# National Toxicology Program

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

## Peer Review Panel Meeting

## October 1-2, 2012

## National Institute of Environmental Health Sciences
## Research Triangle Park, NC

***Summary Minutes***

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*Summary Minutes*

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## I. Attendees

**Members in Attendance:**

Cheryl Broussard, Centers for Disease Control and Prevention (CDC)
Michael Greene, Massachusetts General Hospital
Julia Lawrence, Wake Forest University
John Mulvihill, University of Oklahoma
Janine Polifka, University of Washington
Tina Rizack, Brown University
Judith Ann Smith, M.D. Anderson Cancer Center
Catherine Spong, National Institute of Child Health and Human Development (Chair)
Kristel Van Calsteren, UZ Gasthuisberg Leuven, Belgium

**NTP Board of Scientific Counselors Liaison:**

Melissa McDiarmid, University of Maryland

**Other Federal Agency Staff:**

Gayle DeBord, National Institute for Occupational Safety and Health (NIOSH) (by telephone)
Paul Howard, Food and Drug Administration (FDA)

**National Institute of Environmental Health Sciences (NIEHS) Staff:**

Danica Andrews
Linda Birnbaum
Abee Boyles
John Bucher
Robbin Guy
Kembra Howdeshell
Gloria Jahnke
Barry McIntyre
Robin Mackar
Hazel Nichols
Katherine Pelch
Andrew Rooney
Mike Shelby
Kyla Taylor
Kristina Thayer
Nigel Walker
Vickie Walker
Lori White
Mary Wolfe
Rick Woychik

**Public Attendee**

Frank Coviello - Polymedco

## II. Introductions and Welcome

The National Toxicology Program (NTP) Peer Review Panel for the Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy convened on October 1 and 2, 2012, in Rodbell Auditorium, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. Dr. Catherine Spong served as chair. The other Peer Review Panel members present were Drs. Cheryl Broussard, Michael Greene, Julia Lawrence, John Mulvihill, Janine Polifka, Tina Rizack, Judith Ann Smith, and Kristel Van Calsteren. Dr. Melissa McDiarmid attended as the NTP Board of Scientific Counselors liaison. Dr. Paul Howard attended representing the FDA. Dr. Gayle DeBord attended by telephone, representing NIOSH. Representing the NTP were NIEHS/NTP Director Dr. Linda Birnbaum and Associate Director Dr. John Bucher. Representing the Office of Health Assessment and Translation (OHAT) and primary authors of the monograph were Director Dr. Kristina Thayer, Dr. Kembra Howdeshell, Dr. Mike Shelby, and Vickie Walker. Dr. Mary Wolfe of the NTP served as the Designated Federal Official.

Dr. Spong welcomed everyone to the meeting and asked all attendees to introduce themselves. Following introductions, Drs. Birnbaum, Bucher and Thayer also made brief remarks welcoming the participants. Dr. Wolfe read the conflict of interest policy statement. Dr. Spong asked if there were any oral public comments; there were none. She briefed the panel on the format for the peer review. She noted that there would be a vote on each of the five main findings.

## III. Introduction to the Evaluation, Methods and Limitations of the Data

Setting the stage for the panel's consideration of the draft monograph, Dr. Howdeshell presented introductory material regarding the incidence of cancer chemotherapy during pregnancy, the sources of literature reviewed in the preparation of the draft monograph, the purpose of the monograph, and the five health outcomes focused on within the document. She also described the methods used, including the literature search strategy and its results, which identified 431 reports of a total of 1271 conceptuses. Finally, she outlined the limitations of the data, which were largely due to the inclusion of case reports and case series. The limitations included lack of a referent group, small number of cases per chemotherapeutic agent, lack of long-term follow-up evaluations, and possible publication bias of adverse pregnancy outcomes being reported more frequently than normal outcomes.

Dr. Mulvihill asked whether a pair of monozygotic twins were considered one or two conceptuses within the monograph's methodology. Dr. Howdeshell said that any twin reports were considered to be two conceptuses.

First reviewer Dr. Polifka commended OHAT for undertaking the enormous task embodied in the draft monograph. She felt that the information provided in the Introduction was "basically correct, clearly stated, and objectively presented." She liked the detail provided in the tables, and felt that they were easy to understand, but she did have some suggestions. She recommended that all references to the FDA Pregnancy Categories be removed from the monograph. She suggested it is more accurate and meaningful to state "nearly all chemotherapeutic agents are cytotoxic and have an effect on DNA/RNA synthesis and apoptosis, both of which play a major role in embryonic development, so of course there is a concern that use of these agents during pregnancy (particularly in the first trimester) may cause harm to the embryo."

Referring to the third paragraph of the Introduction, Dr. Polifka recommended that the description of the limitations of animal studies used to predict teratogenic risk in humans be expanded to include mention of several other relevant limitations (Scialli et al. 2004). She suggested that it be clearly stated that the monograph does not address whether previous treatment with chemotherapy affects subsequent pregnancies. She found the second sentence of the paragraph confusing, and noted that she there was no mention in the Methods section of a brief review of studies on occupational exposures to antineoplastic agents during pregnancy. In section 3.3.3 (publication bias), she recommended insertion of the phrase "or voluntary termination of pregnancy" in the next-to-last sentence regarding under-detection.

She noted that in general she liked the way the data were compiled and presented in the Introduction and Methods sections, although she was unclear as to the reference notations.

Second reviewer Dr. Mulvihill began his review by noting that he had some objections to use of terms in the monograph. First, he said that "developmental" means different things to different scientists and clinicians: in toxicology and teratology, it refers to "embryonic and fetal morphogenesis," while in clinical pediatrics it is often limited to brain and behavioral functions, in the sense of "developmental" landmarks. He urged that any such reference be made clear in the context of usage.

He also alluded to the need for precision in use of the term "major congenital malformations." He said that "major" could mean in terms of morbidity to the patient, or in terms of biological importance as a manifestation of teratogenicity. He noted that some references in the monograph to "minor" malformations could be major or minor to the patients, citing examples of each. He also said that the presence of three or more minor malformations could be a flag for the presence of internal major malformations and a flag for recognizing syndromes. He felt that the monograph lacked a dysmorphologist's perspective on the data.

He objected to the use of the "and/or" term, finding it confusing when referring to trimesters, suggesting substitution of "or" or "and." He encouraged the use of proprietary names for the agents, to add to accessibility and readability. He also discouraged use of the term "gestational age," calling it confusing, and suggested substitution with more precise terms such as "menstrual age." He recommended more precise definitions of some of the endpoints alluded to in the Methods section, citing confusion about terms such as "intrauterine growth restriction" and "small for gestational age infants." He questioned the terminology in the draft regarding "moderate to severe oligohydramnios."

Regarding the issue of fetal weight by gestational age, he said that the international curves for gestational age and growth measurements are uniform enough for use.

He noted that the term "incidence" is used occasionally in the document, and he suggested that it be replaced throughout with rates of frequency.

He noted that since the OHAT literature review, the Selig et al. 2012 article had appeared. By his count, there were 133 references that were only in the Selig paper, with 164 in the NTP monograph that did not appear in the Selig review. Selig had included some agents not covered in the NTP monograph, and had included non-English-language articles. He recommended that the references be cross-checked.

He said that the fact that malformations were not expected in third trimester exposure was obvious and should not be portrayed as a surprise.

Responding to the reviewers' comments, Dr. Howdeshell said that the confusion about the references in the document were due to a formatting error and would be addressed. Regarding the inclusion of patients specifically treated during pregnancy, she clarified the fact that patients who were diagnosed and then had a spontaneous abortion or terminated the pregnancy prior to treatment were not included; however, pregnancies in which the patient had been treated and then subsequently experienced a spontaneous or induced abortion were included. She also said that use of the terms "intrauterine growth restriction" and "small for gestational age" would be clarified. She said that an initial review of the references in the Selig et al. 2012 paper showed that it would yield 27 additional patients and 28 additional pregnancies for inclusion in the monograph. Regarding confusion about how amniotic fluid reductions were reported, she said the authors' wording was what had been used in the tables; thus the apparent discrepancies in reporting. She said OHAT was open to input on that topic.

Dr. Spong opened the discussion to the full panel. Dr. Broussard suggested that the monograph include women who had cancer prior to becoming pregnant, versus women who were diagnosed with cancer during their pregnancy. Dr. Howdeshell replied that

the monograph included both groups. Dr. Van Calsteren added that European registries include both groups, and mentioned the resource, http://cancerinpregnancy.org.

Dr. Howard said that the impression that animal treatment is always at higher doses than clinical doses is untrue and could lead to erroneous conclusions. He agreed that the FDA pregnancy categories should not be used, as they change often, and that would keep the document from quickly becoming dated.

Dr. Van Calsteren agreed that growth restriction should be more carefully defined within the monograph. Dr. Greene said he sympathized with the report's authors in the challenge of defining terminology, since often those definitions change over time. He cited the current use of the term "intrauterine growth restriction" versus the outdated "intrauterine growth retardation," which had too many negative connotations, and noted that even the current term was problematic due to centile differences in growth. He said there was a similar problem with the term "reduced amniotic fluid." He said those terms have been "garbled" within the field over the course of 60 years, and it would be best to report them as is, with the understanding that those reading the document would recognize that such limitations are inherent in such a review. He also noted the imprecisions in the data respecting gestational age, and said that they could not be resolved within the document. He said that overall it was good that the monograph describes several limitations.

Dr. Smith asked that there be clarification in the review as to why the 52 agents were selected. Dr. Lawrence said that there should be another limitation discussed regarding hereditary cancer syndromes. Regarding non-statistical methods, Dr. Mulvihill urged avoidance of tenths of a percent, noting that if the numerator is just 1, the tenth of a percent is meaningless and should be removed throughout the document.

Dr. Howdeshell noted that in the description of growth restriction of fetuses, she had included any mention of growth restriction. She said she would make sure that was modified in the methods to be more specific.

Dr. Spong summarized the discussion thus far, noting the panel's concerns about the inclusion of the FDA pregnancy categories, the need for more information on animal study limitations, the inherent limitations in usage of certain terms, and the suggestion to incorporate any new cases from the Selig paper.

## IV. Main Findings

Dr. Spong described the procedure to be used for the five main findings, to culminate in a vote on each one individually by the panel.

### A. Main Finding on the Frequency of Congenital Malformations by Trimester

Dr. Howdeshell presented the information from the monograph regarding frequency of congenital malformations by trimester, including the initial conclusion to be considered by the panel.

Dr. Spong asked for clarification questions from the panel. Regarding Figure 1, Dr. Mulvihill asked whether the data had been collapsed by mechanism of action. Dr. Howdeshell said it had not, but that agents were looked at individually. Also regarding Figure 1, Dr. Smith asked whether only agents that had actually been given during the first trimester were considered when incidence of any chemotherapy agent in the first trimester was determined. Dr. Howdeshell said that the data combined all cases exposed to chemotherapy in the first trimester [only] and first trimester and subsequent trimesters, and those cases that were exposed in the second and [/or] third trimesters only.

Dr. Smith said that the 9.8% number in the figure (under "% Malformed," for "Any Chemotherapy Agent" in the first trimester) seemed low, in that many of those agents are not given within the first trimester. She asked if the data had been looked at in terms of only considering the agents that had actually been given in the first trimester only. Dr. Howdeshell said no, as they had included cases that were exposed in the first trimester, as well as first and subsequent trimesters. She acknowledged that the issue of the denominator used was a topic for further discussion.

Dr. Thayer noted that there were data available that address mechanism of action by classes, and that Dr. Howdeshell could readily add the data to the report.

Dr. Polifka was the first reviewer for this Main Finding. She said she had found the section to be well written, nicely organized, and objectively presented. However, she felt that the rate of malformations in the first trimester and second and/or third trimesters was not calculated accurately, in that the number of spontaneous and induced abortions without fetal data should not be included in the denominator, because it assumes that they were normal conceptuses, when that is not known. Regarding Table 18, she suggested adding the number of conceptuses exposed to monotherapy, and the number exposed to polytherapy, noting that it would be important to know if most of the malformations were seen in fetuses or infants whose mothers were given a multitude of chemotherapeutic agents. She said that despite the monograph's focus on chemotherapy during pregnancy, there is a risk of mischaracterizing the risk of agents such as methotrexate when other data are left out and rates are reported, even though they are reported as "apparent rates of malformations." The calculated rate for methotrexate was 3%, which is similar to the rate found in the general population, but methotrexate is a well-known chemoteratogen. She disagreed with the statement that

"there were generally no patterns of increased rates of major malformations," citing the examples of methotrexate and cyclophosphamide, both of which have had patterns of malformations associated with their use in the first trimester. She cited Vaux et al. 2003, who described a cyclophosphamide-methotrexate-cytarabine embryopathy comprised of craniofacial abnormalities, eye/ear malformations, limb anomalies, and growth retardation. Thus, she said, it would be important to analyze malformation frequency patterns, as it would be vital information for clinicians and parents.

Dr. Polifka suggested adding two more limitations: first, to reiterate that only studies of cancer patients were included in the analysis, and second, that fetuses from most induced abortions are not evaluated for malformations, which makes it difficult to accurately ascertain the teratogenic risk associated with first trimester exposure. She said that many couples choose to terminate pregnancies in which there was an inadvertent exposure to antineoplastic agents out of fear that the exposure would cause malformations. She noted that clinicians try not to treat women with chemotherapeutic agents in the first trimester, so the risk associated with the agents is probably underestimated. On page 5 of the Executive Summary, she suggested adding a comment that these case studies are difficult to interpret, because every case involves a different combination of disease, drugs, dose, and timing of exposure. She acknowledged the tremendous effort that had gone into compiling the information and that it would be a valuable resource for health care professionals. She would like to see the information provided in a way that will help women and physicians weigh the risks and benefits of treatment during pregnancy. She suggested adding a statement in the Executive Summary about the rate of malformations in the general population, and the potential risk of adverse outcomes if women receive no treatment, allowing comparison of the risk of having an infant with malformations versus the risk of non-treatment. She suggested also that the report include the toll-free telephone number for the Organization of Teratology Information Specialists (OTIS), as a resource for physicians and patients. She agreed with the conclusion about first trimester exposure, but also noted that that was not a surprise, and that it would be more useful to present findings on patterns or frequencies of malformations.

Second reviewer Dr. Rizack found the section to be very concise. She noted that it was difficult to separate multidrug from monotherapy, as cancer is typically treated with multiple drugs. She especially liked the table, and said she would find it useful in her practice. She felt that although the limitations of the current data are not addressed in this section, they are adequately stated elsewhere in the monograph.

Dr. Howdeshell said the group had considered trying to separate the exposures, but had not considered how to analyze the data for single versus poly-therapy. She said that with such a small sample size, it was difficult to consider the many potential

combinations. She said the idea of looking at frequency of malformations based on monotherapy versus polytherapy was intriguing, and would be considered. Dr. Polifka said that would help put the information into perspective.

Dr. Spong observed that there was concern about the inclusion of induced and spontaneous abortions in the denominator for the rates of malformations, and asked for more discussion on it from the panel. Dr. Van Calsteren noted that the incidence of malformations in the first trimester would be under-estimated by assuming fetuses from induced abortions were normal. Dr. Spong noted that it is not possible to see malformations prior to 10 weeks gestation, complicating the issue of the denominator. Delineating those exposed to a certain drug in the first trimester from those exposed in the second or third trimester would be a better way to determine if the malformations are really due to exposure in the first trimester. Dr. Smith mentioned that it is important to look at consistency with whatever animal data might be available, particularly as so little human information is available. She also was concerned with the term "minor malformations," and suggested that the minor ones be expressed as "non-life-threatening."

Dr. Howdeshell responded that she had deliberated on what to use as a denominator. She repeated for confirmation the panel's recommendation that only cases of fetal death for which there is autopsy information should be considered in discussing congenital malformations. Dr. Spong stated that when there is information about cases in the first trimester, there would be no information regarding malformations, so they should not be included in the denominator. Dr. Howdeshell reconfirmed that it was the sense of the panel that spontaneous abortions in the first trimester should not be included. The panel seemed to agree, but observed that the ultimate answer was perhaps more nuanced. Dr. Greene noted that some malformations are hard to miss with ultrasound, even as early as the first trimester. He said the answer would depend on the malformation. He discussed potential definitions of "major" malformations, which could include being lethal or requiring surgery for repair, even in some conditions that would not be life-threatening, such as hypospadias. Also, malformations of major cosmetic significance would qualify. Thus, he proposed a three-way definition that would be more precise than the one included in the draft. Dr. Broussard noted that when working to compare numbers, one would have to work with currently used definitions, which in this case is the Centers for Disease Control and Prevention (CDC) definition. Dr. Mulvihill observed that the rate of malformations increases with age of the mother, which would contribute to some "fuzz" in the rate of malformations. Dr. McDiarmid said that the percentage estimates would be the element most remembered by readers, so it would be critical that they are correct. Thus, the information about conditions that were not counted would be of concern from a public health standpoint in that some major problems may not have been addressed.

Dr. Polifka noted that in all of the summaries, there should be a comment about whether any of the malformations that were observed in humans were similar to those found in animal studies.

Dr. Mulvihill said that he was still troubled by the treatment of the risk of gross malformations in the second or third trimesters, as his observation is that there is no risk at that time. Dr. Shelby replied that the OHAT team had discussed the issue with the CDC, and decided that some major malformations could arise in the second and third trimesters. Dr. Greene noted there were some cerebellar malformations cited in the table that could arise in later trimesters. Dr. Spong agreed, noting that the panel would be uncomfortable saying malformations arising in the second or third trimesters were impossible.

Regarding the denominator issue, Dr. Van Calsteren noted that if a percentage is put into the monograph, "that's what people will use in daily life when they are confronted with a problem." She stressed the importance of getting the number correct, and said that if only pathology or ultrasound results are used, the numbers could be very small and lead to over-estimation of malformations. There is also a danger of under-estimation. She felt that reporting the numbers as they are would be more correct than to calculate percentages. Dr. Spong felt that was an important point. Dr. Polifka mentioned removing the data from spontaneous abortions without fetal data. Dr. Howdeshell said they had run this analysis, removing the spontaneous and induced abortions and stillbirths when there was no data. She said the overall conclusions were the same, that first trimester results in a higher apparent rate of malformations compared to exposure only in the second and/or third trimester. Dr. Polifka noted that removing cases from the analysis would in fact change the rate of malformation data. Dr. Howdeshell asked the panel whether it felt that percentages should be avoided in the monograph. Dr. Greene said it was important to have the numbers, not just percentages, because the weight he would attach to the data would be based on the actual numbers. Dr. Polifka preferred including both the numbers and percentages. Dr. Rizack said that she liked having the percentages available in order to give a patient a ballpark estimate of risk. She also endorsed inclusion of discussion of the risk of major and minor malformations.

Dr. Mulvihill expressed concern about the use of the agents for non-cancerous conditions such as autoimmune disorders. He proposed adjusting the terminology in the main finding to "chemotherapy for cancer" to be more specific. Dr. Howdeshell further suggested "chemotherapy for treatment of cancer," and the panel was in favor of this clarification.

The panel discussed the wording of the first Main Finding on Frequency of Congenital Malformations by Trimester. Originally, it read:

> The evidence in the draft monograph supports NTP's interpretation that cancer chemotherapy use in the first trimester represents a higher apparent risk of major malformations than in the second or third trimesters only.

Following the panel's discussion, the conclusion read:

> The evidence in the draft monograph supports NTP's interpretation that 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.

Dr. Mulvihill moved to accept the Main Finding as edited. Dr. Rizack seconded the motion. The panel voted unanimously to accept the main finding as rewritten (8 yes, 0 no, 0 abstentions).

### B. Main Finding on the Risk of Spontaneous Fetal Death

Dr. Howdeshell presented the information from the monograph regarding risk of spontaneous fetal death, including the initial conclusions to be considered by the panel.

First reviewer Dr. Lawrence said the title for Table 19 should state data are primarily based on case reports, and acknowledge more of the limitations of the data. She also observed that there was no weighting based upon the patient's disease. She reiterated that percentages tend to be misleading. She noted the common breast cancer drugs doxorubicin and cyclophosphamide have more than 400 reported cases, but are associated very few abortions or stillbirths. In contrast, the leukemia drug daunorubicin has a much higher reported rate of abortions and stillbirths. This higher rate could be due to the sicker leukemia patients being unable to delay therapy, and pregnancy tests or decisions about conceptuses may be overlooked. She found the statement that "cancer chemotherapy use in the first trimester does not appear to increase the apparent risk of early spontaneous fetal loss" to be acceptable. She was not certain that the statement regarding the second and/or third trimesters was supported by the available literature. She felt that the statement "apparent risk of late spontaneous fetal death is increased with use of specific agents "in this section could be accounted for by the sick leukemic patients, who have more systemic involvement than breast cancer patients. She said that the concept of classifying drugs would be relevant in that context as well.

Second reviewer Dr. Mulvihill said that Table 19 had the word "incidence" in the title, as opposed to "rate" or "frequency." He noted that there was a lack of consensus about what number of weeks of gestation constituted a stillbirth. He offered a reference on stillbirth after cancer therapy (Signorello et al. 2010).

Dr. Howdeshell asked Dr. Lawrence if she felt that stillbirth incidence would be different in leukemic patients than in other cancer types. Dr. Lawrence replied that she definitely felt that way, in that leukemia undoubtedly would add to adverse fetal outcome.

Dr. Greene agreed with Dr. Lawrence that in order to attribute the fetal deaths to the treatment, there must be a significant number of patients with the disease but without the treatment for comparison. Those patient records are not available, making it very difficult to unscramble the confounding of the data by cancer indication and drugs. Dr. Rizack agreed, citing leukemias and aggressive Stage 4 cancers. She suggested that a disclaimer might be in order at that point. Dr. Smith noted that most of the agents discussed are used in combination regimens, particularly in the systemic cancers leukemia or lymphoma. She suggested that considering cancer indications or the drugs by class might yield better answers.

Dr. Spong summarized the discussion, noting that there was concern about confounding of the data due to the reason for selecting the chemotherapeutic agent, and the conclusions should incorporate that issue.

Referring to the conclusions, Dr. McDiarmid said they were counter to the animal data so it would be important to ensure that the denominators were correct.

Dr. Mulvihill asked Dr. Howdeshell about the stillbirth age cut-off. She replied that they had arbitrarily chosen 22 weeks, as there was ambiguity in the literature. Dr. Greene noted that it is a jurisdictional issue, with states often varying in the gestational age chosen.

The panel discussed the wording of the Main Finding on the Risk of Spontaneous Fetal Death. Originally, it read:

> The evidence in the draft monograph supports the NTP's interpretation that
>
> - Cancer chemotherapy use in the first trimester does not appear to increase the apparent risk of early spontaneous fetal loss (also called spontaneous abortion, ≤22 weeks gestation).
> - Cancer chemotherapy use in the second and/or third trimester only may increase the apparent risk of late spontaneous fetal death (also called stillbirth, >22 weeks of gestation).
> - The apparent risk of late spontaneous fetal death is increased with use of specific agents (i.e., cytarabine alone or in combination with 6-thioguanine and/or daunorubicin).

Following the panel's discussion, the conclusions read:

The evidence in the draft monograph supports the NTP's interpretation that

- There is insufficient reported information in human studies that chemotherapy for treatment of cancer in the first trimester affects early spontaneous fetal loss (also called spontaneous abortion, ≤22 weeks of gestation).
- Data reported for the use of chemotherapy for treatment of cancer in the second and/or third trimester suggest an apparent increase of late spontaneous fetal death (also called stillbirth, >22 weeks of gestation).

Dr. Greene moved to accept the Main Finding as edited. Dr. Lawrence seconded the motion. The panel voted unanimously to accept the main finding as rewritten (8 yes, 0 no, 0 abstentions).

### C. Main Finding on Pregnancy Complication Associations

Dr. Howdeshell presented the information from the draft monograph regarding pregnancy complication associations, including the initial conclusions to be considered by the panel.

Dr. Spong speculated that what was meant in the conclusion was actually preterm birth, as opposed to preterm labor. Dr. Howdeshell said the term was used in the context of preterm labor leading to preterm birth. Dr. Spong pointed out this was not always the case; many preterm labors still have births at term, and spontaneous preterm deliveries can occur in the absence of spontaneous preterm labor.

Dr. Lawrence asked why trastuzumab had risen to such a level of importance regarding a reduction in amniotic fluid, and Dr. Howdeshell described several mechanistic reasons. Dr. Howard noted that prior conclusions had been general and not targeted to a particular therapy in the comments. He wondered if this targeting was desired, or whether a more general phrasing might be more appropriate and consistent with other sections. Dr. Rizack added that trastuzumab is the only agent that has its own registry for pregnancy.

First reviewer Dr. Greene agreed that this section discussed a specific agent while other sections included only general discussions of all the agents. However, he felt the evidence was quite strong that trastuzumab has a real effect, and is an example of some newer agents that target profound biologic mechanisms and signaling pathways; so it is credible that there is a strong association between trastuzumab and oligohydramnios. He recognized that many of the reports were imprecise, but that when known the monograph should state why preterm births occurred. For example: Were they due to interventions motivated by concern for deteriorating maternal or fetal status,

to permit more aggressive cancer chemotherapy for the mother without exposing the fetus, or due to spontaneous preterm labor or preterm rupture of the membranes.

Dr. Smith was the second reviewer. She focused her comments on the tables (20 and 22) in the section. She said that it was confusing to go back and forth between the tables, because the denominator kept changing. She suggested use of an asterisk by the drug name when an agent is used in combination and organization of the tables by drug class rather than in alphabetical order. She recommended that the caveat about the disease itself contributing to preterm birth be included as a footnote on the tables. She felt that separating the data in the tables was misleading; when assessing drug safety in pregnancy the information should all be in the same context. She suggested that information be added to the tables so the reader could look at all of the five major findings at one time, instead of jumping around to multiple tables while making a clinical judgment. She said that within each drug summary, "pregnancy complications" should be clearly labeled and consistent. There should also be a clear statement on the limitations of the information available within drug summaries, with guidance on how to use the information provided to determine risk/benefit ratio. She asked what control to compare to regarding whether the evidence in the monograph supports the tables. She agreed with the explanation for trastuzumab, but thought it would be preferable to refer to a class of agents with similar mechanisms, rather than focusing on trastuzumab. She was also unsure what control to use to determine if the evidence in the monograph supported the interpretation that chemotherapeutic agents do not appear to be associated with spontaneous preterm birth, and thought the statement should be softened.

Dr. Howdeshell replied that she is sensitive to the issue of targeting a useful drug as something that should not be used in pregnant patients. She mentioned that a previous draft had alluded to the need for pregnancies to be monitored for possible complications with the use of certain drugs. She said she was open to the idea of identifying or not identifying trastuzumab in the conclusion, and to coming up with a clearer way of organizing the data. In terms of addressing risk/benefit, she said it was unlikely that the NTP would address that issue, steering clear of clinical guidance issues. Dr. Smith clarified that her main concern was that the information be accessible in one spot, so that the clinician could weigh everything at once. Dr. Howdeshell said she was also aware of the panel's objection to the term "preterm labor."

Dr. Spong said she agreed that most of the pregnancies deliver preterm, because it is often safer to do so in order to best treat the mother, and that most deliveries would be induced. She noted that it would be important to say that most of the agents do not necessarily cause spontaneous preterm birth. She suggested simply changing "labor" to "birth" in the statement.

Referring to the main finding statement about reductions in amniotic fluid, Dr. Polifka said it would be important not to lump all drugs in a class, as every drug is different, with different effects even if they are in the same class. Dr. Spong suggested citing trastuzumab as an example, with a notation that other drugs may also reduce amniotic fluid and require monitoring. Dr. Smith said that there were too many new targeted agents to restrict the statement to trastuzumab alone. Dr. Rizack noted that trastuzumab is a monoclonal antibody and as a biological agent should be separated from the rest of the cancer chemotherapy group. Dr. Greene felt that there had been no attempt to lump rituximab with trastuzumab, as their mechanisms are totally different. He said that trastuzumab was the first in its class having been released approximately ten years ago, and so subsequent agents would have far fewer exposures available for study, particularly in pregnant women. Thus, trastuzumab has the most data available.

Dr. Mulvihill expressed concern about Dr. Rizack's statement that trastuzumab is the only agent that has its own registry, raising the issue of potential publication bias.

Regarding the preterm labor issue, Dr. Van Calsteren suggested addressing preterm birth in the paragraph in question, and including the numbers for spontaneous preterm births and inductions or C-sections, and whether they were a maternal health decision or fetal. Also, the unspecified numbers should be included, she said. The number currently given in the document is likely an underestimation, she noted.

Dr. McDiarmid pointed out that there is a black box warning on the package insert for trastuzumab about this issue, supporting the idea of singling it out in the monograph. Dr. Howard said he was more concerned about going from the general to the specific. Dr. Spong suggested there were likely more data available on trastuzumab, allowing for it to be specifically identified as an agent of concern. Dr. Greene added that "the effect seems quite striking." Dr. Howdeshell suggested that in the wording of the conclusion, trastuzumab be given as an example, rather than the only agent resulting in amniotic fluid reduction.

The panel discussed the wording of the Main Finding on Pregnancy Complication Associations. Originally, they read:

> The evidence in the draft monograph supports the NTPs interpretation that
>
> - Cancer chemotherapy use during pregnancy increases the incidence of reductions in amniotic fluid (e.g., oligohydramnios or anhydramnios).
> - Certain chemotherapeutic agents may be responsible for reductions in amniotic fluid (i.e., trastuzumab).
> - Chemotherapeutic agents do not appear to be associated with spontaneous preterm labor.

Following the panel's discussion, the conclusions read:

The evidence in the draft monograph supports the NTP's interpretation that

- Chemotherapy for treatment of cancer during pregnancy can result in oligohydramnios or anhydramnios primarily attributable to trastuzumab, based on available data.

- Chemotherapy for treatment of cancer during pregnancy does not appear to be associated with spontaneous preterm birth.

Dr. Greene moved to accept the Main Finding as edited. Dr. Rizack seconded the motion. The panel voted unanimously to accept the main finding as rewritten (8 yes, 0 no, 0 abstentions).

**D. Main Finding on Effects on Newborn Weight and Health**

Dr. Howdeshell presented the information from the monograph regarding effects on newborn weight and health, including small for gestational age and its potential relationship to intrauterine growth restriction, transient myelosuppression, and fetal/neonatal cardiotoxicity. She also presented the initial conclusions to be considered by the panel.

Dr. Greene observed that in the material on potential fetal cardiotoxicity with anthracyclines, stillbirths should not be included in the denominator and should be removed, because cardiotoxicity would not be detected in stillborn infants.

The first reviewer Dr. Broussard discussed the statement, "It is possible that when the chemotherapy regimen is discontinued 2 to 3 weeks prior to birth, the intrauterine growth rate has a chance to catch up," noting that both the basis for the statement and how to use this information in practice were unclear. She asked whether it was advisable to stop chemotherapy late in pregnancy, and how should the 2 to 3 weeks prior to birth be interpreted given that many of the women would be delivering preterm. Referring to Section 5.1, she said it was unclear what the "Interestingly," was referring to in the statement on page 41 without knowing what percentage of growth-restricted fetuses were stillborn versus live born, and that the fetal death section did not report on growth restriction or small for gestational age either. She noted that the monograph should be more consistent with terminology for fetal death, citing the example of use of the terms intrauterine fetal death and stillbirth in the text, but intrauterine fetal demise in Table 18. She suggested choosing one term to be used throughout the document.

For fetal/neonatal cardiotoxicity, she noted that in both the Executive Summary and Section 5.1, it was stated that the total count included stillbirths and live births, but neither states how many of each. She quoted from Section 1.0 that "the occurrence of

myelosuppression at birth in the general population is not known," and she assumed that a baseline for fetal/neonatal cardiotoxicity is also not known but that it should be stated either way. She said that Section 5.1 contains a paragraph on infant death up to age 4 months, but wondered why the information is not presented elsewhere, and she asked why the information only ranged through age 4 months. She suggested that Table 21 should be titled "Newborn weight reported" instead of "Pregnancy complication reported." She approved of the addition of a paragraph discussing newborn health issues associated with preterm birth in the Discussion section, but did not notice it in the other relevant sections of the monograph. She was concerned about the conclusion on transient myelosuppression, because it is difficult to interpret the information without knowing the background occurrence of myelosuppression at birth, and thus whether there is an increased risk in this group.

Dr. Van Calsteren was the second reviewer. She noted that intrauterine growth restriction refers to fetal growth, which to her is a pregnancy complication, and would belong in that discussion. She called for more detailed reporting for each agent of numbers of normal birth weight, small for gestational age, and births with no data. She suggested stating again that there is a large amount of data missing in the case reports, and that the methods for determining fetal growth and diagnosing intrauterine growth restriction have changed dramatically over the years. Comparing weights reported in several of the case series reviewed in the monograph and two new case series (Abdel-Hady et al. 2012 and Loibl et al. 2012), she agreed with the overall conclusion of a small number of small for gestational age births. However, she noted, there would be subgroups where the conclusion may be different, specifically hematological malignancies, and that should be reflected in the draft. She cited the example of myeloproliferative neoplasias with increased risk of thrombosis, as reported in Brenner et al. 2012. She agreed that the data did not provide enough details on the cause or the interval between chemotherapy and birth with diagnosis of myelosuppression, and thought several of the cases were actually anemia. On cardiotoxicity, she felt that one of the cases (Leong et al. 2000) should be omitted from the list, and that the case from Siu et al. 2002 could be added. She said that in 3 of the 7 cases, the cardiac changes could be explained by anemia alone. She said that 4 of the 7 cases received anthracyclines, and although there is no clear causal link between the anthracyclines and the cardiac event, a possible link cannot be excluded.

Dr. Greene commented on the sentence stating that intrauterine growth restriction was not always a predictor of a small for gestational age newborn noting that it simply states what every obstetrician knows – that the predictive ability of the formulae for fetal growth is not great; the technology is imprecise at best, making for imprecise actual estimates of low birth weight or small for gestational age.

Dr. Smith asked whether any of the data on chemotherapy-induced renal toxicity had been captured. Dr. Howdeshell replied that it had not been attempted, but that it was a good point and was an endpoint that could be looked at.

The panel discussed the wording of the Main Finding on the Effects on Newborn Weight and Health. Originally, they read:

> The evidence in the draft monograph supports the NTP's interpretation that
>
> - It is not possible to evaluate apparent risk of small for gestational age based on current reports.
> - Cancer chemotherapy use during pregnancy appears to be associated with transient myelosuppression.
> - Chemotherapy agents that induce cardiotoxicity in treated patients also induce cardiotoxicity in fetuses/neonates exposed to the same agents *in utero*.

Following the panel's discussion, the conclusions read:

> The evidence in the draft monograph supports the NTP's interpretation that
>
> - The data on chemotherapy for treatment of cancer during pregnancy are insufficient, but suggestive, of effects on impaired fetal growth and myelosupression.
> - The evidence is inconclusive that chemotherapy for 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*.

Dr. Rizack moved to accept the Main Finding as edited. Dr. Mulvihill seconded the motion. The panel voted unanimously to accept the main finding as rewritten (8 yes, 0 no, 0 abstentions).

Dr. Spong adjourned the meeting for the day around 5:20pm.

### E. Main Finding on Effects on Infant Growth and Development

Dr. Spong welcomed everyone back to the second day of the peer review. She asked everyone in the room to introduce themselves. Dr. Wolfe read the conflict of interest statement.

Dr. Howdeshell presented the information from the draft monograph regarding effects on infant growth and development. She also presented the initial conclusion to be considered by the panel.

Regarding the figures in the draft stating that 96% of children exposed *in utero* to cancer chemotherapy had normal growth and development while 4% did not, Dr. Spong asked how normal growth had been calculated. Dr. Howdeshell replied that the follow-up reports were not very precise, and said they had identified all cases that indicated that there had been some delay as non-normal growth and development.

Dr. Van Calsteren was the first reviewer. She cited Amant et al. 2012 as giving updated information that might be useful for the section. She recommended acknowledging that an important number of the children were born preterm, which would affect their future development. She noted as a limitation that most of the reports are based on what parents tell doctors, not based on clinical examinations. She also noted that the follow-up period is very short, and that the issue of prematurity should be taken into account. She agreed with the interpretation in the draft on growth and development, but suggested that in addition to reproductive function, other possible long-term effects should be followed up including cancer development and behavioral and neurodevelopmental problems.

Second reviewer Dr. Polifka felt that the section was well-written, and was surprised that there were as many infants followed up as there were. She said that it needs to be mentioned that interpreting the significance of the findings is difficult when it is unclear if reliable and appropriate tools were used, or who assessed the children's growth and development, given that follow-up was not done in a systematic fashion. She suggested language be added to the conclusion that the quality and comprehensiveness of follow-up varies greatly among the case reports.

Dr. Howdeshell said that limitations would be added noting that many of the infants were born prematurely, and that the tools of follow-up often involved reports from parents, not medical personnel.

Dr. Mulvihill said that this was a very important area, and that it might be good to give it more emphasis, perhaps even making it a major outcome in the report. He suggested that this area might also be the appropriate place to emphasize cancer as an outcome. He said that the concern about reproductive transgenerational effects is real. He felt that there should be more emphasis on the information from Amant et al. 2012, which involved a large number of children who had been followed up, with all endpoints normal and negative except for subtle changes on cardiac function and cognitive evaluations. Dr. Birnbaum added that those effects could be extremely important on a population basis.

The panel discussed the wording of the Main Finding on Effects on Infant Growth and Development. Originally, it read:

> The evidence in the draft monograph supports the NTP's interpretation that growth and development appear normal during infancy and early childhood (<2 years of age); however, it is important to recognize that certain functional deficits may not be apparent until later in life, e.g., effects on reproductive function.

The panel suggested changing the term 'infant' to 'offspring' so that it was clear the concern of adverse effects extends into adulthood. Following the panel's discussion, the conclusion read:

> The evidence in the draft monograph supports the NTP's interpretation that growth and development of offspring exposed to chemotherapy for treatment of cancer during pregnancy appear normal during infancy and early childhood (<2 years of age); however, 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 reproductive and other organ function.

Dr. Mulvihill moved to accept the Main Finding as edited. Dr. Polifka seconded the motion. The panel voted unanimously to accept the main finding as rewritten (8 yes, 0 no, 0 abstentions).

## V. Cancer Chemotherapy Agents by Mechanism of Action

Dr. Spong introduced this portion of the meeting, noting that Dr. Howdeshell would present background information and Charge Questions for all six classes of agents appearing in the draft as "Agent-Specific" chapters: anti-metabolites, DNA alkylating agents, DNA intercalcating/cross-linking agents, microtubule function inhibitors, topoisomerase II inhibitors/oxygen free radical generators, and targeted therapies. Following the presentation of each class, the information on each individual agent would be reviewed.

### A. Anti-metabolites

Dr. Howdeshell first presented the background information on the purpose and structure of the agent-specific chapters, and then described the data on the anti-metabolites. She noted that as per the panel's suggestion during the first day of the meeting, she had revised the denominators used in the data.

Dr. Greene commented that for many of the chemotherapeutic agents the ability of the drug to cross the placenta is unknown. He suggested that it would be helpful in those situations to list the molecular weight and other relevant physicochemical properties of the drug, such as charged vs. neutral, lipid vs. water soluble, and degree of protein binding. Dr. Smith agreed, and mentioned that she had suggested the inclusion of a

clearly labeled pharmacology section for each of the drug sections, including pharmacokinetics.

Dr. Polifka said she particularly like the summary slides, especially those that listed all of the malformations that had been observed in infants, and wondered whether similar summaries might be included in the final draft monograph.

Dr. Greene noted that many of the neonates in the tables were described as having some "respiratory difficulties" or "breathing difficulties." He said that in those cases it would be very helpful for the readers' assessment of the problem to know whether the respiratory difficulty was transient tachypnea of the newborn or true respiratory distress with surfactant deficiency, as well as the gestation age of the neonates who had had the respiratory difficulty.

Dr. Mulvihill congratulated Dr. Howdeshell for having changed the denominators, but noted that the percentages still were reported in tenths-of-percents, unnecessarily. He felt that the summary paragraphs were too repetitive of the preceding text, and wished for more interpretive comment in the summaries. He noted that the indications for the agents are different from the tumors actually exposed, and so the manufacturer's or FDA's designations are inadequate given off-label uses. Dr. Mulvihill acknowledged submitting a list of references from the Selig paper for consideration (see Appendix).

Dr. Spong introduced the reviews of the six anti-metabolites, with two reviewers for each agent.

### *Anti-metabolites: 5-Fluorouracil*

First reviewer Dr. Polifka agreed with Dr. Mulvihill's comment about the summaries repeating what had been said in the earlier section. She requested a bottom line or conclusion instead, addressing whether a pattern of malformations had been seen, or what the salient malformations were, if any. She liked the format of the tables and the appendices. She said that in the summary for 5-fluorouracil it would be important to mention that 3 of the 4 malformed conceptuses were co-exposed with either methotrexate or cyclophosphamide, and that the features seen in those infants and fetuses are consistent with those typically associated with prenatal exposure to those agents.

Second reviewer Dr. Lawrence had no comments on 5-fluorouracil.

### *Anti-metabolites: 6-Mercaptopurine*

First reviewer Dr. Polifka noted an error in the section on human gestational exposure and effects (5.3.4). In the second paragraph, line 2, where "all had been exposed" in the first trimester was incorrect, because one of the cases (Greenlund et al. 2001) had

been exposed in the second trimester. She pointed out that on page 56, first paragraph, malformations were observed in *two* newborns, not three, because slight cardiomegaly is not considered a malformation, which is stated later in the paragraph. She said it would help clinicians and patients put exposure in perspective if the information also provides what percentage of the therapeutic dose the nursing infant would be expected to ingest through breast milk. She suggested her book as a reference for formatting the information (Friedman and Polifka 1996).

Second reviewer Dr. Smith noted regarding Section 5.3.2 that the peak levels in breast milk transport changed more than six-fold, even though the amount is small this could be significant. She reiterated that FDA Pregnancy Categories should be removed.

***Anti-metabolites: 6-Thioguanine***

First reviewer Dr. Polifka described minor discrepancies. She found 7 conceptuses exposed in the first trimester, with data available on only 4. Thus she felt that the rate of malformations should be 2/4, since there was no information on the other three. For the same reason, in the last paragraph, she felt that the figure should be 4/47, not 4/49. Dr. Howdeshell mentioned that she had recently tweaked some of the numbers, so panelists may see minor differences.

Second reviewer Dr. Van Calsteren noted that there had been one case of severe preeclampsia that should be added (O'Donnell et al. 1979). She mentioned another case involving a chromosomal abnormality that should also be added (Maurer et al. 1971). She recommended separating terminations of pregnancy through fetal losses from miscarriages in the summary. She suggested adding two references to 6-thioguanine: Feliu et al.1988 and Moreno et al. 1977.

***Anti-metabolites: Cytarabine***

Dr. Rizack was the first reviewer. She noted that the indications for the agent should include acute myeloid leukemia, acute promyelocytic leukemia, chronic lymphocytic leukemia, primary central nervous system lymphoma, refractory or relapsed Hodgkin lymphoma and non-Hodgkin lymphoma. Also, she said that on page 95, second paragraph, the abnormal should be normal, as that is what is stated in other parts of the document.

Second reviewer Dr. Mulvihill mentioned that it would be interesting to look at cases that appear syndromic with a dysmorphologist or a dysmorphology database to determine whether they resemble a recognized syndrome. He noted some "oddity of verbiage" that he suspected was direct quotes from authors.

***Anti-metabolites: Hydroxyurea***

First reviewer Dr. Broussard noted that this was the only medication where the data included people who were not treated for cancer, and so it would be cleaner if it were taken out. She added that the justification for including non-cancer data did not make much sense. She said that she was uncomfortable with the terminology used for calculating the occurrence of birth defects, and suggested removing that language.

Dr. Greene was the second reviewer. He said he liked having the information about the non-cancer exposures, because it would help the reader separate the true effect of the drug from the effect of being sick with cancer. He pointed out that there seemed to be duplicate cases of the rare malformations of meningocele and pyloric stenosis, he suggested deleting the duplicates. He mentioned a case cited in the summary referring to a newborn with "low nutrient levels," and suggested that it may be more accurate to characterize it as "electrolyte abnormalities and hypoglycemia." He also wondered about the report by Dilek et al. 2006 describing a 28-week fetus weighing 1,800 grams, and said that either the gestational age or the weight was wrong.

***Anti-metabolites: Methotrexate***

Dr. Lawrence was the first reviewer. She had no comments specific to methotrexate.

Second reviewer Dr. Smith felt the study Al-Saleh et al. 2007 addressing placental transport was poorly designed and should be omitted. She recommended that somewhere in the monograph, the use of methotrexate in medical terminations should be mentioned.

Dr. Spong opened the floor for panel discussion of the anti-metabolites.

Dr. Howdeshell noted that the Dilek et al. 2006 reference was correct. She asked for advice from the panel about where to go for indication data. Dr. Rizack recommended UpToDate, a peer-reviewed information resource listing FDA-indicated uses and non-FDA-indicated uses for drugs. Dr. Smith also recommended the National Comprehensive Cancer Network guidelines. Dr. Howdeshell asked Dr. Broussard to share her thoughts on how to express the total number of major malformations possibly attributed to the specific agent in the summary. Dr. Broussard replied that it was probably unnecessary to provide numbers in the summary, but to say whether the finding was consistent with what had been seen in animals. Dr. Mulvihill added that the new thinking in teratology relates to narrow windows of susceptibility, making it more important to work toward specifying precise exposure periods.

Dr. Broussard said it seemed that the presentation of birth defects in the summary sections differed from the presentation of this information in earlier sections of the same agent, which made it hard to follow. Dr. Polifka added that with methotrexate it is important to include a comment in the summary that even though in cases of cancer the

malformation rate appears to be 3%, the rate is much higher when other diseases are taken into account. Dr. Rizack agreed, noting that even though methotrexate is used less and less for oncology, there are many occasions where it could be used in women who are not yet aware they are pregnant. Dr. Howdeshell asked if it would be more useful to report all malformations and then indicate in the text that some should not be included, in terms of reporting a revised rate. Dr. Spong replied that if the intent of the document is to say whether or not an exposure of a medication for treatment of cancer during pregnancy results in a certain number of anomalies or outcomes, and those outcomes were identified before intervention, it would clearly not be related to that intervention. Dr. Smith said that the same concept comes up in some of the other drugs, and that there should be some explanation of how the malformation rates are derived. Dr. Howdeshell said that more of the logic behind the statements could certainly be added.

### B. DNA Alkylating Agents

Dr. Howdeshell presented the background information and data summary on the six DNA alkylating agents.

#### *DNA Alkylating Agents: Busulfan*

First reviewer Dr. Smith asked how the conclusion in Section 5.8.5 was reached, and felt that further explanation was needed.

Second reviewer Dr. Lawrence had no comments on busulfan.

Dr. Polifka wondered how relevant chick embryo studies were and whether they needed to be included.

#### *DNA Alkylating Agents: Cyclophosphamide*

Dr. Mulvihill was first reviewer. He said he had found 3 cases in the Selig et al. 2012 paper that would apply, and that he would provide them to NTP. He felt that it would be appropriate to allude to the non-cancer indications for cyclophosphamide, which may involve a very large population exposed at a vulnerable age for a long time. He reiterated his earlier point that some of the cases may involve a syndrome and should be reviewed by a dysmorphologist.

Dr. Broussard was the second reviewer. She noted that the American Academy of Pediatrics Committee on Drugs would soon be publishing an updated guidance on drugs in lactation, to replace the 2001 version referenced. She said that in the top paragraph on page 85, it was hard to follow what were considered major versus minor malformations.

#### *DNA Alkylating Agents: Dacarbazine*

First reviewer Dr. Rizack noted that dacarbazine is also used for first line treatment of Hodgkin lymphoma. She said indications should also include soft-tissue sarcomas, islet cell tumors, pheochromocytoma, and medullary carcinoma of the thyroid.

Second reviewer Dr. Mulvihill had no comments on dacarbazine.

***DNA Alkylating Agents: Ifosfamide***

First reviewer Dr. Broussard noted the statement about a "healthy infant with mildly delayed motor skills thought to be due to his premature birth at 32 weeks of gestation" could be made for all of the medications.

Second reviewer Dr. Rizack updated the indications for the drug to include treatment of bladder cancer (metastatic), cervical cancer, head and neck cancers (recurrent or metastatic), ovarian cancer, small cell lung cancer (relapsed), Hodgkin lymphoma (relapsed or refractory), non-Hodgkin lymphomas, thymomas and thymic cancers (advanced), and sarcomas (Ewing's sarcoma, osteosarcoma, and soft tissue sarcoma).

Dr. Polifka commented that in reviewing the animal studies, it would be of interest to mention what the fetal anomalies were.

***DNA Alkylating Agents: Nitrogen Mustard***

Dr. Mulvihill was first reviewer. He wondered whether any of the malformations seen in the laboratory animals resemble what is seen in humans. He noted that percentiles expressed in the summary should be in single digits.

Second reviewer Dr. Lawrence had no comments on nitrogen mustard.

***DNA Alkylating Agents: Procarbazine***

Dr. Smith, first reviewer, noted that Section 5.28.2 should add that it has been established that animal placenta models do not translate to humans. She said that procarbazine does have high penetration to the central nervous system, and as this is mentioned in other sections, it should also be mentioned here for consistency. She also suggested the addition of an appendix for patients charting whether drugs cross the placenta or go into breast milk.

Second reviewer Dr. Greene noted that in the section on human fetal exposure and developmental defects, there was the sentence, "Health anomalies were reported for two other infants." He said he could not find the reference for that, and that there was no explanation of what "health anomalies" were.

Responding to the comments on the DNA alkylating agents, Dr. Howdeshell said that as much detail on animal toxicology as could be found had been included. She said that

some of the information had come from review of the Shepard and Lemire book (*Catalog of Teratogenic Agents*) and the REPROTOX® database. She asked whether it would be useful to comment in the summary statements on which agents the American Academy of Pediatrics suggests avoiding during lactation. Dr. Broussard felt that was a good idea. Dr. McDiarmid noted that the package inserts for these drugs commonly recommend against breastfeeding while they are being used. She said it would be useful to add this to the report's global comments, in a section devoted to the overall facts that the drugs get into breast milk and cross the placenta, while including other explanatory information about molecular weight, charge, and fat solubility to help the reader understand. She also suggested a paragraph about the DNA alkylating agents explaining that they are well-recognized carcinogens and noting that downstream carcinogenesis is a concern, whether in the infant (offspring gestationally-exposed) or in health care workers.

Dr. Spong said that there are instances of these medications being used for reasons other than cancer, and for agents where there is literature not summarized in the draft, a note should refer the reader to those other sources.

Dr. Lawrence asked if the National Cancer Institute's (NCI's) Surveillance, Epidemiology and End Results Registry had been reviewed for potential cancers in children resulting from *in utero* exposures. Dr. Howdeshell said she was not aware of any reporting on that subject, other than one from Zemlickis.

### C. DNA Intercalcating/Cross-linking Agents

Dr. Howdeshell presented the background information and data summary on the eight DNA intercalcating/cross-linking agents.

Dr. Smith said that she would prefer that carboplatin and cisplatin be grouped with the alkylating agents. Dr. Polifka said she would like to see a comment about the similar malformations in humans put into the conclusion paragraph of this section or the Executive Summary. Dr. Howdeshell agreed to carry the information over into a summary statement.

#### *DNA Intercalcating/Cross-linking Agents: Actinomycin D*

First reviewer Dr. Polifka reiterated her opposition to inclusion of chick embryo studies.

Second reviewer Dr. Mulvihill noted that although the draft and the Selig et al. 2012 paper agree on the number of cases (13), they are different cases, and he said he would provide the other reference names he had. He said that the labels in dosing information should be consistent.

#### *DNA Intercalcating/Cross-linking Agents: Carboplatin*

Reviewers Dr. Greene and Dr. Broussard had no comments on the carboplatin section.

### *DNA Intercalcating/Cross-linking Agents: Cisplatin*

Dr. Van Calsteren was first reviewer. She said the main exposure worries are nephrotoxicity and ototoxicity, and recommended they be mentioned separately. She recommended adding that in the case from Caluwaerts et al. 2006 the newborn had increased creatinine. She felt the denominator should only be used when the birth weight is noted for small for gestational age cases, and the denominator should only be used when fetal growth has been monitored for intrauterine growth restriction cases. For pregnancy complications, she commented that one case of placental metastasis (DiPaola et al. 1997) should be mentioned separately.

Second reviewer Dr. Mulvihill discussed a discrepancy in doses notated, with one in µg/mL and another in µg/L. He recommended changing them to the same unit for valid comparison purposes. He said it would help to know if the case of neurofibromatosis is from the first generation or second generation offspring. He asked for definition of the term "hypermetropia."

Dr. Polifka commented that she was uncomfortable with the wording in the first sentence of Section 5.10.2, noting that the literature on maternal transport of cisplatin to the infant via breastfeeding was not actually inconsistent, but that there were just a few case reports with a wide range of breast milk levels reported.

### *DNA Intercalcating/Cross-linking Agents: Daunorubicin*

Reviewers Dr. Greene and Dr. Rizack had no comments on the daunorubicin section.

### *DNA Intercalcating/Cross-linking Agents: Doxorubicin*

Reviewers Dr. Van Calsteren and Dr. Lawrence had no comments on the doxorubicin section.

Dr. McDiarmid mentioned that both daunorubicin and doxorubicin have topoisomerase-II inhibition mechanisms, which becomes important because they are identified as Group I known human carcinogens in the International Agency for Research on Cancer carcinogens list. Dr. Smith said both mechanisms should be included.

### *DNA Intercalcating/Cross-linking Agents: Epirubicin*

Dr. Lawrence was first reviewer. She noted that the summary text had verbiage suggesting there is little concern with epirubicin, but that statement is unjustified and should be removed. She specified removing the phrase in relation to major malformations, "however, this estimate may not be accurate…" (Section 5.17.5).

Second reviewer Dr. Polifka said it should be mentioned in the conclusion that with the malformations observed in the animal offspring, the animals had been exposed to levels below therapeutic levels.

### *DNA Intercalcating/Cross-linking Agents: Idarubicin*

First reviewer Dr. Van Calsteren said that cardiotoxicity was the main issue with idarubicin, so it should be clearly stated that there were three cases in 19. She also recommended starting with the key message in the section on fetal deaths; that there were three unexplained fetal deaths.

Second reviewer Dr. Smith noted that with the half-life of the drug was 22 hours, so the second statement in Section 5.20.2 should be omitted, due to the fact that there would be no drug present at that point. She also recommended that the first two sentences of Section 5.20.3 be omitted, as the data cited is misleading due to unrealistically low doses. She called for an explanation of what the statement about ventricular septal defect not being caused by exposure is based upon, noting that idarubicin is cardiotoxic, so that would seem probable in the absence of data. She added that the chick embryo assay is a standard fetal toxicity assessment tool, so she was not comfortable with omitting it.

### *DNA Intercalcating/Cross-linking Agents: Mitoxantrone*

Reviewers Dr. Smith and Dr. Broussard had no substantial comments on mitoxantrone.

Dr. Howdeshell asked whether daunorubicin and doxorubicin should be moved to a different mechanism of action category, or kept within this one but with acknowledgment that they have other mechanisms of action. Dr. Smith said that taking “cross-linking” agents out of the title of this classification, and moving carboplatin and cisplatin to the alkylating agents would clean things up.

Dr. Howdeshell asked if a statement should be added that idarubicin and the other anthracyclines are known to cause cardiotoxicity in patients, necessitating extra monitoring of the fetus. Dr. Van Calsteren supported that idea. Dr. Rizack felt that the cardiotoxicity should be mentioned wherever appropriate, but should be highlighted with idarubicin.

## D. Microtubule Function Inhibitors

Dr. Howdeshell presented the background information and data summary on the five microtubule function inhibitors.

### *Microtubule Function Inhibitors: Docetaxel*

First reviewer Dr. Lawrence had no comments on docetaxel.

Second reviewer Dr. Rizack added indications for metastatic bladder cancer, ovarian cancer, cervical cancer (relapsed), esophageal cancer, small cell lung cancer (relapsed), soft tissue sarcoma, Ewing's sarcoma, osteosarcoma, and unknown-primary adenocarcinoma. She also wished to add cases from Cardonick et al. 2012 and Zagouri et al. 2012.

***Microtubule Function Inhibitors: Paclitaxel***

Dr. Van Calsteren was first reviewer. She noted that Cremaphor was mentioned in the paragraph on animal toxicity, but felt that it should also be mentioned in the placental transfer paragraph (Sparreboom et al. 1996). She also noted that the additional cases from Cardonick et al. 2012 should be included.

Dr. Greene, the second reviewer, said he realized that for many of the case reports, the draft monograph's text was limited to what the study authors had said. However, he said that although the Bader et al. 2007 *Lancet Oncology* report terms the problem of the fetus exposed to both paclitaxel and trastuzumab as "fetal renal failure," there is enough evidence in the case report to decide that it was not actually renal failure but utero-placental insufficiency, complete with intra-uterine growth restriction and oligohydramnios. In this setting, he said, the physiologic response of the fetus is to reduce blood flow to the kidneys and so it is not surprising that there is oligohydramnios.

***Microtubule Function Inhibitors: Vinblastine***

First reviewer Dr. Polifka said her only comment was regarding the denominator issue; that the spontaneous and induced abortions and intrauterine death should be excluded from the denominators for the two different rates of malformations.

Second reviewer Dr. Smith's only comment related to the summary statement about syndactyly malformations not being related to exposure, asking what data the statement was based on and for further explanation.

Dr. Rizack recommended the addition of a reference to Connors 2008. She said that the paper contains data on 17 pregnant patients with Hodgkin's lymphoma of which 6 were treated with single agent vinblastine.

***Microtubule Function Inhibitors: Vincristine***

Dr. Smith was first reviewer. She questioned again the basis of the conclusion expressed about syndactyly.

Dr. Polifka was the second reviewer. She suggested four additional animal studies for inclusion in the monograph (see Appendix).

### *Microtubule Function Inhibitors: Vinorelbine*

First reviewer Dr. Greene had no comments on vinorelbine.

Dr. Mulvihill was the second reviewer. He suggested the word "prevalence" in the last paragraph should be written instead as "rate of frequency." He said the comparison made between "100% versus 3%" in that paragraph should not be made. He noted missing references (see Appendix).

Dr. Howdeshell appreciated the reviewers' comments and additional references provided for the microtubule function inhibitors.

Dr. McDiarmid suggested mentioning that these agents tend to cause aneuploidy. Dr. Spong recommended including a statement to that effect in the treatment of how the agents work.

## E. Topoisomerase II Inhibitor and Oxygen Free Radical Generator

Dr. Howdeshell presented the background information and data summary on the topoisomerase II inhibitor and the oxygen free radical generator.

### *Topoisomerase II Inhibitor: Etoposide*

Reviewers Dr. Broussard and Dr. Greene had no comments on etoposide.

Dr. Polifka mentioned that in the conclusion of the section it would be helpful to say that malformations were produced in the animal studies at doses that were less than the therapeutic doses. Dr. McDiarmid noted that etoposide causes secondary malignancies.

### *Oxygen Free Radical Generator: Bleomycin*

First reviewer Dr. Rizack had no comments on bleomycin.

Second reviewer Dr. Van Calsteren noted that bleomycin is also used for malignant germ line tumors of the ovary. She also suggested one additional reference, Iriyama et al. 2011.

## F. Targeted Therapies

Dr. Howdeshell presented the background information and data summary on the six targeted therapies.

Dr. Greene noted his preference was to refer to tamoxifen as a "partial agonist" as opposed to an antagonist. Dr. Birnbaum suggested removing reference to tamoxifen as an antiestrogen.

### *Targeted Therapies: All-trans Retinoic Acid*

Dr. Broussard was first reviewer. She noted a paragraph in the section on human exposure discussing infants with patent ductus arteriosus, and said that it is actually considered a normal condition of prematurity rather than a malformation, and should be de-emphasized. She also felt that in the discussion on page 66 there should be more emphasis placed on the fact that the related drug isotretinoin is one of very few documented known human teratogens, with a very high risk, prompting controlled dispensing programs in the United States to avoid pregnancy exposures.

Second reviewer Dr. Polifka said she would like the report to distinguish between systemic and topical exposures, even though cancer patients would only be getting the drugs systemically. For example, she said the first sentence in Section 5.6.3 should begin, "Systemic administration of all-*trans* retinoic acid…" She said it would be important to make the distinction because greater teratogenicity would be expected from systemic administration as opposed to topical use. She also said she would like to see a statement added to the Mechanism section to the effect that endogenous all-*trans* retinoic acid plays a key role in normal embryonic development, and so reductions or increases in levels raise concerns about adverse effects (Sulik 2010). She pointed out that in the second paragraph of Section 5.6.4, it should be noted that all three infants exposed to all-*trans* retinoic acid in the first trimester were normal. Also, in the Summary of Pregnancy Outcomes (Section 5.6.5), the third sentence should read, "Of the three liveborn infants that were exposed to all-*trans* retinoic acid during pregnancy, none had malformations." She wondered why the behavioral teratology studies had not been included in the section on animal studies.

Dr. Rizack said she didn't think all-*trans* retinoic acid comes as a topical preparation. Dr. Smith said that the isotretinoin Dr. Broussard had referred to comes as a topical, and that there have been 30 cases of congenital malformations with Retin-A reinforcing that topical exposure should be differentiated. Dr. Greene said he had a problem with that, as looking at the total dose of all-*trans* retinoic acid in a tube of Retin-A, a woman would need to ingest several tubes worth a day to get a significant systemic exposure. Dr. Spong asked if the topical form was used to treat cancer. The panel said it was not. She suggested that perhaps a sentence or two to clarify the situation would be useful. Dr. Polifka disagreed, noting that it needed to be pointed out that for other indications the drug is used topically, with much lower teratogenic risk. Dr. Birnbaum noted that the topical formulation is recognized to be teratogenic by the manufacturer. Dr. Smith noted that it is actually not recommended by the manufacturer to be used during pregnancy or breastfeeding. Dr. Rizack said that the discussion was on two different drugs, that all-*trans* retinoic acid used for cancer is different from Retin-A used for acne. Dr. Spong summarized that the report should acknowledge that there are two different ways to use

the drug. Dr. Howdeshell said she would work on how to acknowledge that there is a literature that has found adverse effects from topical use.

Dr. Howdeshell said they did not have behavioral study information available for the other agents, and so decided not to include it in this case. She said they would look at that literature again to ensure the effects were acknowledged.

***Targeted Therapies: Imatinib***

Dr. Rizack was the first reviewer. She added indications for imatinib: Philadelphia-positive acute lymphoblastic leukemia, chronic eosinophilic leukemia, and myelodysplastic and myeloproliferative disease associated with platelet-derived growth factor receptor gene rearrangements. She noted that there was mention in the literature that there might be a syndrome associated with the drug.

Second reviewer Dr. Van Calsteren had no comments on imatinib.

***Targeted Therapies: Interferon alpha***

First reviewer Dr. Mulvihill noted that there were three references in the Selig et al. 2012 paper that should be added. He said that the issue of accounting for twins versus conceptuses came up again in the section. He said there was an issue of referring to body surface area versus body weight, resulting in an imperfect comparison. He noted the use of the word "teratogenicity" versus "embryo toxicity," that teratogenicity includes embryo toxicity. He added that since interferon beta is mentioned, the section should be on "interferons."

Second reviewer Dr. Greene had no comments on interferon alpha.

***Targeted Therapies: Rituximab***

Dr. Rizack was first reviewer. She added indications for primary central nervous system lymphoma, lymphocyte predominant Hodgkin's lymphoma, Waldenström's macroglobulinemia, and post-transplant lymphoproliferative disorder. She also noted an additional recent reference, Daver et al. 2012. She added that she struggled to disregard the non-cancer data for rituximab, since that is where most of the data is.

Second reviewer Dr. Van Calsteren had no comments on rituximab.

***Targeted Therapies: Tamoxifen***

First reviewer Dr. Greene reiterated his comment that tamoxifen should be referred to as a partial agonist, and had no other comments.

Second reviewer Dr. Broussard had no comments on tamoxifen.

Dr. Smith suggested that terminology such as “anti-estrogen/estrogenic activity” or “mixed activity” may be more understandable to the lay reader, who may not understand agonist/antagonist terminology. Dr. Birnbaum suggested that it might be useful to discuss how tamoxifen can act like an estrogen in some tissues; it can block estrogen in others. Dr. McDiarmid said that when a drug’s International Agency for Research on Cancer classification is high, it should be mentioned.

### *Targeted Therapies: Trastuzumab*

Reviewers Dr. Lawrence and Dr. Van Calsteren had no comments on trastuzumab.

Dr. Howdeshell expressed her appreciation to the panel for their comments on the agents. She praised their suggestions for improvements to the readability and digestibility of the information in the section.

## VI. Long-term Evaluations of Growth and Development

Dr. Howdeshell presented a brief summary of the Long-term Evaluations of Growth and Development. She noted that it was a separate section because some of the data and discussions did not fall neatly into the format of the references in the Appendix tables.

Dr. Greene was the first reviewer. He said he had no specific comments on the section, noting that it was very clear and well-written.

Dr. Mulvihill was the second reviewer. He pointed out that there was a slight discrepancy in perspective in the discussion of Amant et al. 2012 in the opening paragraph versus the bullet.

Regarding her study mentioned in the section, Dr. Van Calsteren said that the differences in the cardiac measurements were statistically significant; worse than the control group, but still within normal limits. She said it was probably an effect of having too small a group. For the neurodevelopmental functions, she said the effect of prematurity should be stressed, as it is an important confounder, and will always be present in this study group. Dr. Greene asked whether the observers were blinded to the exposures in the babies. Dr. Van Calsteren replied that the observers had spoken to the patients, so they were not blinded in that way.

## VII. Cancer Diagnosed During Pregnancy: Background Information

Dr. Howdeshell presented a brief summary of background information on seven cancers frequently diagnosed during pregnancy, including breast, cervical, and ovarian cancers, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and melanoma. She noted that it was not the main focus of the draft NTP monograph.

### *Breast Cancer*

Primary reviewer Dr. Lawrence said that it should be recognized that with cancers, there has been a shift in staging over time, and so citations from the 1970s treat staging differently. Looking at prognosis by stage across pregnant versus non-pregnant women, she noted that there are also real life limitations in how breast cancer is staged, as a woman might not have full staging to avoid radiation and therefore be understaged. She said there would also be differences in care, and that should be recognized in any case/control comparison. She also mentioned the issues of recurrence of breast cancer and metastasis of breast cancer; when and how to treat those individuals and with what drugs. She acknowledged, however, that those questions were not really the goal of the monograph.

Dr. Howdeshell asked Dr. Lawrence if there was anything that could be added to the draft to acknowledge the challenges in treating recurrent breast cancer, or whether what was presented would be sufficient for its use in the document. Dr. Lawrence felt that the material was sufficient for its use.

Dr. Rizack mentioned that the National Comprehensive Cancer Network guidelines had recently been updated and supported the use of taxanes to treat breast cancer during pregnancy. She suggested changing the language on page 16 to reflect that update.

### *Cervical Cancer*

Primary reviewer Dr. Greene said that given the low occurrence rates for cervical cancers, the section would be easier to read if incidences were stated as per 100,000 rather than per 1,000. He asked Dr. Howdeshell if she had noticed in the literature that the histopathologic type of cervical cancer had been changing over the decades, from almost all strictly squamous cell cancers to increasing numbers of adenocarcinomas of the cervix and endocervix. He noted that cervical cancer is generally a long-term disease, and the reference to one-year survival in Baltzer et al. 1990 is not terribly informative, as it would be shocking to find a difference in such a short time. He said it would be helpful if the average durations of the follow-ups in the studies could be stated, to help the reader interpret the utility of the findings.

Dr. Birnbaum asked Dr. Greene to send some citations regarding his statement about the shift in pathology to adenocarcinomas, because NIEHS thinks this could be related to something in the environment. Dr. Greene agreed, noting also speculation around earlier and earlier acquisition of human papilloma virus. [Following the meeting Dr. Greene submitted three citations (see Appendix) on October 10, 2012.]

Dr. Howdeshell said there was a plan to adjust the rates of occurrence to be clearer.

Regarding treatments, Dr. Rizack said that the primary treatment for early disease is surgery, but that if radiation is to be used, radio-sensitizing chemotherapy is almost always used with it. Dr. Smith recommended updating the data in Table 5 to 2012 numbers, and suggested adding topotecan to the list of drugs approved by the FDA for treatment of cervical cancer.

***Leukemia***

Primary reviewer Dr. Rizack recommended adding under chemotherapy agents both chemotherapy for acute myelogenous leukemia and acute lymphoblastic leukemia, as well as agents for both chronic myelogenous leukemia and chronic lymphocytic leukemia. She noted that currently only acute myelogenous and chronic myelogenous leukemias are included. She added that the impact of the disease, more so than with solid tumors, should be mentioned as a possible confounding factor.

***Hodgkin Lymphoma***

Dr. Rizack was primary reviewer. She suggested changing the definition to read, "usually marked by the presence of a type of cells called the Reed-Sternberg cell or its variant."

***Non-Hodgkin Lymphoma***

Dr. Smith was primary reviewer. She suggested updating Table 9 to current numbers. She also suggested using common acronyms for each agent in Section 4.4.4 following first use to aid readability. She recommended adding a footnote to Table 10 listing the agents that were not reviewed with an explanation.

Dr. Howdeshell noted that they would check as to whether all of the cases were listed in the sections, or also in the Appendix tables, including the agents mentioned.

Dr. Smith added that there were two conflicting statements in Section 4.4.3, with the first paragraph implying that pregnancy did not impact prognosis, but a second statement implying that pregnancy promotes earlier or more rapid progression after delivery. She suggested more discussion to reconcile the statements.

Dr. Lawrence commented that the listing of all of the chemotherapy regimens would be out of date by the time the monograph is published. She said it was not necessary, and would not be helpful to practitioners. Dr. Howdeshell asked the panel whether the listing of specific agents used to treat the different cancer types was useful. The panel responded that it was.

***Ovarian Cancer***

Primary reviewer Dr. Van Calsteren felt that the section was very well-written. Her only comment was that ovarian cancer during pregnancy is now often diagnosed at an earlier stage due to the performance of so many ultrasounds in pregnancy.

***Melanoma***

Dr. Broussard was primary reviewer. She said that Table 15 is out of date, and asked if there was a way to further stratify the data; at least men versus women.

Dr. Rizack commented that the chemotherapy table in the melanoma section was from 2008, and is out of date, as there are several new agents now available for melanoma.

Regarding Dr. Rizack's comment on the Hodgkin lymphoma definition, Dr. Shelby said that had been taken directly from NCI, and, therefore, they would prefer to leave it as is unless Dr. Rizack could provide a reference. He said he had looked at the NCI's Surveillance, Epidemiology and End Results database, and it did not provide information on occurrence of these cancers among women of reproductive age. He spoke with a statistician at NCI, who suggested that such data could be compiled for women aged 15-44, but that it would take great effort to glean that information. Dr. Broussard mentioned that she had asked someone in the CDC Cancer Group to compile such information.

Dr. Van Calsteren suggested adding a sentence to the melanoma and leukemia sections addressing the issue of fetal metastases.

Although it was acknowledged that this cancer section is not the main focus of the monograph, Dr. Polifka wondered if there might be case reports regarding women who deferred treatment until after delivery, to include information about what kind of pregnancy complications they experienced. Dr. Howdeshell said that issue had not been part of the literature review, and asked Dr. Polifka for suggestions on where and how to address the topic. Dr. Van Calsteren noted that if there is no treatment during pregnancy, the malignancy would progress. She said there are data available for delay in treatment of cervical cancer, although it is a very slow-progressing disease. Dr. Polifka added that without knowing the risks involved, it would be difficult for women and their physicians to make an informed decision. Dr. Bucher said that he felt that adding such information would be overreaching the scope of the document, and could be misused. Dr. Greene agreed that there was a strong chance of misinterpretation, and recommended not adding the information.

Dr. Howdeshell asked the panel whether they should keep the current treatments for different cancer types in the document, or remove them because they will be outdated quickly. Dr. Spong asked for a straw poll of panel members, and they agreed that the information should be removed.

## VIII. Pregnancy Outcomes of Medical Personnel

Dr. Howdeshell briefed the panel on one subset of the population also exposed to cancer chemotherapeutic agents: health workers, including women of reproductive age.

First reviewer Dr. Broussard felt that the section was a valuable addition to the document. She noted that although the levels of exposure are expected to be lower, they are often unrecognized, can occur over long periods of time, and may involve multiple chemotherapeutic agents. She said that references for the last paragraph only address spontaneous abortion, while the text discusses published studies reporting associations with malformations, low birth weight, and infertility.

Second reviewer Dr. Smith felt that custodial workers, who remove bio-hazardous waste, should be added to the list of those potentially exposed. She felt that the recent improvements in safety practices and equipment that have limited workplace exposure should be alluded to in the text. She also suggested adding a section on recommendations for safe handling of chemotherapeutic agents in the workplace and mentioned two more recent references than those cited in the document.

Dr. Polifka said she liked the section, because there is much concern about this type of exposure. Dr. Mulvihill added that there have been lawsuits in this area.

Dr. Greene pointed out a mistake on page 178, second paragraph, second sentence: the word “birth” should be “chemotherapy.”

## IX. Research Needs and Communication Strategies

### A. Communication Strategies

Dr. Howdeshell presented the main discussion points regarding communication strategies to the panel, noting that NTP would like to effectively disseminate the information presented in the monograph, and would like to make available a database of the pregnancy outcomes collected for the monograph.

Dr. Polifka predicted that teratogen information counselors and genetic counselors would like the monograph and would find it to be a valuable resource.

Dr. Rizack suggested that the target audiences should include obstetrician/gynecologists, medical hematologist/oncologists, gynecologic oncologists, radiologists, geneticists, and clinical pharmacists.

Dr. Mulvihill said the national meetings should be targeted, with a verbal presentation of the monograph. He specifically mentioned the Society of Toxicology, as well as teratology, pediatrics, medical genetics, obstetric/gynecology and cancer meetings. He recommended publication of summary articles in the *New England Journal of Medicine*,

*JAMA*, *Nature Medicine*, *Science*, or *Environmental Health Perspectives*. He felt that the data on breast milk and placenta exposure would make an excellent short article for wide distribution. He encouraged training, and engagement with local lay women and their physicians who might benefit from the information contained in the document and would be willing to share their stories. He recommended partnering with NCI, the National Institute of Child Health and Human Development (NICHD), the NIH Office of Rare Diseases, the CDC's Maternal and Child Health Bureau and the FDA to disseminate through those institutions' press offices. He said the Cancer Information Service would be very interested in the monograph, and it should be added to NCI's Physician Data Query database. He suggested partnering with PhRMA, and potentially interested media such as National Public Radio, Public Broadcasting Service (PBS), and network news programs. He also suggested networking with the March of Dimes, the American Cancer Society, and the Lance Armstrong Foundation. He recommended consideration of whether this would be an appropriate topic for an NIH Consensus or State-of-the-Science conference.

Dr. Spong noted that the project had been a huge undertaking and that it would be difficult to publish a single, succinct overview, but asked if there was a plan to publish a summary document in a highly referenced, highly read journal. Dr. Howdeshell said the team had had some preliminary discussions about where the document would go, noting that previous products by the Center for the Evaluation of Risks to Human Reproduction, the predecessor to OHAT, had been published in the journal *Birth Defects Research*. She said that an editorial in one of the prominent medical journals would also help target the maternal and fetal community. She added that there is a symposium planned for next year's Teratology Society meeting, including a presentation on the results of the monograph. Dr. Spong mentioned that journals often reserve editorials to accompany articles published within the journal, but that it would still be worth speaking to the editors to assess their needs.

Dr. Smith echoed the idea of reaching out to the larger national organizations, adding the Hematology/Oncology Pharmacy Association and the International Society of Oncology Pharmacy Practitioners to the list, suggesting links to the monograph from their home pages. She felt there would be strong interest from the lay press as well.

Dr. Polifka added that the Teratology Society has a section on its website for documents, so the monograph should be there. She also suggested making it available on the Organization of Teratology Information Specialists (OTIS) website, as a way of reaching many pregnant women or those contemplating pregnancy, as well as physicians. She also mentioned the American College of Obstetricians and Gynecologists is an organization that should be involved, and that the reproductive databases such as the Teratogen Information System (TERIS) and Reprotox®, as well

as Shephard's Catalog, should cite the monograph in their agent summaries. Dr. Bucher added that the monograph would be in PubMed. Dr. Rizack added the American Society of Hematology and the Society of Gynecologic Oncology to the list of professional organizations. Dr. Broussard added the National Library of Medicine's LactMed database on drugs and lactation.

Dr. Birnbaum asked the panel for suggestions about communication to the media and the general public. Dr. Mulvihill said he felt strongly about the need to engage women advocates, as the press often wants a patient story first. Dr. Birnbaum appreciated that suggestion, but was asking more about how the institute should respond. Dr. Spong noted that panel members would likely get calls, and suggested that they be provided with bulleted talking points. She said that knowing the message to be communicated is actually more important than the specific question being asked. Dr. Mulvihill suggested that an FAQ list would also be helpful. Dr. Wolfe asked that panel members let NTP know if they are contacted by the media, so that responses could be coordinated, with clear and succinct messages.

Dr. Smith mentioned resources available at NCI. Dr. Spong pointed out that some of those resources would be beyond the scope of the monograph, but would clearly be of interest to patients. She said that being informed about where to direct patients for information would be valuable. Dr. Howdeshell said it was important to make it clear that the ultimate decision is up to the patient. Dr. Broussard said she did not see patients reading the monograph, and that it should be focused as a resource for clinicians. Dr. Spong suggested having a vetted presentation with take-home messages included available for download on the website, so that people in their home institutions who may want to discuss the topic with their patients or medical students would have a reliable reference guide. Dr. Greene felt that the monograph would likely be accessed for targeted information by patients and doctors, in a similar manner to UpToDate®, an evidence-based, peer-reviewed information resource for practitioners and their patients. He said the authors of the oncology sections of UpToDate® should be made aware of the monograph when it is released. Dr. Van Calsteren noted that the databases searched as part of preparing the monograph should be informed about it, as well as the registry sites. Dr. Mulvihill added that part of the big message should be that there are still gaps in the knowledge, and that researchers' help will be needed in the future to expand that knowledge and fill those gaps.

### B. Research Needs

Dr. Howdeshell presented briefly identified research needs, including suggested objectives to improve the understanding of the effects of gestational exposure to cancer chemotherapy and efforts to develop and improve consensus guidelines for diagnosis, staging, and treatment of pregnant women.

Dr. Greene said that research gaps are obvious and need attention from looking at the data, which are incomplete and imprecise. He said it should be expected that there will never be randomized trials, so better quality of individual reports should be promoted, because that will continue to be the primary source for literature on this topic. He wondered whether there might be a registry established and curated by a national group. He recognized the tension over who should pay for the registry, perhaps being the drug makers, but he noted also that many of the agents involved are now off-patent and it would be hard to attract a drug manufacturer. Therefore, he said that a national organization that watches the data may be better suited, such as the CDC, the FDA, or NIH. He suggested getting journal editors to require standardization of case reports, with ideas from the panel regarding desirable reporting elements.

Dr. Spong suggested that OHAT publish on its website a document outlining the desired elements of a case report. Dr. Greene noted that case reports come from a wide variety of different sources, such as oncologists and pediatricians, or obstetricians/gyncologists, and so collaborative efforts to report the cases would make it less likely that important aspects of the case are overlooked. Dr. Bucher said that the NTP previously tried putting guidelines out for reports on the characterization of nanomaterials with unsatisfactory results, but it would certainly be worth trying for this topic. Dr. Mulvihill said that there are precedents of editors agreeing on certain elements for a journal article, so sending a 2-page document to the top 100 journals may be worth pursuing.

Dr. Greene noted that with the advent of electronic publishing, the field is no longer restricted to paper. Journals are always concerned about the expense of publishing pages, he said, but the type of information being discussed could easily be stored on journal websites.

Dr. Howdeshell added that as the project was being conceived, there had been an article in *Nature* about the need for more information about both maternal and fetal health during different health conditions, including pregnancy.

Dr. Mulvihill mentioned the need for a population base for more systematic evaluation of pregnancy and fetal outcomes. He suggested two routes. Pregnant women are excluded from virtually every clinical trial. The moment the exclusion takes place would be the ideal time for capturing the woman for a registry of pregnant women diagnosed with cancer, as she would not yet have received therapy and the outcome is not yet known. Another idea he proposed was to mine record-linkage studies from Denmark. He said they would be a rich source of data, and that he had already spoken with a Danish colleague who expressed willingness to work on a project.

Dr. Polifka noted that OTIS does collaborative studies with the European Network of Teratogen Information Services. She said that such collaboration can help collect large enough samples of women who have been exposed to the various agents to acquire meaningful data. She said OTIS might be interested in doing a study involving women exposed to the neoplastic agents, following them and their offspring.

Dr. Rizack mentioned that it is not always easy to register patients. She said it would be helpful to have guidelines on how hospitals should include pregnant patients in tumor registries, since that is often a first source of information. Dr. Mulvihill added that his registry is now available on line, with a seven-page form to be filled out. Dr. Smith endorsed the idea of a nationwide tumor registry as a vehicle to capture data. Dr. Spong summarized the discussion about establishing and optimizing a registry as a source of information.

Dr. Van Calsteren described two other important elements that are presently lacking: long-term follow-up and data on the pharmacokinetics of chemotherapy during pregnancy. Dr. Smith agreed that pharmacokinetics should be a high priority for research, as there are few data, and grant reviewers tend to give applications low scores for significance due to the relative rarity of cancer chemotherapy during pregnancy. She called for long-term, follow-up data on kidney, liver, and cardiac function. Dr. Mulvihill added dysmorphology evaluation to that list, citing the example of the discovery of fetal alcohol syndrome. He suggested that the NICHD, with its available resources, would be appropriate for undertaking the project of conducting such examinations. Dr. Polifka noted the example of the California Teratogen Information Service initiative, the Womb to Classroom Screening Program, for the detection of agents with adverse effects on neuropsychological development (Adams et al. 2012).

Dr. Broussard said that although prospective studies clearly are needed, case/control studies are also an important means of studying rare outcomes such as birth defects. Dr. Polifka asked Dr. Broussard about the CDC funded case/control study, the National Birth Defects Prevention Study. Dr. Broussard described the study, and said that there may be a study of cancer drugs included at some point.

Dr. DeBord said she was concerned about both men and women taking the chemotherapy drugs and then conceiving, particularly in light of emerging studies describing epigenetic changes. She suggested that the follow-up with the children involved extend beyond just the first few years. She also suggested trying to acquire information from the pregnant women's partners and other family members about what types of exposures they may have had to the chemotherapeutic agents as caregivers.

Dr. Spong asked for comments from the panel on the five "other questions regarding research needs" they had been asked to consider.

1. Please comment on potential areas for improvements in current procedures used to detect possible long-term effects of cardiotoxicity in children gestationally exposed to cancer chemotherapy.

Dr. Van Calsteren said that the children need ultrasound, electrocardiogram, and clinical examination on a regular basis, such as every three years, until they are adults. The length of follow-up is the important element, using current, widely available, cardiac examination techniques.

2. Please comment on strategies that could be used to differentiate between adverse effects of *in utero* exposure to cancer chemotherapy and the adverse effects of preterm birth.

Dr. Spong said that it was an excellent question given that preterm birth itself has so many sequelae and consequences. She suggested a case/control study with preterm and term infants, and infants exposed to chemotherapeutic agents for treatment of cancer in pregnancy, so that the pertinent groups would all be represented and outcomes could be compared. Dr. Mulvihill said that a group of non-cancer patients receiving an agent would be important in that scenario as well.

3. Please identify research approaches that could be used to assess potential effects of cancer chemotherapy use during pregnancy on long-term development of children, including the potential for increased cancer risk and effects on organ systems (e.g., neurological, hematological, immunological, and/or reproductive systems).

Dr. Spong said the question involves the previous discussion on registries, and how important it would be to look at the long-term physiological functions of the children exposed during pregnancy, with the realization that it could take a very long time to get good information. Dr. Mulvihill added that this is where the notion of a registry and record linkage enters in, particularly linking offspring to mothers.

4. In general, the NTP did not identify any obvious patterns of developmental toxicity or pregnancy outcomes based on specific classes of agents (e.g., anthracycline antibiotics) or specific mechanism of action. Please comment on whether there are health effects that suggest a pattern based on specific class of agents or specific mechanism of action other than those that have been identified in the draft monograph.

In response, Dr. Polifka brought up the methotrexate/cyclophosphamide issue, as had previously been discussed. Dr. Mulvihill added the previously discussed suggestions about showing the data combined by agent class, and adding bottom-line summaries on the classes. Dr. Spong noted that this would be where tying into the reproductive animal data would be helpful. Dr. Smith felt that animal studies could be informative as to how to prevent long-term toxicities in the fetus associated with exposures. Dr. Spong speculated that one idea would be to increase the time between chemotherapy doses to allow function to return.

5. Please suggest strategies (e.g., better use of existing registries, publication of registries) that might improve availability of data for research on effects of cancer chemotherapy use during pregnancy. How might these strategies be effectively implemented or communicated to targeted groups?

Dr. Spong reiterated the panel's conclusion about the importance of registries to this field, and the importance of these being easily accessible in order to get the needed data, which is difficult when they are not financially supported. Dr. Polifka wondered whether there might be a role for the FDA to require or mandate the establishment and support of registries, as the agency has successfully done with some manufacturers of newly marketed drugs. Dr. Howard noted that there is much pressure for the FDA to do so, but there is also much pressure from the manufacturers' side not to, due to the expense involved. Dr. Mulvihill asked whether the FDA has adverse effect reports that may not have been looked at in this area. Dr. Howard said that there is a very comprehensive adverse event reporting system, and that the reports are looked at carefully by the agency. Dr. Mulvihill asked whether anyone had looked at them through this particular lens. Dr. Howard said that he could not answer that query with any confidence, given that there are 113 chemotherapy drugs currently in use. He said that he could certainly direct that question to the appropriate parties within the agency.

Dr. DeBord noted that NIOSH has a list of hazardous drugs, including most of the chemotherapeutic agents, which have been evaluated in terms of teratology, mutagenicity and other factors. She said the list is updated every two years, including new chemotherapeutic agents or old drugs with new warnings.

Dr. Smith said there is a need for consistency in preventing incidental exposure associated with research criteria, in terms of how women of child-bearing age are dealt with from protocol to protocol, including the form of contraception identified In the protocols to prevent pregnancy from occurring during the trials. She felt that there should be a consistent message, particularly with the new target agents coming out.

Dr. McDiarmid suggested that there be mention in the monograph about drugs with male-mediated reproductive toxic effects. Dr. Mulvihill noted that there had been three

international conferences on male-mediated reproductive toxicity, the summaries of which could be used as references.

## X. Closing Comments and Adjournment

Dr. Howdeshell acknowledged and thanked her team members for their contributions to the draft monograph project, and expressed her gratitude to the panel members for their participation. Dr. Thayer added her appreciation for the panel's fruitful discussions, especially given the monograph's balance of aggregating the data in a useful manner while not attempting analyses that were inappropriate given all of the limitations.

Dr. Bucher noted that the conclusions voted upon by the panel would be the main conclusions in the document, and that the additional information provided by the panel members would be included, possibly in an appendix. He added his thanks to the panel for its extraordinarily productive review, and especially thanked Dr. Spong for her excellent service as chair.

Dr. Spong adjourned the meeting at 1:30pm, October 2, 2012.

## XI. Appendix: References Submitted by Panel Members

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These summary minutes have been read and approved by the Chair of the October 1-2, 2012, National Toxicology Program Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy Peer Review Panel Meeting.

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Dr. Catherine Spong
Chair, NTP Monograph Peer Review Panel Meeting

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