, serum (Cmax):	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 38**.

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 2008b).

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 a mg/m^2 basis) (SkyePharma 2003). In rats, cytarabine induced deformed appendages when 20 mg/kg was administered as a single intraperitoneal dose on day 12 of gestation (about 4 times the recommended human dose on a mg/m^2 basis). In rats administered single intraperitoneal doses of 50 mg/kg (about 10 times the recommended human dose on a mg/m^2 basis) on day 14 of gestation, reduced prenatal and postnatal brain size and permanent impairment of learning ability were observed. When cytarabine was 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 a 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 a 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 gestation day 16 in mice and gestation day 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), fetal toxicity and defects of the digits were found in the fetuses of rats administered oral doses of cytarabine on days 7 to 17 with doses up to 10 mg/kg bw. 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 pregnant rat and mice dams administered cytarabine intravenously at doses ranging from 1.5 to 15 mg/kg bw on gestation days 7 to 12 in the mouse and 15 to 60 mg **[/kg bw]** on gestation days 9 to 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 Jcl: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 to 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

having 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 that included 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, on 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 on account of 4 patients having 2 pregnancies each (Schafer 1981, Plows 1982, Avilés 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 with daunorubicin, vincristine, 6-thioguanine, and hydroxyurea (Doney *et al.* 1979). A normal fetus with abnormal chromosomes (i.e., a mosaicism of Trisomy group C) was observed in an induced abortus exposed in the second trimester to cytarabine and co-treatment with 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 that followed first-trimester exposure to cytarabine and co-treatment with the following: daunorubicin only (1 pregnancy) (Zuazu *et al.* 1991), daunorubicin and all-*trans* retinoic acid (1 pregnancy), daunorubicin and mitoxantrone (1 pregnancy) (Chelghoum *et al.* 2005), and 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 1 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 the following: 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 were observed in multiple areas of 1 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 2 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 live-born infants gestationally exposed to cytarabine (**Table 39**). 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

Table 39: Major malformations observed following *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 fifth 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 1 bone in the lower leg (instead of 2), and each foot was composed of an os calcis and only 2 lateral metatarsals	
2nd and/or 3rd only	Hypospadias	4% (4/109)
	Ventricular septal defect, sacral dimple, short digits and limbs, dysplastic fingernails, prominent frontal skull with micrognathia	
	Down syndrome	
	Polydactyly	
Not specified	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. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

Chemothera-peutic Agents

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 fifth 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 2 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; in addition, the right hand had a lobster claw with only 3 digits, each leg had a malformed femur and only 1 bone in the lower leg (instead of 2), and each foot was composed of an os calcis and only 2 lateral metatarsals (Wagner *et al.* 1980). Thus, the 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).

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 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 because of 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 infants and 1 stillbirth for which timing of exposure to cytarabine was not specified (0%, 0/13 conceptuses).

Minor Malformations

Minor malformations were observed in 2 liveborn infants, and chromosome abnormalities were reported for 1 liveborn infant and 1 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, 1 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 1 singleton pregnancy (Artlich *et al.* 1994). Oligohydramnios occurred in 3 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 1 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 and Price (1996) appear to be the same case, but are considered as 2 separate case reports in this evaluation.]** Fetal cardiac effects were observed in 3 singleton pregnancies, including the following: 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 1 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 the following: 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 1 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 delivery, and 26 infants were 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 1 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, Avilés 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), and 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 (Avilés 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 2 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, 1 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 to 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 81**). 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) (**Table 39**). 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 the following: 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 specified (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 81**). 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 US population (MacDorman and Kirmeyer 2005). The stillbirth rate for cytarabine was among the higher apparent rates when compared to other chemotherapy agents (see **Table 82** to **Table 86**). 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

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 40**.

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

Table 40: 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 (Cmax):	**[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.

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 because of 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 1,000 mg/kg bw) (Chaube 1973). Malformations of the forelimb, hindlimb, paws, and tail (kinky and short), as well as cleft palate, micrognathia, open eyes, encephalocele, and microcephaly were observed in rat fetuses following a single injection of 400 to 1,000 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 56 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

C, 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 2 pregnancies of the same patient (Dilek *et al.* 2006) and 1 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 on account of 1 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 to 33 weeks of gestation (mean=22 weeks) (Jameel and Jamil 2007); it was assumed that these 2 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 3 pregnancies exposed to dacarbazine. No malformations were observed in the 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 2 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 1 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 eighth 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 2 infants with gestational exposure to dacarbazine (**Table 41**). One infant had a floating thumb malformation on the left hand, involving the partial agenesis of a metacarpal and hypoplasia of 2 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).

Syndactyly of the fourth and fifth 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

Table 41: Major malformations observed following *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 2 phalanges	11% (1/9)
2nd and/or 3rd only	Syndactyly of fingers	2% (1/45)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 rate 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 2 liveborn infants. Plagiocephaly, a minor malformation, was reported in 1 infant with exposure in the second and third trimesters to dacarbazine, bleomycin, doxorubicin, and vinblastine (Cardonick *et al.* 2010). In addition, 1 infant had microphthalmia and severe hypermetropia, which was diagnosed at age 1 year (Li *et al.* 2007); the pregnancy was exposed in the first and second 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 1 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 on account of 1 set of twins) (**Table 82**). 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) **(Table 41)**. 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 1 infant with first-trimester exposure to dacarbazine. One newborn had a floating thumb malformation, which consisted of partial agenesis of a metacarpal bone and hypoplasia of 2 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 1 infant with exposure in the second and third trimesters to dacarbazine in polytherapy: syndactyly of the fourth and fifth 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

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 42**.

Table 42: 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 (Cmax):	**[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.

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 to 30.5 weeks gestation (Germann *et al.* 2004). Tissue samples were collected at 1 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 exposure was not identified, but they were presumed to be during organogenesis]**. Pregnant rats administered daunorubicin at 0.05 mg/kg bw (~0.01 times 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 (~one-half 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 rat dams were 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 (~one-third 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 (~one-twentieth 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 to 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 to 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 1 case in which cancer type was not specified.

A total of 108 conceptuses were exposed to daunorubicin, including 1 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 1 set of twins). Timing of exposure was not specified for 6 singleton pregnancies (6 conceptuses); however, it was assumed that 1 of these pregnancies was likely exposed in the second and/or third trimester with

the age of initiation of chemotherapy ranging from 12 to 33 weeks of gestation (mean=24 weeks) (Jameel and Jamil 2007). Thus, the total number of pregnancies exposed in the second and/or third trimester was calculated to be 84 (85 conceptuses), and timing of exposure was not specified for 5 singleton pregnancies (5 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 2 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 3 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 was 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), daunorubicin, cytarabine, 6-thioguanine, and vincristine (1 embryo) (Zuazu *et al.* 1991), daunorubicin, cytarabine, and all-*trans* retinoic acid (1 embryo), and 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 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 exposure, 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, and then 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 to daunorubicin and vincristine (Jameel and Jamil 2007); and in the third trimester 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 2 maternal and fetal deaths that occurred following exposure during the second trimester to daunorubicin, vincristine, and cytarabine (Greenlund *et al.* 2001) and 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 1 infant exposed during the first trimester (**Table 43**). One infant had skeletal malformations of the distal limbs and cranium, as well as 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).

Major malformations were reported in 3 liveborn infants following exposure to daunorubicin in the second and/or third trimester only. Polydactyly on 1 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 1 infant (Roy *et al.* 1989) following second-trimester exposure to daunorubicin, cytarabine, and 6-thioguanine. Hypospadias was reported in 1 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 in 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 the 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

Table 43: Major malformations observed following *in utero* exposure to daunorubicin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Mild hypotelorism, severebrachycephaly; hypoplasia of the anterior cranial base; supra-orbital structure, and naso-and orpharynx; premature closure of both coronal sutures and the metopic suture; bilateral 4-fingered hands with hypoplastic thumbs; bilateral absent radii; small ostium secundum type atrial septal defect	20% (1/5)
2nd and/or 3rd only	Polydactyly	4% (3/75)
	Down syndrome	
	Hypospadias	
Not specified	None	(0/5)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 1 fetus with poor growth (Roy *et al.* 1989) and 2 fetuses with a preterm cessation of fetal growth (Murray *et al.* 1994, Scherf and Price 1996). Polyhydramios occurred in 1 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 1 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 1 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 1 case, labor was induced because the mother was seriously ill (Roy *et al.* 1989). As mentioned above, toxemia due to preeclampsia caused 1 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 1 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.* 2009a), 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 2 children. At 13 months, 1 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 1 set of twins) (**Table 83**). 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) **(Table 43)**. 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 1 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 with developmental toxicity studies of cytarabine in laboratory animals (see Section **5.12.3**). 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 1 maternal and fetal death).

Major malformations were observed in 3 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 the cause of 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). 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 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 1 singleton pregnancy (Garcia *et al.* 1999), and 1 newborn was treated for congestive heart failure (Okun *et al.* 1979).

5.15 Docetaxel

5.15.1 Mechanism, route of administration, and indications

Table 44: Pharmacology of docetaxel in adult humans

Molecular weight:	807.885
Protein binding:	~94%-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 (Cmax):	**[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 44**.

Docetaxel is indicated for the treatment of breast cancer, non-small cell lung cancer, gastric adenocarcinoma, squamous cell carcinoma of the head and neck, 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 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 3 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/day in rats and 3.0 mg/kg bw/day in rabbits when administered during the period of organogenesis (one-fiftieth and one three-hundredth, respectively, the daily maximum recommended human dose on a mg/m² basis). Docetaxel did not induce teratogenic effects in fetuses, even at the highest doses intravenously administered to rat (1.8 mg/m²/day) or rabbit dams (1.2 mg/m²/day) (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 1 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 where 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 following gestational exposure to docetaxel.

Rate of Occurrence of Congenital Malformations

Major Malformations
Major malformations were observed in 2 liveborn infants exposed to docetaxel **(Table 45)**. No major malformations were observed in the 2 liveborn infants exposed to docetaxel during the first trimester.

Major malformations were observed in 2 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 because of 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 5% (1/19 conceptuses, based on 19 liveborn infants).

Minor Malformations
Two infants had minor malformations that resolved without treatment following gestational exposure to docetaxel. Suspected holoprosencephaly was

Table 45: Major malformations observed following *in utero* exposure to docetaxel

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	None	0% (0/2)
2nd and/or 3rd only	Pyloric stenosis	11% (1/19)
	Ventriculomegaly (diagnosed prior to chemotherapy)	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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), 3 weeks after initiation of doxorubicin and cyclophosphamide, and prior to administration of docetaxel monotherapy beginning at gestation week 26 and continuing 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 4 fetuses, including in 1 fetus where anhydramnios was diagnosed prior to chemotherapy (Rouzi *et al.* 2009) Two pregnancies with anhydramnios also had intrauterine growth restriction, and were co-exposed to trastuzumab in the second trimester (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 2 pregnancies (Potluri *et al.* 2006), including 1 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 delivered 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 2 newborns had health issues. Transient myelosuppression was reported for 2 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 84)**. 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) **(Table 45)**. 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 1 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 4 singleton pregnancies that experienced reductions in amniotic fluid following exposure to docetaxel, anhydramnios was likely caused by the co-administration of trastuzumab in 2 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 84**).

5.16 Doxorubicin

5.16.1 Mechanism of Action, Route of Administration, and Indications

Table 46: Pharmacology of doxorubicin in adult humans

Molecular weight:	543.5221
Protein binding:	70%-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/m²; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta
Time to peak, serum (Cmax):	**[Information not located]**
Excretion:	Feces (~40%-50% as unchanged drug); urine (~5%-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 46**.

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, and 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 1 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 one-fourteenth the human dose **[of 60-75 mg/m2]** based upon surface area) (Pharmacia & UpJohn Company 2010). The period of organogenesis was most vulnerable to doxorubicin exposure. For example, intraperitoneal injection of 1 to 2 mg doxorubicin/kg bw to pregnant Sprague Dawley rats on days 6 to 15 or 6 to 9 of gestation induced significantly more malformations than pregnant rats treated on gestation days 9 to 12 or 12 to 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 bw/day on days 6 to 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 to 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 to 10 µg/egg on day 1 or 2 were as follows: 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 the following: 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 as follows: Hodgkin lymphoma (52 cases), 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), 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 3 twin pregnancies (Nantel *et al.* 1990, Lycette *et al.* 2006, Cardonick *et al.* 2010) and 3 patients who had 2 pregnancies each (Avilés 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 on account of 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 gestational age at initiation of chemotherapy ranged from 11 to 34 weeks (median, 23 weeks) (Hahn *et al.* 2006) or 12 to 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 1 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 1 maternal/fetal death. One spontaneous abortion was reported following exposure to doxorubicin and vincristine during the first trimester, and no fetal data were provided (Peres *et al.* 2001). One spontaneous abortion was reported following exposure to doxorubicin, cytarabine, and vincristine, and no fetal data were provided (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 to 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 to 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 eighth month of pregnancy after second- and third-trimester exposure to bleomycin, vinblastine, and dacarbazine (Dilek *et al.* 2006).

In addition, 1 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

Major malformations were observed in 10 liveborn infants gestationally exposed to doxorubicin, including 5 infants exposed during the first trimester (Table 47). Skeletal malformations of the digits were reported in 3 infants with first-trimester exposure to doxorubicin. One infant exposed during the first trimester had a floating thumb malformation (e.g., partial agenesis of a metacarpal bone and hypoplasia of 2 phalanges) (Dilek *et al.* 2006); this infant was exposed prenatally to doxorubicin, bleomycin, vinblastine, and dacarbazine. Bilateral loss of radius and fifth 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 were 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).

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 fourth and fifth fingers occurred in 1 infant exposed in the second and third trimesters to doxorubicin, bleomycin, vinblastine, and dacarbazine (Cardonick

Table 47: Major malformations observed following *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 2 phalanges)	13% (5/39)
	Bilateral loss of radius and fifth 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	2% (6/383)
	Pyloric stenosis	
	Pulmonary fistula	
	Syndactyly of fingers (2 infants)	
	Down syndrome	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

et al. 2010). Bilateral partial syndactyly of digits 2 and 3 occurred in 1 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 1 infant each after second- and third-trimester exposure to doxorubicin, cyclophosphamide, and 5-fluorouracil (Hahn *et al.* 2006). Pyloric stenosis occurred in 1 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 the second and third trimesters to doxorubicin and cyclophosphamide (Van Calsteren *et al.* 2010a). Pectus excavatum occurred in 1 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 2 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 infant 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 2 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, 1 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 1 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 that also experienced premature rupture of membranes (Webb 1980, Karp *et al.* 1983, Meador *et al.* 1987). Transient preterm labor was reported in 2 pregnancies (Meyer-Wittkopf *et al.* 2001, Lycette *et al.* 2006). Fetal distress was reported in 2 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 2 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 1 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 (Avilés and Niz 1988, Nakajima *et al.* 2004, Cardonick *et al.* 2010), 2 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 infant 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 liveborn 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 2 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 4 neonates, including 2 infants with sepsis (Willemse *et al.* 1990, Cardonick *et al.* 2010), 1 infant with necrotizing enterocolitis (Garcia *et al.* 1999), and 1 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 2,860 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 2 children with speech delays, including 1 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 1 child of school age (Hahn *et al.* 2006). At age 5.8 years, 1 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 83**). 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) (**Table 47**). 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 1 infant was likely due to doxorubicin polytherapy, including co-treatments with 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, 3 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 because 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% (2/383 conceptuses, based on 380 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 48: 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 (Cmax):	**[Information not located]**
Excretion:	Feces (34%-35%); urine (20%-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 48**.

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 3 hours of intravenous dose administration to the mother (Van Calsteren *et al.* 2010b); 3 of the 8 fetal blood samples were below the lower limit of quantification. Levels of epirubicin reached up to 9 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 manufacturer's 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 post-implantation 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

the following: 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 were 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 to 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 cases and in the second and/or third trimester only in 60 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 first and second fingers of both hands, shortened second and third fingers on both hands, and osseous syndactyly of fourth and fifth metatarsal bones on both feet.

Spontaneous Fetal Death

Spontaneous fetal death occurred in 4 pregnancies exposed to epirubicin, including 2 spontaneous abortions and 2 stillbirths. No examination of the fetus was reported for the 2 spontaneous abortions that 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 2 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 3 liveborn infants and 1 induced abortus following *in utero* exposure to epirubicin (**Table 49**).

The only reported occurrence of major malformations following first-trimester exposure to epirubicin was in an induced abortus 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 first and second fingers of both hands, shortened second and third fingers on both hands, and osseous syndactyly of fourth and fifth 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).

Major malformations were observed in 3 liveborn infants in 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 to epirubicin and cyclophosphamide (Cardonick *et al.* 2010). Rectal atresia was observed in 1

Table 49: Major malformations observed following *in utero* exposure to epirubicin

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Micrognathia, skin syndactyly of first and second fingers of both hands, shortened second and third fingers on both hands, and osseous syndactyly of fourth and fifth metatarsal bones on both feet	20% (1/5)
2nd and/or 3rd only	Polycystic kidney	5% (3/58)
	Clubfoot	
	Rectal atresia	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

infant with gestational exposure to epirubicin mono-therapy 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 2 infants. One infant had a left eye hemangioma following exposure in the second and third trimesters to 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 1 pregnancy each. Spontaneous preterm labor preceded preterm delivery in 2 cases (Andreadis *et al.* 2004, Sharma *et al.* 2009). Intrauterine growth restriction due to placental insufficiency occurred in 1 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 3 infants, including respiratory distress (2 infants) (Ring *et al.* 2005b) and mild transient tachypnea requiring oxygen treatment (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 1 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 83**). 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 5% (3/63 conceptuses, based on 62 liveborn infants and examination of the fetus of 1 induced abortion)(**Table 49**). 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 1 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 because of 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 3 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 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

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 50**.

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 1 lactating patient. One case report measured etoposide in breast milk collected every 3 to 4 hours for 1 week beginning with the third of 5 daily doses of etoposide (80 mg/m^2) of a third 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.

Table 50: Pharmacology of etoposide in adult humans

Molecular weight:	588.5588
Protein binding:	94%-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 (Cmax):	**[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; Vd, volume of distribution.

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 (~one-twentieth 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 (~one-seventh and one-half of the human dose on a mg/m² 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 (one-sixteenth of the human dose on a mg/m² basis) administered intraperitoneally on days 6, 7, or 8 of gestation. When administered at 1.5 mg/kg intraperitoneally to pregnant 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 to 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), adeno-carcinoma (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 1 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 second and/or third 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 2 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 (**Table 51**). 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

Table 51: Major malformations observed following *in utero* exposure to etoposide

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	None	0% (0/4)
2nd and/or 3rd only	Cerebral atrophy and ventriculomegaly	5% (2/39)
	Neurofibromatosis and genetic hearing loss	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 1 stillbirth). No major malformations were reported in the 4 liveborn infants exposed to etoposide during the first trimester (0/4 conceptuses, based on 4 liveborn infants).

Minor Malformations
Minor malformations were observed in 1 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 2 singleton pregnancies (Horbelt *et al.* 1994, Siu *et al.* 2002, Benjapibal *et al.* 2010), premature rupture of membranes was reported in 1 singleton pregnancy (Ghaemmaghami and Hasanzadeh 2006), and spontaneous preterm labor was reported in 3 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 2 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 at 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 1 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 6 infants (Raffles *et al.* 1989, Murray *et al.* 1994, Scherf and Price 1996, Elit *et al.* 1999, Malhotra and Sood 2000, Lam 2006), including 1 infant with severe respiratory distress and pneumothorax (Raffles *et al.* 1989). Transient myelosuppression was reported in 6 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 intra-uterine 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 4 children. One child had genetic hearing loss and a spontaneous mutation for neurofibromatosis, and another child had motor/language delay at age 1 year (Cardonick *et al.* 2010). One 14-month-old infant had delayed motor skills, which the author suspected were due to premature birth (Lam 2006). Moderate sensorineural hearing loss, but normal neurodevelopmental progress, were reported for another 1-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 85**). 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% (2/43 conceptuses, based on 42 liveborn infants and examination of the fetus of 1 stillbirth)(**Table 51**). 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 1 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 38 liveborn infants and examination of the fetus of 1 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 exposure occurs 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

Table 52: Pharmacology of hydroxyurea in adult humans

Molecular weight:	76.0546
Protein binding:	**[Information not located]**
Metabolism:	60% via hepatic and gastro-intestinal 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 (Cmax):	1-4 hours
Excretion:	Urine

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

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 2010a); however, treatment with radiation is generally not recommended for pregnant women. Hydroxyurea is administered orally 1 to 3 times per day. Additional information on the pharmacology of hydroxyurea (parent compound) is located in **Table 52**.

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 2010a).

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 1 lactating patient (Sylvester *et al.* 1987). Milk samples were collected 2 hours following the last dose of the day in a hydroxyurea dosing regimen that included a 500 mg dose given 3 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 2010a). 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 2010a)).

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 2,000 mg/kg bw on gestation day 14 (Fritz and Hess 1980), with impaired cardiac development and neural tube defects in hamster fetuses after a single intravenous dose to the dam of 50 mg on gestation day 8 **[400-500 mg/kg bw/day based on bw of 100-125 gm]** (Ferm 1966), and with 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/day 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 on account of 1 set of twins). The drug was administered in the second and/or third trimester only in 19 cases (20 conceptuses on account of 1 set of twins), including 4 cases that began hydroxyurea treatment between gestation weeks 12 and 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, 1 case (2 conceptuses) that was switched from hydroxyurea to interferon alpha at gestation week 27, and 1 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 that 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 3 liveborn infants and examination of the fetus of 1 stillbirth) (**Table 53**).

Only 1 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).

Three major malformations were observed in 2 liveborn infants and 1 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,

Table 53: Major malformations observed following *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	14% (3/21)
	Hypospadias	
	Meningocele	

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 occurred in 1 pregnancy (Dilek *et al.* 2006), and spontaneous preterm labor occurred in 2 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 1 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 2 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 1 infant (Fitzgerald and McCann 1993). Normal growth and development were reported for all but 1 child (Doney *et al.* 1979). The remaining child had normal neurodevelopment at ages 4 and 13.5 months, but had growth parameters below the third 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 on account of 2 set of twins (**Table 81**). 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) (**Table 53**). 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 1 major malformation observed following exposure during the first trimester to hydroxyurea monotherapy (premature closure of cranial sutures in 1 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 3 major malformations observed following second- and/or third-trimester only exposure to

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hydroxyurea, 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 1 larger case series that included non-cancerous conditions, 1 major malformation (hip dysplasia, 1 infant) and 2 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 54**.

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

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.

Table 54: Pharmacology of idarubicin in adult humans

Molecular weight:	497.497
Protein binding:	94%-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 2,250 L); extensive tissue binding: CSF
Time to peak, serum (Cmax):	1-5 hours
Excretion:	Oral: Urine (~5% of dose; 0.5%-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.

5.20.3 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 1 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 3 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, and to 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 1 infant gestationally exposed to idarubicin (**Table 55**). This infant was

Table 55: Major malformations observed following *in utero* exposure to idarubicin

Trimester exposed	Major malformations observed	Apparent rate (affected/ total conceptuses[a])
During 1st	None	(0/1)
2nd and/or 3rd only	Ventricular septal defect, sacral dimple, short digits and limbs, dysplastic fingernails, pronounced frontal skull with macrognathia	7% (1/14)
Not specified	None	(0/5)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 to 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 1 stillbirth).

No major malformations were observed in 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 2 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, 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 3 pregnancies (Peres *et al.* 2001, Carradice *et al.* 2002, Matsuo *et al.* 2004). Intrauterine growth retardation was observed in 4 pregnancies (Claahsen *et al.* 1998, Peres *et al.* 2001, Baumgartner *et al.* 2009), including 1 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 1 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 3 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 1 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 1 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, 2 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 5 newborns (Achtari and Hohlfeld 2000, Carradice *et al.* 2002, Siu *et al.* 2002, Baumgartner *et al.* 2009, Ganzitti *et al.* 2010), including 1 preterm newborn in poor condition with pulmonary hypoplasia and bilateral pneumothoraces (Carradice *et al.* 2002). Cyanosis of the extremities at birth was observed in 1 infant

(Niedermeier *et al.* 2005). Myelosuppression occurred in 2 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 2 infants (Claahsen *et al.* 1998, Ganzitti *et al.* 2010). Finally, meconium-stained amniotic fluid was reported for 2 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, an 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, an 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 2 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 83**). 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) (**Table 55**). 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 1 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) and 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 2 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 is needed.

5.21 Ifosfamide

5.21.1 Mechanism of Action, Route of Administration, and Indications
Ifosfamide is a DNA alkylating agent that is a synthetic structural analogue of cyclophosphamide, another cytotoxic agent. It is thought to act by inhibiting cell proliferation by cross-linking with DNA, and it is cell-cycle non-specific. Ifosfamide is administered by intravenous injection. Additional information on the pharmacology of ifosfamide is located in **Table 56**.

Ifosfamide is indicated for treatment of germ cell testicular cancer (Baxter 2007). Other uses of ifosfamide not included in the prescribing information include the treatment of bone and soft tissue sarcomas, as well as lung, cervix, and ovarian cancers (*http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695023.html*).

Chemotherapeutic Agents

Table 56: 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 (3,800-5,000 mg/m^2): ~15 hours; lower dose (1,600-2,400 mg/m^2): ~7 hours
Distribution:	Vd: 5.7-49 L; penetrates CNS, but not in therapeutic levels
Time to peak, serum (Cmax):	**[Information not located]**
Excretion:	High dose (5,000 mg/m^2): Urine (70%-86%; 61% as unchanged drug); lower dose (1,600-2,400 mg/m^2): Urine (12%-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.

5.21.2 Evidence of Placental and Breast Milk Transport

Placental transfer of ifosfamide in humans was not detected in 1 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 2007).

5.21.3 Laboratory Animal Developmental Toxicity

Ifosfamide is reported to induce teratogenic effects in rats, mice, and rabbits (Baxter 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 2007).

Teratogenic effects of ifosfamide are also described in the peer-reviewed literature. As reviewed in 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 1 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 1 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 1 pregnancy exposed to ifosfamide. Stillbirth at gestation week 26 was reported for a singleton pregnancy 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 1 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, Merimsky *et al.* 1999, Nakajima *et al.* 2004). In addition, reductions in amniotic fluid and intrauterine growth restriction occurred in 1 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 2 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 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 1 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 82**). 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 1 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

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 57**.

Table 57: 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 (Cmax):	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 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 2,452 ng/mL in placental tissue at 12 hours after a maternal dose. Further evidence of fetal exposure was the presence of detectable levels of imatinib in umbilical cord blood (338.0 ng/mL) and in neonatal peripheral blood (478.0 ng/mL) at 16 hours post-maternal dose; maternal blood levels of imatinib were 1,562 ng/mL at 16 hours post-dose (Ali *et al.* 2009b). Imatinib is detected in human breast milk collected 10 to 16 hours following the 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), as well as 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 5 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 on account of 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 on account of 2 sets of twins (Meera *et al.* 2008, Pye *et al.* 2008). Imatinib was administered during the first trimester in 149 pregnancies (151 conceptuses on account of 2 sets of twins), including 16 singleton pregnancy 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 administered as monotherapy in 46 cases, and was administered as polytherapy in 2 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 on account of 1 set of 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, it was 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 as concerns 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 were available for any of the spontaneous abortions, which were exposed to imatinib monotherapy (1 pregnancy) (AlKindi *et al.* 2005) or to co-treatments that were not specified (18 pregnancies) (Pye *et al.* 2008).

Meningocele, a major malformation, was reported in 1 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

Major malformations following *in utero* exposure to imatinib were observed in 8 liveborn infants and the examination of 3 induced abortions and 1 stillbirth (**Table 58**). 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 either 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 1 side of the vertebrae), and 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 2 liveborn infants, including 1 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 1 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 were observed in a fetus from an induced abortion with no co-treatments during pregnancy. Abnormally high alpha fetoproteins were reported for an induced abortion; elevated alpha fetoproteins 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 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

Table 58: Major malformations observed following *in utero* exposure to imatinib

Trimester exposed	Major malformations observed	Apparent rate (affected/ total conceptuses[a])
During 1st	Small exomphalos and scoliosis	12% (12/100)
	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	
	Meninogcele	
	Warfarin embryopathy	
2nd and/or 3rd only	None	0% (0/6)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

on 95 liveborn infants and examination of the fetuses of 4 induced abortions and 1 stillbirth).

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 second and/or third trimester only 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 1 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 1 set of twins), 1 infant was delivered via induced vaginal delivery, and 3 infants were delivered via C-section (including 1 set of twins); route of delivery was not specified for 1 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 1 to 53 months. Age at follow-up was not noted for 2 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 2 sets of twins (157 conceptuses) (**Table 86**). 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) (**Table 58**). 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 fetoproteins (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 1 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 PDGFRα (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

Table 59: 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: 12-40 L
Time to peak, serum (Cmax):	IV: 30 minutes
Excretion:	Not detected in urine (catabolized in the kidney)

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

Alpha interferons are a family of naturally occurring proteins that inhibit viral replication, influence cellular protein production, elicit immunomodulatory effects, and cause anti-proliferative effects (Chard 1989, Ferrantini *et al.* 2007).

The exact mechanisms by which alpha interferons exert anti-tumor activity are 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 59**.

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 IU/mL) at 1 and 4 hours after administration of the drug at 19 and 24 weeks of gestation in 2 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 2 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 2 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 (1,551 versus 1,249 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/day (20-500 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/day (3-5 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 1 patient each with Hodgkin lymphoma and multiple myeloma.

A total of 41 pregnancies yielding 43 infants were born to these patients, including 2 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 on account of 1 set of twins) and in the second and third trimester only to 20 patients (21 conceptuses on account of 1 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), 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 (**Table 60**). Exomphalos, right renal agenesis, and hemivertebrae were observed in 1 infant who was exposed to interferon **[timing of exposure not**

Table 60: Major malformations observed following *in utero* exposure to interferon alpha

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Exomphalos, right renal agenesis, hemivertebrae	6% (1/20)
2nd and/or 3rd only	None	(0/21)
Not specified	None	(0/2)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

specified, but presumed to be during the first trimester] 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 2 other infants exposed to imatinib monotherapy in the first trimester had similar malformations. Thus, the adjusted 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 2 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 2 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 1 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 1 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 2 set of twins (43 conceptuses) (**Table 86**). 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) (**Table 60**). 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 1 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 61**.

Table 61: 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 third-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 (Cmax):	Oral: 1-2 hours; IM: 30-60 minutes
Excretion:	Urine: 80-90% as unchanged drug; 5-7% 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 noncancerous diseases, such as 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 1 case report, methotrexate was detected in cord blood at a concentration of 1.86×10^{-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 1 case. Johns *et al*. (1972) detected low levels of methotrexate in breast milk of a 1-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 to 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, as well as 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 intravenously 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 1 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), choriocarcinoma (6 cases, including 1 case each of the ovary, uterus, and vagina, respectively), and Ewing sarcoma (1 case). The cancer type was not specified for 1 case.

A total of 84 pregnancies (87 conceptuses) were exposed to methotrexate on account of 1 patient gestating 2 singleton pregnancies (Avilés and Niz 1988) and 3 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 on account of 3 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 1 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 first and second fingers of both hands, shortened second and third fingers on both hands, and osseous syndactyly of fourth and fifth 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 the following: 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 62**).

Major malformations were observed in a fetus from an induced abortion following exposure to methotrexate in the second trimester with co-treatments of 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 first and second fingers of both hands, shortened second and third fingers on both hands, and osseous syndactyly of fourth and fifth 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 3 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 2 infants: 1 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

Table 62: Major malformations observed following *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	Skin syndactyly of 1st and 2nd fingers, shortened 2nd and 3rd fingers, osseous syndactyly of 4th and 5th metatarsal bones, micrognathia	2% (1/58)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, and stillbirths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

chemotherapy exposure *in utero*. **[It is possible that 1 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 detected 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 2 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 2 singleton pregnancies (Matsouka *et al.* 2008), including 1 case of intrauterine growth restriction thought to be caused by placental insufficiency (Ring *et al.* 2005b). Transient oligohydramnios occurred in 1 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 1 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, Avilés and Niz 1988, Avilés *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 2 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 2 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 (Avilés 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, 1 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 fifth 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 methotrexate occurred in 85 pregnancies, including 3 sets of twins (88 conceptuses) (**Table 81**). 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) (**Table 62**). 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 1 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, as well as 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% (1/24 conceptuses, based on 23 liveborn infants and examination of the fetus of 1 stillbirth). In contrast, the adjusted apparent rate of major malformations possibly 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

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 63**.

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 in 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, respectively.

Table 63: 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: >1,000 L/m^2; distributes extensively into tissue (pleural fluid, kidney, thyroid, liver, heart) and red blood cells
Time to peak, serum (Cmax):	**[Information not located]**
Excretion:	Feces (25%); urine (6%-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 steady state.

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 occurred in rats and increased incidence of premature delivery in rabbits administered mitoxantrone during the period of organogenesis at ≥ 0. 1 mg/kg bw/day (1% of the recommended human dose on a body-surface-area 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 25). 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 1 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 2 pregnancies exposed to mitoxantrone, including 1 spontaneous abortion and 1 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 the patient 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 1 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 1 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 2 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, 1 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 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 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, 1 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 1 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 Outcomes For Mitoxantrone
In utero exposure to mitoxtantrone was reported for 17 singleton pregnancies (17 conceptuses) (**Table 83**).

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 64: 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 (Cmax):	**[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 pro-liferating cells (Merck 2010). Nitrogen mustard acts via the cross-linking of its active metabolites to DNA, which results in inhibition of DNA synthesis and func-tion (Perry and McKinney 2008). Nitrogen mustard is administered via intravenous injection. Additional information on the pharmacology of nitrogen mus-tard is located in **Table 64**.

Nitrogen mustard is indicated in the treatment of several types of cancer, such as Hodgkin lymphoma, lymphosarcoma, chronic myelocytic or chronic lym-phocytic 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 con-taining 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 mus-tard 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 to 0.7 mg/kg bw (Chaube *et al.* 1968). Malformations included the following: encephalo-cele or exencephaly, cleft palate, retarded or clubbed fore or rear leg, ectrodactyly, polydactyly, syndactyly, and brachydactyly, as well as 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 2 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 ret-rospective cohort studies (6 cases), and 1 retrospec-tive survey (1 case) (Appendix C, Table 24). Nitrogen mustard was used to treat Hodgkin lymphoma (28 cases) and acute lymphocytic leukemia (1 case). Can-cer type was not specified in 2 cases.

A total of 31 singleton pregnancies (31 concep-tuses) were exposed to nitrogen mustard. Nitrogen mustard was administered during the first trimester in 18 pregnancies (18 conceptuses) and in the sec-ond and/or third trimester only in 13 pregnancies (13 conceptuses). Nitrogen mustard was adminis-tered as monotherapy in 7 cases, including 2 cases co-administered radiation therapy (2 conceptuses) and 1 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, vin-cristine, 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 dur-ing 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 mus-tard, vincristine, and procarbazine (Blatt *et al.* 1980, Zemlickis *et al.* 1992b).

Spontaneous Fetal Death

Spontaneous abortion occurred in 2 pregnancies exposed to nitrogen mustard. A fetus from a spon-taneous 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
Major malformations were reported in 3 liveborn infants with gestational exposure to nitrogen mustard, including 2 liveborn infants exposed during the first trimester (**Table 65**). One newborn had 4 digits per foot, webbing between the third and fourth 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 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).

Bilateral syndactyly of digits 2 and 3 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 1 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 1 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 for 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 1 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

Table 65: Major malformations observed following *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 third and fourth digits, bowing of the right tibia, and an abnormal right pinna	13% (2/15)
	Hydrocephaly	
2nd and/or 3rd only	Syndactyly of digits 2 and3	8% (1/13)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 3 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, 1 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 82**). 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) (**Table 65**). 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 2 infants with first-trimester exposure. One newborn had 4 digits per foot, webbing between the third and fourth 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 13% (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 1 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

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 2010d). 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 66**.

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 2010d).

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 one-one hundredththe 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).

Table 66: Pharmacology of paclitaxel in adult humans

Molecular weight:	853.9129
Protein binding:	89%-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 (Cmax):	**[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 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 times more paclitaxel passed into the fetus compared to pregnant mice that were only exposed to paclitaxel at 1 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 sanctuary" 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 2010d). 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 2010d).

5.27.3 Laboratory Animal Developmental Toxicity

Paclitaxel is embroylethal in rabbits, mice, rats, and chicks as per the product label (Bristol-Myers Squibb 2010d). 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 2010d).

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 and implantation number, and it induced malformations at 2.0 mg/kg bw, including exencephaly/anencephaly, ventral wall defects, facial clefts, anophthalmia, diaphragmatic hernia, and defects 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 26). 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 on account of 2 sets 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 1 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

Major malformations were reported in 1 liveborn infant with gestational exposure to paclitaxel (**Table 67**). Pyloric stenosis was reported in an infant exposed in the second and third trimesters to polytherapy consisting of paclitaxel, doxorubicin, and cytarabine, and followed by docetaxel monotherapy (Cardonick *et al.* 2010).

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 1 pregnancy with normal placental function that experienced cessation

Table 67: Major malformations observed following *in utero* exposure to paclitaxel

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	No data	(0/0)
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. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

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 1 singleton pregnancy (Azim *et al.* 2009b), and 2 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 because of 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. 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 1 infant had neutropenia (Cardonick *et al.* 2010). Jaundice was reported in 2 infants (Cheung *et al.* 2009, Cardonick *et al.* 2010). Another infant had transient renal failure and 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 1. 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 2 sets of twins (39 conceptuses) (**Table 84**). 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) (**Table 67**). 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 1 liveborn infant 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 68: 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 (Cmax):	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 68**.

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 includes 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 to 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 embryolethal 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 to 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 embryolethality and malformations when administered during the period of organogenesis. Procarbazine also induced malformations when administered at doses of 5 to 10 mg/kg bw orally to pregnant rats on gestation days 8 to 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 Gestational Exposure and 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 27). Among these patients, procarbazine was used to treat Hodgkin lymphoma (28 cases), non-Hodgkin lymphoma (1 case), and diffuse histiocytic lymphoma (1 case). 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 with 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 (**Table 69**). One infant had only 4 toes on each foot with webbing between the third and fourth toes of the right foot, as well as 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, as well as co-treatment with vinblastine from the 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

<div style="text-align: right">Chemothera-
peutic Agents</div>

Table 69: Major malformations observed following *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 third and fourth toes on the right foot, an abnormal pinna and a bowed tibia on the right leg	27% (4/15)
	Cleft lip and cleft palate	
	Small secundum atrial septal defect	
	Hydrocephalus	
2nd and/or 3rd only	Bilateral syndactyly of digits 2 and 3	8% (1/12)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

liveborn infants and examination of the fetuses of 2 induced abortions).

Major malformations were observed in only 1 liveborn infant following exposure to procarbazine in the second and/or third trimester. Bilateral syndactyly of digits 2 and 3 was observed in 1 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 2 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 first trimester (through gestation day 38) (Wells *et al.* 1968). As mentioned above, the autopsies of 2 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 1 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 had 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 2 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 1 case at birth: villus degeneration and toxic vascular degeneration (Peres *et al.* 2001).

Infant Deaths

There were 3 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 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 82**). 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) (**Table 69**). 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), and 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 1 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 70: 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 (Cmax):	[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 70**.

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 1 case report, the cord blood level of rituximab (32.1 µg/mL) was 3 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 2 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 (4 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-cell 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 6 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 Gestational 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 1 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 1 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; no examination of the fetus was reported (Peterson *et al.* 2010).

Rate of Occurrence of Congenital Malformations

Major Malformations
Major malformations were observed in 1 liveborn following gestational exposure to rituximab (**Table 71**). 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 1 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) and spontaneous preterm labor (2 cases) (Decker *et al.* 2006), including 1 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 4 infants. A deficiency or absence of B-cells was reported for 2 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 2 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 2 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 86**). 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 4% (1/24 conceptuses, based on 23 liveborn infants and examination of the fetus of 1 stillbirth) (**Table 71**). As a point of reference, the

Table 71: Major malformations observed following *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. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

prevalence of major malformations in the general population of the US is 3% (Correa *et al.* 2007). Only 1 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 2 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, only the cases of cancer (i.e., Hodgkin or non-Hodgkin lymphoma patients) were included in the current NTP monograph (Chakravarty *et al.* 2011).

5.30 Tamoxifen

5.30.1 Mechanism of Action, Route of Administration, and Indications

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 72**.

Tamoxifen is indicated for the treatment of estrogen receptor-positive breast cancer (Savient 2005).

Table 72: 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 (Cmax):	~ 5 hours
Excretion:	Feces (26%-51%); urine (9%-13%)

Data from Brunton *et al*. (2011). Abbreviations: Cmax, time to reach maximal concentration in serum.

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 2 hours after delivery (Shaaban 1975).

5.30.3 Laboratory Animal Developmental Toxicity

Tamoxifen exposure during pregnancy induced teratogenicity in rats, but not in 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 that did not terminate pregnancy) (reviewed in Furr and Jordan 1984). No fetal abnormalities were noted among the offspring of pregnant marmosets treated with tamoxifen at 10 mg/kg bw/day (about twice 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 30). 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 1 set of twins (Beale *et al.* 2009). Tamoxifen was administered during the first trimester of pregnancy in 11 cases (12 conceptuses) and in the second and/or third trimester only in 3 cases. Tamoxifen was administered as monotherapy in 7 cases (7 conceptuses), including 1 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 73**).

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 1 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) and clubfoot, as well as 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 1 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 25% (3/12 conceptuses, based on 12 liveborn infants).

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 2 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 with 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 3 cases (Andreadis *et al.* 2004), including 1 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 1 case (Beale *et al.* 2009). Oligohydramnios or anhydramnios complicated 2 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).

Table 73: Major malformations observed following *in utero* exposure to tamoxifen

Trimester exposed	Major malformations observed	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. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

There were 15 liveborn infants with *in utero* exposure to tamoxifen. Early preterm delivery (<34 weeks) was reported for 7 infants (including 1 set of twins), late preterm delivery (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 5 infants, including 1 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 because of 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, 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 were 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 1 set of twins (14 conceptuses) (**Table 86**). 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 20% (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) (**Table 73**). Major malformations were observed in only 3 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 2 infants. Similar craniofacial malformations have been observed in cases of retinoic acid embryopathy, leading some researchers to hypothesize that tamoxifen may act on early organogenesis in a way similar to that of 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

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 74**.

Table 74: Pharmacology of trastuzumab in adult humans

Molecular weight:	145,531.5
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 (because of the large molecule size)
Time to peak, serum (Cmax):	**[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 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 and non-human primates, as well as for 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 anticancer 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 to 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 because of 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 endothelial 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 on account of 1 twin pregnancy (Beale *et al.* 2009). Trastuzumab was administered during the first trimester in 13 pregnancies (14 conceptuses on account of 1 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 2 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 because of an ectopic pregnancy (Berveiller *et al.* 2008); the authors stated that no histological examination of the embryo was 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 2 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 1 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 (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 2 infants (Bader *et al.* 2007b, Sekar and Stone 2007); placental function was only reported in 1 of these 2 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 1 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 2 infants.

Failure of kidney function occurred in 3 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 because of 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 because of multiple organ failure (Witzel *et al.* 2008). Pulmonary hypoplasia and atelectasis (collapse of lung tissue) were 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 the following: 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, 4 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 1. 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 because

of decreased kidney function (Weber-Schoendorfer and Schaefer 2008). One newborn, who had a very strong capillary leak at birth, ultimately died at 21 weeks because of 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 1 child (El-Safadi *et al.* 2012). All infants were healthy and without malformations, including 1 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 86**). Overall, the apparent rate of major malformations among all trastuzumab-exposed offspring, regardless of the nature of the malformations or the gestational stage at exposure, was 0% (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 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 3 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 because of 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

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 75**.

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).

Table 75: 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 (Cmax):	**[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; CNS, central nervous system; Vd, volume of distribution.

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 90 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 3 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 to 14 of gestation. Intraperitoneal injection of vinblastine (0.25 mg/kg bw/day) on gestation days 7 to 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 6-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 31). Among these patients, vinblastine was used to treat Hodgkin lymphoma (75 cases), ovarian cancer (3 cases), Kaposi sarcoma (1 case), and choriocarcinoma of the ovary (1 case); cancer type was not specified in 2 cases.

A total of 84 pregnancies and 85 conceptuses were exposed to vinblastine, with 2 cases having 2 singleton pregnancies (Dilek et al. 2006) (Nisce et al. 1986) and another case giving birth to twins (Cardonick et al. 2010). Vinblastine was administered during the first trimester in 18 pregnancies (18 conceptuses) and in the second and/or third trimester only in 58 pregnancies (59 conceptuses on account of 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 1 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 2 additional induced abortions, 1 following first-trimester exposure to vinblastine and procarbazine (Thomas and Peckham 1976), and the other following 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 1 spontaneous abortion and 1 stillbirth. A spontaneous abortion occurred at gestation week 6 following first-trimester exposure to 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 76**). Partial agenesis of metacarpal and hypoplasia of 2 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 the 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 fourth and fifth fingers, which required surgery following exposure in the second and third trimesters to vinblastine, doxorubicin, bleomycin, and dacarbazine (Cardonick *et al.* 2010). Bilateral syndactyly

Table 76: Major malformations observed following *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 2 phalanges	31% (5/16)
	Bilateral absence of 1 toe per foot, webbing between the third and fourth 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	
2nd and/or 3rd only	Clubfoot	5% (3/57)
	Syndactyly of the fingers (2 infants)	
Not specified	None	(0/8)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

of the second and third 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 1 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 2 infants, such as transient tachypnea (Malone *et al.* 1986) and, as mentioned above, respiratory distress (Thomas and Peckham 1976). Anemia was reported for 2 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 1 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 otitis media, and asthma (Cardonick *et al.* 2010). One healthy child tested positive for 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 84**). 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) (**Table 76**). 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 5 liveborn infants following exposure to vinblastine in the first trimester. The craniofacial malformations observed in 2 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 2 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

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 77**.

Vincristine is indicated for the treatment of acute leukemia (Hospira 2008a). 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).

Table 77: 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 (Cmax):	**[Information not located]**
Excretion:	Feces (~80%); urine (10%-20%; <1% as unchanged drug)

Data from Brunton *et al.* (2011). Abbreviations: Cmax, time to reach maximal concentration in serum.

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 of 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 a variety of laboratory animals (Hospira 2008a). Ferm *et al*. (1963) report a dose-dependent increase in the rate of fetal mortality of golden hamster dams administered vincristine at 0.1 to 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 1 of 3 dose levels of vincristine (0.125, 0.15, or 0.2 mg/kg bw) on the eighth and ninth days of gestation

(Tamaki *et al.* 1966). In the rat, fetal mortality was highest (48%-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 (0.5-0.7 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%-32% of surviving fetuses) in 3 strains of mice (C3H, DBA/2J, and Swiss ICR/ Ha strains) (Joneja and Ungthavorn 1969). Another study in Swiss albino mice reported that 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 an intravenous injection of 0.15 to 0.2 mg vincristine/kg on individual gestation days 27, 28, 29, 33, or 34 (Courtney and Valerio 1968). Syndactyly and encephalocele were observed in 2 monkey offspring exposed *in utero* to 0.175 mg vincristine/kg on gestation day 27 or 29, respectively. The remaining 3 monkey offspring were normal (Courtney and Valerio 1968). A subsequent developmental toxicity study in rhesus monkeys reported no teratogenic effects at doses 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 2 or 4 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 5 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 32). 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), and 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 1 patient who had 2 pregnancies (Avilés and Niz 1988) and 2 twin pregnancies (Turchi and Villasis 1988, Nantel *et al.* 1990). Vincristine was administered during the first trimester in 59 pregnancies (59 conceptuses). It was

administered in the second and/or third trimester only in 166 pregnancies (168 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 to 33 weeks of gestation (mean=24 weeks) (Jameel and Jamil 2007). Timing of exposure was not specified for 1 singleton pregnancy (1 conceptus). 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 2 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 6 singleton pregnancies exposed to vincristine during the first trimester, and no examination of the fetuses was 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); epirubicin and methotrexate (Giacalone *et al.* 1999); methotrexate and 6-mercaptopurine (Bergstrom and Altman 1998); and nitrogen mustard and procarbazine (Zemlickis *et al.* 1992b). One spontaneous abortion occurred following exposure to doxorubicin and cytarabine in the second trimester (Awidi *et al.* 1983).

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 the following: 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); 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 1 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 **[at approximately 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

Major malformations were reported in a total of 5 liveborn infants, including 4 liveborn infants exposed to vincristine during the first trimester (**Table 78**). One newborn had bilateral loss of the radius and the fifth 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 9% (4/44 conceptuses, based on 41 liveborn infants and examination of the fetuses of 2 induced abortions and 1 maternal/fetal death).

One major malformation occurred in 1 infant following exposure to vincristine in the second and/or third trimester only. Bilateral syndactyly of digits 2 and 3 occurred in an infant exposed during the second and third trimester to vincristine, nitrogen mustard, procarbazine, doxorubicin, bleomycin, and 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% (0/159 conceptuses, based on 154 liveborn infants and examination of the fetuses of 2 induced abortions and 3 stillbirths). No major malformations were reported in the 1 liveborn infant for which timing of exposure was not specified (Sears and Reid 1976).

Table 78: Major malformations observed following *in utero* exposure to vincristine

Trimester exposed	Major malformations observed	Apparent rate (affected/total conceptuses[a])
During 1st	Bilateral loss of the radius and the fifth digit and an atrial septal defect	9% (4/44)
	Cleft lip and cleft palate	
	Small secundum atrial septal defect	
	Hydrocephalus	
2nd and/or 3rd only	Syndactyly of fingers	1% (1/159)
Not specified	None	(0/1)

[a] Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

Minor Malformations

Two liveborn infants had minor malformations following exposure in the second and third trimesters. Pectus excavatum was reported in 1 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), 1 case of preeclampsia that 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, Weed *et al.* 1979, Tobias and Bloom 1980, Webb 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, Avasthi and Agarwal 1993, Martin *et al.* 1997, Decker *et al.* 2006, Brudie *et al.* 2011). 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 3 singleton pregnancies yielding liveborn infants (Lambert *et al.* 1991, Matsouka *et al.* 2008), including 1 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 3 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 2 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 1 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, Avilés 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 1 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 3 early preterm infants (Fernandez *et al.* 1989, Veneri *et al.* 1996, Achtari and Hohlfeld 2000). Cardiac effects were observed in 2 infants, including acute cardiac failure on day 1, which resolved in 3 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) (Avilés and Niz 1988), gastroenteritis resulting in the death of 2 infants at age 90 days (Avilés 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 2,860 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 (Avilés and Niz 1988). Gastroenteritis resulted in the death of 2 infants at age 90 days (Avilés 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), and 2 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 third percentile at 13.5 months (Doney *et al.* 1979). At 26 months, another child's body weight was <10th percentile, and the child had a constant cold (Gulati *et al.* 1986); however, the infant's immune function test and complete blood count were normal. In addition, 1 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 1 case with 2 singleton pregnancies and 2 sets of twins (**Table 84**). 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) (**Table 78**). 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 liveborn infants with exposure to vincristine during the first trimester. The cranial and skeletal malformations as well as 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% (4/42 conceptuses, based on 39 liveborn infants and examination of the fetuses of 2 induced abortions and 1 maternal/fetal death). Major malformations were observed in 1 liveborn infant exposed to vincristine in the second and third trimesters: bilateral syndactyly of digits 2 and 3 (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% (0/159 conceptuses, based on 154 liveborn infants and examination of the fetuses of 2 induced abortions and 3 stillbirths). No major malformations were reported in 1 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 79: Pharmacology of vinorelbine in adult humans

Molecular weight:	778.942
Protein binding:	80%-91%
Metabolism:	Extensively hepatic, via CYP3A4, to 2 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%-91%)
Time to peak, serum (Cmax):	**[Information not located]**
Excretion:	Feces (46%); urine (18%, 10%-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 79**.

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 embryolethal 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 one-third and one-sixth 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 33). Among these cases, vinorelbine was used to treat cancer of the

breast (11 cases) and lung (3 cases), as well as 1 case with rhabdomyosarcoma.

A total of 15 singleton pregnancies (15 conceptuses) were exposed to vinorelbine. Vinorelbine was administered during the first trimester in 1 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 1 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
One liveborn infant had major congenital malformations following gestational exposure to vinorelbine (**Table 80**). 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).

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 2 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, 1 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, 1 infant was delivered via induced vaginal delivery and 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 2 infants with anemia and 1 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 2 births of normal infants. One placenta had vacuolization and nuclear pleomorphism, extravillous trophoblasts of the chorion laeve, villous hypermaturity, and multifocal villous edema (Abellar et al. 2009). Another placenta had areas of infarction (Cardonick et al. 2010).

Table 80: Major malformations observed following 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	(0/14)

a Data based on liveborn infants as well as examination of the fetuses of induced abortions, spontaneous abortions, stillbirths, and maternal/fetal deaths. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by in utero exposure to chemotherapy.

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 84**). 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) (**Table 80**). 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 1 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 because of 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 to 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 1 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 2 fetuses exposed to vinorelbine polytherapy in the second or second and third trimesters were likely due to co-treatment with trastuzumab.

Table 81: Summary table of apparent rates 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)	2% (3/161)	--
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)	10% (4/42)	--	50% (2/4)	5% (2/44)	--
Cytarabine	17% (4/24)	4% (4/114)	(0/13)	20% (4/20)	8% (9/110)	8% (1/13)	19% (4/21)	4% (4/109)	(0/13)
Hydroxyurea	(0/13)	(0/20)	--	8% (1/13)	5% (1/20)	--	8% (1/13)	14% (3/21)	--
Methotrexate	14% (4/28)	(0/57)	--	4% (1/24)	2% (1/57)	--	4% (1/24)	2% (1/58)	--

[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 first trimester only and exposure in the first trimester and subsequent trimesters.

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f] (No. of affected/total liveborn infants)	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h] (No. of affected/total offspring)
	Early preterm	Late preterm	Term	Not specified		SGA	Normal	Not specified	
5-Fluorouracil	6% (11/171)	16% (27/171)	9% (16/171)	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)

[e] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[f] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation.
[g] 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.
[h] Denominator includes only the gestationally exposed offspring with follow-up evaluations.

Table 82: Summary table of apparent rates 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)	17% (1/6)	0% (0/5)
Carboplatin	--	6% (1/17)	--	--	(0/16)	--	--	6% (1/17)	--
Cisplatin	(0/4)	1% (1/100)	--	(0/4)	1% (1/99)	--	20% (1/5)	4% (4/99)	--
Cyclophosphamide	10% (4/43)	(0/367)	--	5% (2/39)	1% (4/367)	--	18% (7/40)	1% (5/366)	--
Dacarbazine	(0/8)	(0/47)	--	(0/8)	4% (2/47)	--	11% (1/9)	2% (1/45)	--
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)	8% (1/13)	--
Procarbazine	7% (1/14)	(0/12)	--	(0/13)	(0/12)	--	27% (4/15)	8% (1/12)	--

[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 first trimester only and exposure in the first trimester and subsequent trimesters.

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f] (No. of affected/total liveborn infants)	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h] (No. of affected/total offspring)
	Early preterm	Late preterm	Term	Not specified		SGA	Normal	Not specified	
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)

[e] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[f] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation.
[g] 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.
[h] Denominator includes only the gestationally exposed offspring with follow-up evaluations.

Chemothera-peutic Agents

Table 83: Summary table of apparent rates 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)	--	--	6% (1/16)	--
Daunorubicin	50% (4/8)	3% (2/78)	(0/5)	(0/4)	11% (8/76)	(0/5)	20% (1/5)	4% (3/75)	(0/5)
Doxorubicin	3% (1/39)	0.3% (1/386)	--	(0/38)	2% (6/385)	--	13% (5/39)	2% (6/383)	--
Epirubicin	33% (2/6)	(0/60)	--	(0/4)	3% (2/60)	--	20% (1/5)	5% (3/58)	--
Idarubicin	--	(0/15)	(0/5)	--	13% (2/15)	20% (1/5)	(0/1)	(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 ≥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 first trimester only and exposure in the first trimester and subsequent trimesters.

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f] (No. of affected/total liveborn infants)	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h] (No. of affected/total offspring)
	Early preterm	Late preterm	Term	Not specified		SGA	Normal	Not specified	
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)

[e] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[f] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation.
[g] 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.
[h] Denominator includes only the gestationally exposed offspring with follow-up evaluations.

NTP Monograph on Cancer Chemotherapy during Pregnancy

Table 84: Summary table of apparent rates 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)	11% (2/19)	--
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)	5% (3/57)	(0/8)
Vincristine	13% (6/48)	1% (1/164)	(0/1)	(0/42)	5% (8/163)	(0/1)	9% (4/44)	1% (1/159)	(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 first trimester only and exposure in the first trimester and subsequent trimesters.

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f] (No. of affected/total liveborn infants)	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h] (No. of affected/total offspring)
	Early preterm	Late preterm	Term	Not specified		SGA	Normal	Not specified	
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)

[e] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[f] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation.
[g] 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.
[h] Denominator includes only the gestationally exposed offspring with follow-up evaluations.

Table 85: Summary table of apparent rates 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)	5% (4/80)	--
Topoisomerase II inhibitor									
Etoposide	(0/4)	(0/40)	--	(0/4)	5% (2/40)	--	(0/4)	5% (2/39)	--

[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 first trimester only and exposure in the first trimester and subsequent trimesters.

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f] (No. of affected/total liveborn infants)	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h] (No. of affected/total offspring)
	Early preterm	Late preterm	Term	Not specified		SGA	Normal	Not specified	
Oxygen radical generator									
Bleomycin	12% (11/94)	17% (16/94)	39% (37/94)	32% (30/94)	10% (9/94)	13% (12/94)	69% (65/94)	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)

[e] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[f] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation.
[g] 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.
[h] Denominator includes only the gestationally exposed offspring with follow-up evaluations.

Table 86: Summary table of apparent rates 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)	4% (1/24)	--
Imatinib	17% (19/115)	(0/6)	--	1% (1/96)	(0/6)	--	12% (12/100)	(0/6)	--
Interferon alpha	(0/20)	(0/21)	(0/2)	(0/20)	(0/21)	(0/2)	5% (1/20)	(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.
[d] Includes exposures in the first trimester only and exposure in the first trimester and subsequent trimesters.

Agent	Timing of birth[e] (No. of affected/total liveborn infants)				Spontaneous preterm birth[f] (No. of affected/total liveborn infants)	Body weight at birth[g] (No. of affected/total liveborn infants)			Adverse health effects at follow-up[h] (No. of affected/total offspring)
	Early preterm	Late preterm	Term	Not specified		SGA	Normal	Not specified	
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)

[e] Early preterm is <34 weeks of gestation, late preterm is 34 to <37 weeks of gestation, and term is ≥37 weeks of gestation.
[f] Spontaneous preterm birth is defined as spontaneous vaginal births at >37 weeks of gestation.
[g] 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.
[h] Denominator includes only the gestationally exposed offspring with follow-up evaluations.

6.0 DISCUSSION

6.1 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 because of 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% (62/1,156, conceptuses based on 1,118 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 US 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, clubfoot, 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.

A review of the data by individual chemotherapeutic agent shows that the apparent rates of major malformations attributed to some agents were higher than others in the first trimester (**Figure 1**). For example, the apparent rates of major malformations were higher following exposure to cyclophosphamide (18%, 7/40 conceptuses) and 5-fluorouracil (31%, 4/13 conceptuses) compared to interferon alpha (5%, 1/20 conceptuses). However, these data are challenging to interpret because of differences in the timing of exposure in relation to the period of organogenesis, the small sample size, and the fact that combination therapies employ agents of various mechanisms of action. Generally, there were no differences in rates

of major malformations in comparisons of the data by classes of agents working via similar mechanisms of action (see **Table 81** to **Table 86**). 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 is 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) has 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 reduce side effects in cancer patients. Similar to the animal data, there were no major malformations observed in liveborn infants gestationally exposed to trastuzumab reviewed in the NTP monograph. For rituximab, 1 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 2 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).

6.2 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% confidence interval, 10%-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 US from 1990 to 2004 (0.3%-0.4%) (MacDorman and Kirmeyer 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).

6.3 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% (33/1,118 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

Figure 1: Apparent rates of major malformations (±95% confidence interval) reported following cancer chemotherapy use during pregnancy. Data are presented by individual agent, combining mono- and polytherapy exposure.

Figure 1 (continued)

Agent	Trimester Exposed	% Malformed ± CI [b]
Etoposide	During 1st [a] 2nd and/or 3rd Only	0.0 ± 0.0 (0/4) 5.1 ± 6.9 (2/39)
Hydroxyurea	During 1st 2nd and/or 3rd Only	7.7 ± 14.5 (1/13) 14.3 ± 15.0 (3/21)
Idarubicin	During 1st 2nd and/or 3rd Only	No Data 7.1 ± 13.5 (1/14)
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	12.0 ± 6.4 (12/100) 0.0 ± 0.0 (0/6)
Interferon alpha	During 1st 2nd and/or 3rd Only	5.0 ± 9.6 (1/20) 0.0 ± 0.0 (0/21)
Methotrexate	During 1st 2nd and/or 3rd Only	4.2 ± 8.0 (1/24) 1.7 ± 3.4 (1/58)
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) 7.7 ± 14.5 (1/13)
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) 8.3 ± 15.6 (1/12)
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) 5.3 ± 5.8 (3/57)
Vincristine	During 1st 2nd and/or 3rd Only	9.1 ± 8.5 (4/44) 0.6 ± 1.2 (1/159)
Vinorelbine	During 1st 2nd and/or 3rd Only	100.0 ± 0.0 (1/1) 0.0 ± 0.0 (0/14)

Legend:
- 3% Prevalence of birth defects in general population
- Exposure during 1st trimester
- Exposure following 2nd and/or 3rd trimester only

Percent Malformed (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100)

[a] 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%. These data are raw (unadjusted) apparent rates; whereas, the table in the prepublication copy reported adjusted apparent rates. Malformations may or may not have been caused by *in utero* exposure to chemotherapy.

fluid were exposed to trastuzumab (42%, 14/33 live-born 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. 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).

6.4 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 a 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% (97/1,118 liveborn infants). In a review of 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 the following: 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.

6.5 Newborn Health Issues

6.5.1 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 (<10th percentile body weight for gestational age). The data were insufficient, but suggestive, concerning the effects of chemotherapy for the treatment of cancer during pregnancy with respect to impaired fetal growth. The apparent rate of small for gestational age newborns following gestational exposure to chemotherapy was 8% (90/1,118 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), and because many studies do not provide information on body weight (e.g., no body weight data or body weight and gestational age data were provided for 395 of 1,118 conceptuses in the NTP monograph). Small for gestational age infants were 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 1 large prospective series, small for gestational age infants 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%).

As concerns 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 animals that were administered these agents (see Section **5.8** and Section **5.15**). While it is possible that cancer chemotherapy during pregnancy may negatively affect fetal growth, more research on cancer subtypes and treatment regimens is 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).

6.5.2 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 1,118 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 3 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 determine 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, given that complete blood counts are not regularly evaluated in healthy newborns (Christensen *et al.* 2009).

6.5.3 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 1,118 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 be limited to 1 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 mitoxantrone (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 1 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 1 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).

6.6 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 (670/1,118 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, 98% (n=276/282) of children exposed *in utero* to cyclophosphamide had normal growth and development at ages ranging from 6 months to 22 years (age at their last follow-up evaluation) (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 1 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 and 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 4 infants (Ruiz Reyes and Tamayo Perez 1961, Avilés *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 because of 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 to 5 years of age, 59 children (13%) at >5 to 12 years of age, 16 children (4%) at >12 to 17 years of age, and 3 children (1%) at >17 to 22 years of age. The few studies that 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, Avilés *et al.* 2012). However, the authors of 1 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 intelligence quotient (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 2 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 (1966-2001) 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 1 month to 22 years, and the children were 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 (Avilés and Niz 1988, Avilés *et al.* 1991, Avilés and Neri 2001, Avilés *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 (Avilés 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, and 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, 16 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, as well as fractional shortening of the left ventricle, and they selected an fractional shortening value of <28% to define the presence of cardiac toxicity. The authors report that echocardiograms provided no evidence of cardiac disease and that fractional shortening 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, as well as a blood pool Doppler to assess diastolic function; echocardiographic data were compared to a matched control group. The children ranged in age from 2 to 66 months. Three children born prematurely showed neurologic abnormalities: 1 born at 32 weeks had a persistent asymmetric tonic neck reflex and delayed visual fixation at 10 weeks, 1 born at 28 weeks had a minor delay in expressive language development at 21 months, and 1 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 3 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, 16.8-211.6 months). The authors concluded that for all the health endpoints assessed, the children exposed prenatally to chemotherapy were not different from

Discussion

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 at 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 are 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 is 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).

6.7   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 the following:

- **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 of 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 were carefully examined and its condition reported, it would provide additional information of value to analyses such as 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 regimens 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, which 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 patients treated for breast cancer with 5-fluorouracil, epirubicin, 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 2 registries of patients with cancer during pregnancy in the US: at Cooper University Hospital in Camden, New Jersey, coordinated by Dr. Elyce Cardonick (*www.cancerandpregnancy.com*), and at the University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma, coordinated by Dr. John Mulvihill. In addition, there are at least 2 registries for such patients outside of the US: at the Toronto Hospital of Sick Children in Ontario, Canada (*www. MotherRisk.com*), and at the University of Frankfurt and German Breast Group (*http://www.german-breastgroup.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 US 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 outcomes 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) (Appendix F). 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.

Discussion

7.0 REFERENCES

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