NTP
National Toxicology Program

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

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Agent-Specific Chapters

Cancer Chemotherapy Use during Pregnancy

Agent-specific chapters

- Purpose:
  - provide pregnancy outcome data and background information on an individual chemotherapy agent basis
    - For agents with greater than 10 cases reported
    - Pregnancy outcome data are summarized from Appendix tables specific to each individual agent
      - Cases included single agent and in combination therapy exposure
- Structure:
  - Mechanism of action, route of administration, and indications
  - Evidence of placental and breast milk transport
  - Laboratory animal developmental toxicity
  - Human gestational exposure and effects
  - Summary of pregnancy outcomes

Anti-metabolites

- Background information

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
5-Fluorouracil	Inhibits thymidine synthase	--	Yes	--	--	Yes	Yes
6-Mercaptopurine	Inhibits purine synthesis; nucleotide interconversion	Yes (low)	--	Yes (low)	--	Yes	Yes
6-Thioguanine	Inhibits purine synthesis; nucleotide interconversion	Yes (low)	--	Yes (low)	--	Yes	Yes
Cytarabine	Inhibits DNA polymerase	--	Yes	--	--	Yes	Yes
Hydroxyurea	Inhibits ribonucleotide reductase	--	Yes	Yes	--	Yes	Yes
Methotrexate	Inhibits dihydrofolic acid reductase	Yes	--	Yes	--	Yes	Yes

-- indicates no data; low indicates low levels

Anti-metabolites: Summary

- All data are affected/total

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Stillbirths
	During 1st	2nd and/or 3rd only		
5-Fluorouracil	26.7% (4/15)	1.3% (2/160)	1.7% (3/175)	0.6% (1/175)
6-Mercaptopurine	5.3% (2/38)	0.0% (0/42)	7.1% (6/84)	3.6% (3/84)
6-Thioguanine	28.6% (2/7)	0.0% (0/43)	2.0% (1/50)	10% (5/50)
Cytarabine	12.5% (4/32)	0.0% (0/118)	4.0% (6/151)	8.6% (13/151)
Hydroxyurea	2.3% (1/43)	4.3% (1/23)	1.5% (1/68)	7.4% (5/68)
Methotrexate	3.4% (1/29)	0.0% (0/54)	4.8% (4/83)	2.4% (2/83)

Agent	Stillborn and liveborn pregnancies		Stillborn and liveborn conceptuses	Liveborn infants			Children
	↓ in Amniotic fluid	Spontaneous preterm labor	IUGR	SGA	Myelo-suppression	Cardio-toxicity	Health effects at follow-up
5-Fluorouracil	1.2% (2/168)	3.6% (6/168)	1.2% (2/169)	3.0% (5/169)	Yes (5)	No	4/129
6-Mercaptopurine	1.3% (1/75)	17.3% (13/75)	1.3% (1/76)	0.0% (0/73)	Yes (5)	No	1/51
6-Thioguanine	2.3% (1/44)	11.4% (5/44)	4.7% (2/44)	0.0% (0/39)	Yes (3)	No	2/32
Cytarabine	4.7% (6/128)	7.0% (9/128)	7.8% (10/128)	0.0% (0/116)	Yes (12)	Yes (2)	4/77
Hydroxyurea	0.0% (0/57)	3.5% (2/57)	3.3% (2/60)	0.0% (0/55)	No	No	1/22
Methotrexate	1.4% (1/73)	12.3% (9/73)	2.6% (2/76)	4.1% (3/74)	Yes (5)	No	2/51

Anti-metabolites: Summary

- All data are affected/total
- Preliminary revised data (in red):
  - Major malformations minus fetal deaths without autopsy data
  - Spontaneous fetal death minus induced abortions and other fetal deaths

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Stillbirths
	During 1st	2nd and/or 3rd only		
5-Fluorouracil	26.7% (4/15) 36.4% (4/11)	1.3% (2/160)	1.7% (3/175) 1.7% (3/173)	0.6% (1/175) 0.6% (1/174)
6-Mercaptopurine	5.3% (2/38) 6.1% (2/33)	0.0% (0/42) 0% (0/40)	7.1% (6/84) 6.1% (5/82)	3.6% (3/84) 2.5% (2/81)
6-Thioguanine	28.6% (2/7) 40.0% (2/5)	0.0% (0/43) 0% (0/37)	2.0% (1/50) 6.5% (3/46)	10% (5/50) 8.9% (4/45)
Cytarabine	12.5% (4/32) 19% (4/21)	0.0% (0/118) 0% (0/107)	4.0% (6/151) 4.4% (6/136)	8.6% (13/151) 8.7% (12/138)
Hydroxyurea	2.3% (1/43) 2.8% (1/36)	4.3% (1/23)	1.5% (1/68) 1.6% (1/61)	7.4% (5/68) 7.9% (5/63)
Methotrexate	3.4% (1/29) 4.2% (1/24)	0.0% (0/54)	4.8% (4/83) 4.9% (4/81)	2.4% (2/83) 1.2% (1/82)

Charge questions for each Agent-Specific Summary:

1. Please comment on whether the scientific information in the text and table is technically correct, clearly stated, and objectively presented. Please provide additional references and/or specific comments to improve the text or tables.
2. Please comment on whether the summary text at the end of each section is technically correct, clearly stated, and objectively presented. Please identify any changes that might improve the summary.

DNA-alkylating agents

- Background information

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
Busulfan	Forms DNA cross-links, inhibits DNA synthesis and function	--	--	--	--	Yes	--
Cyclophosphamide	Forms DNA cross-links, inhibits DNA synthesis and function	Yes	Yes	Yes	--	Yes	Yes
Dacarbazine	Forms DNA cross-links, inhibits DNA synthesis and function	--	--	--	--	Yes	Yes
Ifosfamide	Forms DNA cross-links, inhibits DNA synthesis and function	--	--	Yes	--	Yes	Yes
Nitrogen mustard	Forms DNA cross-links, inhibits DNA synthesis and function	--	--	--	--	Yes	--
Procarbazine	Inhibits transmethylation, free radical damage to DNA	--	Yes	--	--	Yes	Yes

-- indicates no data

DNA alkylating agents: Summary

- All data are affected/total

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Still births
	During 1st	2nd and/or 3rd only		
Busulfan	15.0% (3/20)	20.0% (1/5)	3.2% (1/31)	0.0% (0/31)
Cyclophosphamide	15.2% (7/46)	0.8% (3/362)	1.2% (5/408)	1.2% (5/408)
Dacarbazine	11.1% (1/9)	0.0% (0/48)	1.8% (1/57)	1.8% (1/57)
Ifosfamide	0.0% (0/1)	0.0% (0/10)	0% (0/1)	9.1% (1/11)
Nitrogen mustard	11.8% (2/17)	0.0% (0/13)	6.7% (2/30)	0.0% (0/30)
Procarbazine	21.1% (4/19)	0.0% (0/12)	3.2% (1/31)	0.0% (0/31)

Agent	Stillborn and liveborn pregnancies		Stillborn and liveborn conceptuses	Liveborn infants			Children
	↓ in Amniotic fluid	Spontaneous preterm labor	IUGR	SGA	Myelo-suppression	Cardio-toxicity	Health effects at follow-up
Busulfan	0.0% (0/28)	7.1% (2/28)	0.0% (0/28)	0.0% (0/28)	Yes (7)	No	1/22
Cyclophosphamide	1.3% (5/391)	6.1% (24/391)	1.0% (4/394)	3.1% (12/389)	Yes (19)	Yes (2)	8/282
Dacarbazine	0.0% (1/51)	0.0% (0/52)	3.8% (2/53)	1.9% (1/52)	No	No	0/38
Ifosfamide	36.4% (4/11)	0.0% (0/11)	36.4% (4/11)	0.0% (0/10)	No	No	1/8
Nitrogen mustard	0.0% (0/24)	4.2% (1/24)	0.0% (0/24)	0.0% (0/24)	No	No	0/15
Procarbazine	1.4% (1/73)	4.2% (1/24)	0.0% (0/24)	0.0% (0/24)	No	No	0/13

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DNA intercalating/cross-linking agents

- Background information

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
Actinomycin D	Binds to DNA, inhibits RNA synthesis	--	Yes	--	--	Yes	--
Carboplatin	Forms interstrand crosslinks in DNA, causes DNA strand breaks	Yes	Yes	--	--	Yes	Yes
Cisplatin	Form DNA cross-links, causes DNA strand breaks	Yes	Yes	Maybe	--	Yes	Yes
Daunorubicin	Binds to DNA, inhibits DNA synthesis and function	Yes	--	--	--	Yes	Yes
Doxorubicin	Binds to DNA, inhibits DNA and RNA synthesis	Yes	Yes	Yes	--	Yes	Yes
Epirubicin	Binds to DNA, inhibits DNA and RNA synthesis	--	Yes	--	Yes	Yes	Yes
Idarubicin	Binds to DNA, inhibits DNA and RNA synthesis, topoisomerase II inhibitor	--	--	--	--	Yes	Yes
Mitoxantrone	Binds to DNA causes strand breaks, topoisomerase II inhibitor	--	--	Yes	--	No (only tested at low doses)	No (only tested at low doses)

-- indicates no data

DNA intercalating/cross-linking agents: Summary

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Stillbirths
	During 1st	2nd and/or 3rd only		
Actinomycin D	0.0% (0/0)	0.0% (0/13)	0.0% (0/13)	0.0% (0/13)
Carboplatin	NA	0.0% (0/17)	5.9% (1/17)	0.0% (0/17)
Cisplatin	0.0% (0/4)	1.0% (1/97)	1.0% (1/101)	1.0% (1/101)
Daunorubicin	5.6% (1/18)	0.0% (0/84)	4.7% (5/106)	9.4% (10/106)
Doxorubicin	9.5% (4/42)	0.5% (2/378)	0.7% (3/420)	1.2% (5/420)
Epirubicin	14.3% (1/7)	3.3% (2/61)	2.9% (2/69)	2.9% (2/69)
Idarubicin	0.0% (0/1)	0.0% (0/16)	0.0% (0/22)	13.6% (3/22)
Mitoxantrone	0.0% (0/1)	0.0% (0/12)	5.9% (1/17)	5.9% (1/17)

Agent	Stillborn and liveborn pregnancies		Stillborn and liveborn conceptuses	Liveborn infants			Children
	↓ in Amniotic fluid	Spontaneous preterm labor	IUGR	SGA	Myelo-suppression	Cardio-toxicity	Health effects at follow-up
Actinomycin D	7.7% (1/13)	23.1% (3/13)	7.7% (1/13)	0.0% (0/13)	No	No	0/8
Carboplatin	6.3% (1/16)	6.3% (1/16)	6.3% (1/16)	6.3% (1/16)	No	No	1/15
Cisplatin	4.1% (4/97)	5.2% (5/97)	7.1% (7/99)	2.0% (2/98)	Yes (7)	Yes (1)	2/68
Daunorubicin	3.6% (3/84)	8.3% (7/84)	7.1% (6/85)	0.0% (0/75)	Yes (9)	Yes (1)	2/48
Doxorubicin	1.5% (6/410)	3.9% (16/410)	1.9% (8/413)	2.9% (12/408)	Yes (10)	No	7/312
Epirubicin	0.0% (0/66)	3% (2/66)	1.5% (1/66)	0.0% (0/64)	Yes (2)	No	0/48
Idarubicin	15.8% (3/19)	0.0% (0/19)	21.1% (4/19)	6.3% (1/16)	Yes (2)	Yes (1)	1/11
Mitoxantrone	6.7% (1/15)	6.7% (1/15)	20.0% (3/15)	7.1% (1/14)	Yes (4)	Yes (2)	1/13

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Microtubule function inhibitors

- Background information

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
Docetaxel	Binds to microtubules, inhibits their polymerization	--	Yes	--	--	No	Yes
Paclitaxel	Binds to microtubules, inhibits their polymerization	--	No	--	Yes	Yes	Yes
Vinblastine	Binds to microtubules, inhibits their polymerization	--	Yes	--	--	Yes	Yes
Vincristine	Binds to microtubules, inhibits their polymerization	--	--	--	--	Yes	Yes
Vinorelbine	Binds to microtubules, inhibits their polymerization	--	Yes	--	--	Yes	Yes

-- indicates no data

Microtubule function inhibitors: Summary

- All data are affected/total

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Stillbirths
	During 1st	2nd and/or 3rd only		
Docetaxel	0.0% (0/1)	5.3% (1/19)	0.0% (0/20)	0.0% (0/20)
Paclitaxel	NA	3.2% (1/31)	0.0% (0.31)	0.0% (0/31)
Vinblastine	31.3% (5/16)	0.0% (0/55)	1.4% (1/73)	1.4% (1/73)
Vincristine	7.1% (4/56)	0.0% (0/167)	3.4% (6/223)	3.6% (8/223)
Vinorelbine	100.0% (1/1)	0.0% (0/14)	0.0% (0/15)	0.0% (0/15)

Agent	Stillborn and liveborn pregnancies		Stillborn and liveborn conceptuses	Liveborn infants			Children
	↓ in Amniotic fluid	Spontaneous preterm labor	IUGR	SGA	Myelo-suppression	Cardio-toxicity	Health effects at follow-up
Docetaxel	15.0% (3/20)	0.0% (0/20)	10.0% (2/20)	0.0% (0/20)	Yes (1)	No	0/13
Paclitaxel	6.5% (2/31)	9.7% (3/31)	3.2% (1/31)	3.2% (1/31)	Yes (2)	No	0/28
Vinblastine	1.5% (1/68)	1.5% (1/68)	2.9% (2/69)	1.5% (1/68)	No	No	0/40
Vincristine	1.5% (3/199)	8.5% (17/199)	2.0% (4/201)	1.5% (3/193)	Yes (11)	Yes (2)	5/135
Vinorelbine	13.3% (2/15)	0.0% (0/15)	0.0% (0/15)	0.0% (0/15)	Yes (3)	No	0/12

Charge questions for Chemotherapeutic Agents:

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2. Please comment on whether the summary text at the end of each section is technically correct, clearly stated, and objectively presented. Please identify any changes that might improve the summary.

Topoisomerase II inhibitor and oxygen free radical generator

- Background information

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
Etoposide	Topoisomerase II inhibitor	--	--	Yes	--	Yes	Yes

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
Bleomycin	Oxygen free radical generator, DNA strand breaks	--	--	--	--	Yes	Yes

-- indicates no data

Topoisomerase II inhibitor and oxygen free radical generator

- All data are affected/total

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Stillbirths
	During 1st	2nd and/or 3rd only		
Topoisomerase II inhibitor				
Etoposide	0.0% (0/3)	2.6% (1/39)	0.0% (0/42)	4.8% (2/42)
Oxygen free radical generator				
Bleomycin	6.7% (1/15)	1.3% (1/76)	0.0% (0/95)	1.1% (1/95)

Agent	Stillborn and liveborn pregnancies		Stillborn and liveborn conceptuses	Liveborn infants			Children
	↓ in Amniotic fluid	Spontaneous preterm labor	IUGR	SGA	Myelo-suppression	Cardio-toxicity	Health effects at follow-up
Topoisomerase II inhibitor							
Etoposide	9.8% (4/41)	7.3% (3/41)	22.0% (9/41)	2.6% (1/39)	Yes (6)	No	4/25
Oxygen free radical generator							
Bleomycin	2.2% (2/91)	4.4% (4/91)	6.5% (6/93)	2.2% (2/92)	Yes (2)	No	2/72

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Targeted therapies

- Background information

Agent	Mechanism of action	Placental Transport		Breast Milk Transport		Developmental toxicity in animals	
		Human	Animal	Human	Animal	Malfor-mations	Embryo-toxicity
All-*trans* retinoic acid	Induce cytodifferentiation and decrease proliferation of cancer cells	Yes	--	--	--	Yes	Yes
Imatinib	Protein kinase inhibitor	Yes	--	Yes	--	Yes	Yes
Interferon alpha	Influence cellular protein production, elicit immunomodulatory effects, and cause anti-proliferative effects	No	--	Yes	--	No	Yes
Rituximab	Monoclonal antibody against CD20 antigen on B lymphocytes	Yes	--		Yes	No	No
Tamoxifen	Antiestrogen; binds to estrogen receptor	--	--	--	--	Yes	Yes
Trastuzumab	Monoclonal antibody to HER2; blocks activation of its tyrosine kinase	--	Yes	--	Yes	No	No

-- indicates no data

Targeted Therapies: Summary

- All data are affected/total

Agent	Conceptuses			
	Major Malformations (by trimester)		Spontaneous abortion	Stillbirths
	During 1st	2nd and/or 3rd only		
All-*trans* retinoic acid	0.0% (0/5)	0.0% (0/24)	3.4% (1/29)	3.4% (1/29)
Imatinib	7.9% (12/152)	0.0% (0/5)	12.1% (19/157)	1.3% (2/157)
Interferon alpha	4.8% (1/21)	0.0% (0/20)	0.0% (0/43)	0.0% (0/43)
Rituximab	16.7% (1/6)	0.0% (0/18)	4.2% (1/24)	8.3% (2/24)
Tamoxifen	27.3% (3/11)	0.0% (0/3)	0.0% (0/14)	0.0% (0/14)
Trastuzumab	0.0% (0/14)	0.0% (0/6)	0.0% (0/20)	0.0% (0/20)

Agent	Stillborn and liveborn pregnancies		Stillborn and liveborn conceptuses	Liveborn infants			Children
	↓ in Amniotic fluid	Spontaneous preterm labor	IUGR	SGA	Myelo-suppression	Cardio-toxicity	Health effects at follow-up
All-trans retinoic acid	7.7% (2/26)	15.4% (4/26)	7.4% (2/27)	0.0% (0/26)	No	Yes (3)	1/19
Imatinib	0.0% (0/100)	1.0% (1/100)	0.0% (0/100)	0.0% (0/100)	No	No	0/15
Interferon alpha	2.4% (1/41)	0.0% (0/41)	4.7% (2/43)	0.0% (0/43)	Yes (1)	No	0/25
Rituximab	4.3% (1/23)	8.7% (2/23)	4.3% (1/23)	4.8% (1/21)	Yes (4)	No	0/7
Tamoxifen	14.3% (2/14)	21.4% (3/14)	0.0% (0/14)	0.0% (0/14)	No	No	0/8
Trastuzumab	72.2% (13/18)	0.0% (0/18)	10.5% (2/19)	5.3% (1/19)	No	No	0/11

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