PEER REVIEW REPORT FOR THE DRAFT NTP BRIEF ON BISPHENOL A

from the

NTP BOARD OF SCIENTIFIC COUNSELORS MEETING

on June 11, 2008

National Toxicology Program

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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1. Introduction

In December 2005, The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) announced its intention to conduct an evaluation of the potential for bisphenol A to cause adverse effects on reproduction and development in humans. CERHR selected bisphenol A for evaluation because of:

- Widespread human exposure
- Public concern for possible health effects from human exposures
- High production volume
- Evidence of reproductive and developmental toxicity in laboratory animal studies

Bisphenol A (CAS RN: 80-05-7) is a high production volume chemical used primarily in the production of polycarbonate plastics and epoxy resins. Polycarbonate plastics are used in some food and drink containers; the resins are used as lacquers to coat metal products such as food cans, bottle tops, and water supply pipes. To a lesser extent bisphenol A is used in the production of polyester resins, polysulfone resins, polyacrylate resins, and flame retardants. In addition, bisphenol A is used in the processing of polyvinyl chloride plastic and in the recycling of thermal paper. Some polymers used in dental sealants and tooth coatings contain bisphenol A. The primary source of exposure to bisphenol A for most people is assumed to occur through the diet. The highest estimated daily intakes of bisphenol A in the general population occur in infants and children.

CERHR follows a formal process for review and evaluation of nominated chemicals that includes multiple opportunities for public comment (http://cerhr.niehs.nih.gov/aboutCERHR/index.html). As part of that process, the NTP prepared a draft Brief on Bisphenol A. The goal of the NTP Brief is to provide the public, as well as government health, regulatory, and research agencies, with the NTP's conclusions regarding the potential for bisphenol A to adversely affect human reproductive health or children's development. The draft NTP Brief on Bisphenol A was released for public comment in April 2008. The NTP Board of Scientific Counselors (supplemented with several non-voting ad hoc reviewers, see "Attendees") conducted a peer review of the draft NTP Brief on Bisphenol A on June 11, 2008. The Peer Review Report for the NTP Brief on Bisphenol A contains a summary of that peer review as well as NTP's response to major comments and recommendations made during the peer review. Verbatim transcripts and video of the peer review meeting are available on the NTP web site at http://ntp.niehs.nih.gov/go/32964.

The final NTP Brief will be released as part of the NTP-CERHR Monograph on BPA which is available on the CERHR website (http://cerhr.niehs.nih.gov see Bisphenol A under "CERHR Chemicals" or http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.html) and in hardcopy or CD from CERHR. Information related to the evaluation of bisphenol A is available on the CERHR website.

2. Summary of Peer Review

2.1 Exposure

Primary reviewer comments: Katharine Hammond, PhD (BSC member; University of California Berkeley) and Ruthann Rudel, MS (ad hoc reviewer; Silent Spring Institute)

Dr. Katharine Hammond said the NHANES/CDC data demonstrate wide-spread exposure to BPA. Moreover, because BPA has a relatively short half-life in humans, ~ 5 hours, the exposure must be both ubiquitous and continuous. In addition, the NHANES data indicate that exposures to BPA are increasing over time. More specifically, the median level doubled (from 1.3 μg/L to 2.7 μg/L) and the 95th percentile values tripled (from 5.2 μg/L to 15.9 μg/L) between NHANES III (1988-1994) and NHANES 2003-2004. Dr. Hammond suggested the NTP expand the discussion of exposures to the general population to emphasize the point that exposure is continuous.

Dr. Hammond noted that 10% of the total BPA detected in urine samples by the CDC was in the unconjugated form (Ye *et al.* 2005) and a higher percentage, > 50%, of total BPA detected in breast milk was in the unconjugated form (Ye *et al.* in press).[1] Other studies suggest that pregnant women may have higher concentrations of unconjugated BPA in blood compared to other populations (Padmanabhan *et al.* 2008; Schönfelder *et al.* 2002).[2] These findings are not necessarily predicted for a rapidly metabolized compound and suggest that exposures during vulnerable periods in development, such as pregnancy and infancy, may involve higher exposures to the unconjugated form of BPA.

Dr. Hammond questioned whether all routes of exposure have been adequately considered. For example, BPA is used in epoxy paints and coatings. This is certainly a source of exposure for workers but may also result in inhalation exposure to the general population during periods of painting in the home. Although fairly extensive assessments to identify sources of exposure have been conducted (Wilson *et al.* 2003; Wilson *et al.* 2007), these assessments did not include biological measurements such as urinary concentration of BPA. A biological measurement would be helpful in determining if the identified sources of exposure sufficiently characterize human exposures.

Dr. Hammond also commented on the occupational standard for BPA in the workplace. As summarized in the expert panel report, the only occupational standard available for BPA is the workplace environmental exposure level (WEEL) of 5 mg/m^3. This number is a default value used for nuisance particulates and is probably not based on a toxicological assessment. Dr. Hammond suggested including more discussion of occupational exposures in the NTP Brief.

[1] Dr. Richard Wang, CDC, said the higher percentage of unconjugated BPA in breast milk compared to urine may be related to the more lipophilic nature of the unconjugated form compared to the more water soluble conjugated forms. Additional data are needed to determine if BPA is "stored" in lipids.

[2] According to Dr. Wang, the NHANES data includes urinary concentrations for pregnant women but these concentrations have not been compared to the concentrations for non-pregnant women. In addition, no attempt has been made to associate the dietary data from NHANES with BPA concentrations in urine.

Ruthann Rudel supported the NTP conclusion that the best available method to estimate daily intake is based on "back calculating" from total BPA measured in urine (Lakind and Naiman). However, this approach does not address concentrations of unconjugated BPA in circulation or in target tissues in fetuses and infants. She also supported NTP's consideration of non-oral studies in neonatal animals for four main reasons.

First, inhalation exposure, which is not subject to first pass metabolism, occurs in workers. She has detected BPA in the air at an occupational setting at a concentration that is ~100 times higher than ambient levels (Rudel *et al.* 2001). However, this is likely an underestimate because her measurements were made at a time of very little activity in the workplace. More research on characterizing occupational exposures and potential health impacts in workers is warranted. Ms. Rudel believed the NTP would be justified in increasing the level of concern for workers.

Second, medical uses of BPA have been reported which may result in non-oral exposures. In particular, the use of BPA in PVC plastic has been mentioned and, if still occurring, could result in exposures in medical settings by non-oral routes of exposure. In this respect, it is worth noting that the studies that reported relatively high concentrations of free BPA in blood used samples that were collected from women in the hospital for delivery (Padmanabhan *et al.* 2008; Schönfelder *et al.* 2002). Women in delivery are routinely connected to an IV. A higher level of concern for adults, including those not occupationally exposed, could be supported if PVC medical devices prove to be a source of exposure.

Third, unconjugated BPA has been found in human urine, breast milk and blood. It does not seem likely that these measurements can be completely accounted for by potential contamination from labware or conversion of BPA-glucuronide to BPA during sample processing. Current thinking related to human pharmacokinetics and sources of exposure will need to be reassessed if these measurements of unconjugated BPA are accurate. The impact of contamination and conversion can be assessed empirically and more research related to the detection of unconjugated BPA in serum that controls for these factors is needed, especially in vulnerable populations.

Finally, Ms. Rudel thought the consideration of the non-oral studies in young animals is warranted because of the data that indicate less efficient metabolism of BPA early in life.

Ms. Rudel suggested the NTP Brief present the maximum detected concentrations of total BPA in urine and the corresponding estimated daily intakes along with the information presented for the 95th percentile. This is important because exposure data are typically skewed to the right such that the maximum values are often much higher than those at the 95th percentile. BPA is no exception and the urinary concentration of BPA at the 95th percentile is an order of magnitude lower than the maximum. It may be misleading not to present the maximum values as these represent the upper end of the exposure range.

General Discussion

Dr. Kenny Crump made general comments on the quality of the human exposure data, most notably the lack of any biologic measurements in infants. Another area that needs to be better

characterized is the extent to which BPA appears in human breast milk. The available data from the CDC are based on relatively small numbers of women (Ye *et al.* in press; Ye *et al.* 2006). The estimated ranges of daily intakes for infants are based on assumptions that rely on maximum detected values and worst case scenarios. Thus, it is difficult to compare these estimates to the doses used in toxicology studies. Having the most realistic assessment of exposure is especially important for BPA so that a determination can be made as to how close concentrations in humans are in relation to the doses at which adverse outcomes have been detected in rodents. Dr. Hammond agreed, but emphasized the importance of also characterizing high end exposures. Small percentages of people with high levels of exposure translate to a large number of people nationwide.

Dr. Steven Leeder suggested adding information in the "Are People Exposed" section of the NTP Brief stating that the available data, although limited, indicate fetal exposure to BPA. Available data show that while the placenta can serve to some extent as a "sink" for BPA, fetal concentrations were generally similar to maternal concentrations (Schönfelder *et al.* 2002). In addition, fetal concentrations exceeded maternal concentrations in a subset of 14 of the 37 samples included in the study. It is worth noting that 12 of those 14 samples were males.

2.2 Consideration of Non-Oral Route of Administration

Ad hoc reviewer comments: Steven Leeder, Pharm.D, PhD. (Children's Mercy Hospitals and Clinics)

Dr. Leeder said the draft NTP Brief accurately presents information related to glucuronidation of BPA. However, he believed that other metabolic pathways for BPA, namely sulfation, are also important to consider and should be discussed more in the document. Dr. Leeder expressed qualified support for NTP's consideration of studies that use a subcutaneous (sc) route of administration in neonatal animals. He would have more confidence in considering oral and sc routes of administration as comparable in young animals if this conclusion were also supported by dosimetry data at the tissue level. Dr. Leeder thought more research on the metabolism of BPA is needed to better interpret the laboratory animal studies for estimating potential risk to humans following BPA exposures during development.

He said the emphasis on glucuronidation pathways to metabolize BPA can be partly attributed to the techniques used to measure conjugated BPA metabolites. Bisphenol A- glucuronide (BPA-G) is usually measured indirectly by determining the concentration of parent BPA present in the sample before and after a deconjugation procedure with the difference in the two measurements representing the amount of BPA that was present in a conjugated form (usually assumed to be BPA-G). However, the commercial β-glucuronidase preparations used to convert BPA conjugates to the parent compound during the deconjugation stage differ in their ability to deconjugate the glucuronide and sulfate metabolites. One of the most common enzyme preparations is the β-glucuronidase isolated from *Helix pomatia* that contains both glucuronidase and arylsulfatase activities. Thus, estimates of BPA-G based on this preparation could be an overestimation to some degree because the proportion of conjugated metabolite due to the BPA-sulfate content is not determined. The CDC used a glucuronidase enzyme preparation that only had glucuronidase activity and was able to determine that ~20% of the measurable metabolite

was in the sulfate form. This issue is important in considering age-specific differences in ability to metabolize BPA because UDP glucuronosyltransferase (UGT) and sulfotransferase (SULT) isoforms do not necessarily show the same maturational patterns. For example, the human fetal liver has high sulfotransferase content for some SULT isoforms that can decrease during postnatal life. Although it is true that neonatal UGT and SULT enzymes systems may have underdeveloped capacity to deal with foreign compounds, this does not mean there is no capacity to metabolize. The data are insufficient to determine the impact for humans exposed to BPA during development.

UGT2B1 has been identified as the principle UGT isoform that metabolizes BPA to BPA-G in the rat (Matsumoto *et al.* 2002). This isoform shows low expression and activity during development. However, it is important to note that this study only characterized UGT2B1 activity during development and did not include other members of the UGT2B family. Thus, the understanding of BPA metabolism during development in the rat is still incomplete. In addition, it is difficult to translate the rat findings to humans because the UGT isoform(s) that metabolize BPA in humans have not been identified. Humans have 7 members of the UGT2 family that have functional activity, one UGT2A and six UGT2B isoforms. Tissue specific expression of these enzymes also occurs, and the ontogeny of each isoform in humans is not well characterized.

In contrast, there is information on the SULT isoforms that metabolize BPA in humans. In humans, SULT1A1 has been identified as the SULT with the highest catalytic activity towards BPA, although SULT1E1, SULT2A1 and a SULT1C isoforms are also capable of catalyzing BPA-S formation (Suiko *et al.* 2000). For reference, SULT1A1 prefers planar phenols as substrates, including thyroxine, whereas 17β-estradiol and dehydroepiandrosterone (DHEA) are prototypic substrates for SULT1E1 and SULT2A1 respectively. In humans, SULT1A1 activity is comparable in fetal and postnatal liver although there are differences in cellular localization (hematopoietic stem cells during fetal life and hepatocytes after birth).

The ability of BPA to perturb the normal function of these enzyme systems during development should also be considered. These enzymes regulate the synthesis or catabolism of small molecular weight endogenous compounds that need to be tightly controlled during development. For example, SULT2A1 is expressed at very high levels in the fetal adrenal gland and controls the final step in the synthesis of DHEA sulfate which is then further processed by the liver and converted to estriol in the placental trophoblasts. In humans, there is an approximate 5 to 10-fold increase in estriol concentration during pregnancy compared to estradiol. However, estradiol is the estrogen of interest in laboratory animals because it is the predominant estrogen that is formed during pregnancy. In this respect, there are species differences that may complicate the interpretation of the rodent data for humans.

Although a new study did not report any significant differences in plasma area under the curve (AUC) based on oral and sc routes of administration (Taylor *et al.* 2008), Dr. Leeder thought additional work is needed to identify possible differences in tissue distribution. In this study, he noted that there appears to be a dip in the plasma concentration of BPA following sc administration that is not apparent following oral dosing. This may reflect movement of BPA from the plasma to tissues and back to the blood compartment that does not occur following oral

dosing. For this reason, he thought assessing the comparability of tissue distribution would be an important step in evaluating the similarity of oral and sc administrations.

General Discussion

Dr. Jim Riviere agreed with NTP's consideration of studies that use sc injection in neonatal rodents although there are still significant data gaps. He agreed with Dr. Leeder that a significant amount of research is needed to understand the metabolism of BPA, e.g., specific isoforms of metabolizing enzymes in humans and across rodent species/strains. While sc dosing may allow greater control of administered dose, information related to metabolism is needed to compare these studies with those that use oral administration.

Dr. Gail McCarver agreed with the conclusion that human infants have reduced ability to glucuronidate and sulfate compared to adults. The magnitude of the maturational differences is less for sulfation compared to glucuronidation.

2.3 Behavior

Ad hoc reviewer comments: Michael Baum, PhD (Boston University)

Dr. Baum concurred with the draft NTP Brief that there is "some concern" for neurobehavioral effects during development. These effects include a loss of sexual dimorphism in non-reproductive behaviors. Specifically, sexual dimorphisms in activity in the open field test and the elevated plus maze test are attenuated following perinatal BPA exposures. In addition, a couple of well-conducted studies reported differences in the morphology of the brain regions involved in reproduction, i.e. the anteroventral periventricular nucleus (AVPV) of the rostral preoptic area that is involved in controlling the preovulatory lutenizing hormone surge in rodents and the locus coeruleus (LC) that is associated with the regulation of attention.

Dr. Baum thought the literature on brain and behavior is more consistent than indicated in the draft NTP Brief. For example, Rubin *et al.* (2006) showed that perinatal exposure to low doses of BPA significantly reduced the number of tyrosine hydroxylase (dopaminergic) neurons in the AVPV of female mice, bringing this value down to that seen in control and BPA-exposed males. This finding correlates with an earlier study by this same group that reported disrupted estrous cyclicity in adult female mice following perinatal exposure to BPA (Rubin *et al.* 2001). Dr. Baum noted that the relevance to humans of the reported masculinizing effects of perinatal BPA exposure on the morphology of the female mouse AVPV is unclear as there is no homologous hypothalamic structure in humans. Furthermore, in contrast to rodent species, old world primates including humans do not exhibit a sexual dimorphism in the ability of ovarian steroids to elicit a preovulatory LH surge. Dr. Baum believed more research in this area is warranted, perhaps in higher species than rodents, such as mini-pigs or rhesus monkeys, to assess long-term impacts from perinatal BPA exposure.

Several of the behavioral studies were very well-designed. These studies all controlled rigorously for potential litter effects (Gioiosa *et al.* 2007; Rubin *et al.* 2006; Ryan and Vandenbergh 2006). In addition, these studies took precautions to control for the possible confounding effect of group

differences in the availability of ovarian estradiol at the time of testing by only testing animals in the same stage of estrous.

The central hypothesis in these studies of brain morphology and behavior was that perinatal exposure to BPA, acting as an estradiol receptor agonist, permanently "organized" brain circuits in females that controls the release of the cyclic (preovulatory) gonadotrophin releasing hormone (GnRH) as well as female-typical emotional responses so as to make them more male-like. The case for such a reorganization is convincing in the morphological studies showing that perinatal BPA exposure masculinized (reduced) AVPV cell number in female mice (Rubin *et al.* 2006) and locus coeruleus volume and cell number in female rats (Kubo *et al.* 2001; Kubo *et al.* 2003). Previous research suggests that these two morphological sexual dimorphisms are not affected by adult variations in circulating sex hormones. The argument for an organizational effect on behavior is less compelling when based on studies that did not control for differences in adult levels of circulating sex hormones. This is an important issue because sex hormones in adult animals can reflect activational effects of hormone signaling as opposed to perinatal ("organizational") actions of BPA on brain circuits that control those behaviors. Observed behavioral effects of perinatal BPA could reflect "hard-wired" changes in brain connectivity accomplished during the normal perinatal period of brain sexual differentiation ("organizational") or, alternatively, they could simply reflect group differences in plasma levels of circulating sex hormones at the time of adult testing. Aside from the studies by Rubin *et al.* (2006), Ryan and Vandenbergh (2006), and Gioiosa *et al.* (2007) the other studies cited in the draft NTP Brief did not address this issue.

Another issue that is raised by the studies reviewed in the NTP report, but which is only mentioned in passing, involves the implicit presumption in nearly all of the neurobehavioral studies reviewed that estradiol, formed perinatally in the male rodent brain via the aromatization of testosterone (secreted from the fetal/neonatal testes), is solely responsible for male-typical brain and behavioral sexual differentiation. As such, any effects of perinatal BPA exposure would reflect either an agonist action of the compound at neural estradiol receptors (female subjects) or an antagonist action (male subjects). Normal sex differences in all of the above-mentioned neural (AVPV and LC volume/cell number) and behavioral (locomotor activity; exploration in the plus maze) variables that are convincingly modulated by perinatal BPA exposure have previously been shown to depend on estrogen signaling in the male during development. However, the translation of such results to human neural and behavioral development is not immediately obvious because there is currently no evidence that estrogen receptor signaling plays an essential role in male-typical brain/behavioral sexual differentiation in primates including humans. To the extent that data are available, they suggest that perinatal neural androgen receptors directly mediate fetal/neonatal testosterone actions in controlling male-typical primate brain and behavioral sexual differentiation. At lease one *in vitro* study (reporter gene assay system) suggests that BPA can act as an anti-androgen (Sun *et al.* 2006) whereas results of another *in vitro* study (Richter *et al.* 2007) suggests that BPA exposure can upregulate androgen receptor expression in fetal mouse prostate gland primary culture. There are also examples of male-typical brain and behavioral sexually dimorphic traits in mice that have been shown to depend on perinatal androgen receptor signaling. Androgen receptor-dependent morphological murine brain sexual dimorphisms include size of the spinal nucleus of the bulbocavernosus, the postero-dorsal medial amygdalar nucleus, the ventromedial hypothalamic

nucleus, and the suprachiasmatic nucleus. Examples of androgen receptor-dependent social behaviors include play fighting and the preference of males to seek out female vs same-sex (male) urinary odors. In addition, using the reporter gene, Fos, the male-typical profile of forebrain responses to male and female pheromones was shown to be organized perinatally by neural androgen receptor activation. A thorough assessment of the potential ability of perinatal BPA exposure to disrupt any or all of these androgen receptor-dependent neural and behavioral characteristics in male mice and/or to augment these end points in females would be useful, and of direct relevance to the possible neurobehavioral effects of perinatal BPA exposure in humans.

In a written public comment on the draft NTP Brief on BPA, Dr. Baum pointed out that Dr. Mardi K. Mountfort of the International Formula Council criticized the conclusion that there is "some" concern for neural and behavioral effects of BPA in human fetuses, infants, and children at current human exposures. First, Dr. Mountfort dismissed the usefulness of several studies on the grounds that they used sc as opposed to oral routes of BPA administration. For reasons outlined in the draft NTP Brief, Dr. Baum did not concur with the dismissal of results on these grounds. In addition, Dr. Baum did not think that studies that use sc administration to pregnant animals, including use of an osmotic mini-pump, should automatically be dismissed when evaluating BPA. Second, Dr. Mountfort cited numerous methodological shortcomings of several studies of the neurobehavioral effects of BPA—most of which were already acknowledged in the draft NTP Brief. Specifically, Dr. Mountfort criticized the conclusion of Rubin *et al.* (2006) that fetal exposure to BPA (administered sc to the mother during gestation and lactation) eliminated the normal sex difference in open field activity. He argued "none of the alterations in behavior between males and females had a statistically significant association with BPA." Dr. Baum said this statement obscures the fact that whereas robust (statistically significant) sex differences in open field behaviors were observed in control (vehicle-treated) mice, these significant differences in behavior were eliminated in male and female mice whose mothers received BPA during gestation/lactation. Dr. Mountfort also argued that results of a study by Ema *et al.* 2001 showed that there was no effect of maternal BPA treatment (administered via gastric intubation) on the open field behavior of F1 rat offspring (Ema *et al.* 2001). Dr. Baum pointed out that these authors presented no data to document the existence of a reliable sex difference in the open field behavior of their vehicle-treated animals. Thus, their assertion that there was no effect of fetal BPA treatment on rats in open field behavior is not convincing.

2.4 Mammary Gland

Ad hoc reviewer comments: Robert Cardiff, MD, PhD (University of California - Davis)

Dr. Cardiff agreed with the conclusions presented in the draft NTP Brief related to the mammary gland. He interpreted the reported effects as presenting "limited evidence" for adverse effects primarily because there is no biological indication that the reported preneoplastic lesions progress to invasive carcinoma (Durando *et al.* 2007; Murray *et al.* 2007). It is critical to determine whether the lesions are truly precancerous or simply the author's interpretation of lesions that may become precancerous. In addition, Dr. Cardiff questioned the author's classification of the lesions with cribiform-like structures as carcinoma *in situ*. Dr. Bucher added that the NTP received input from a number of pathologists during preparation of the draft NTP Brief and they concurred with Dr. Cardiff on the uncertainty of the carcinoma *in situ* diagnosis.

Dr. Cardiff discussed the issue of hyperplastic lesions as risk factors for the development of invasive breast cancer in women. The lesions that present more concern are atypical ductal hyperplasia which are characterized by focal areas of atypical cells rather than a more diffuse hyperplasia. His interpretation of the lesions reported in Durando *et al.* (2007) and Murray *et al*. (2007) is that they appear to be a more "physiological" type of hyperplasia compared to a neoplastic-related atypical hyperplasia. Dr. Cardiff thought the histological figures presented in these publications are somewhat limited in conveying what the authors are classifying as hyperplasia.

General Discussion

Dr. Nancy Kerkvliet noted that the NTP cancer bioassay for BPA did not detect mammary gland carcinomas in female rats or mice. She understood that this study did not include perinatal exposure and wondered if that factor alone could account for the apparently discrepant results in the literature. An absence of lesions or tumors in animals only exposed during adulthood would not necessarily be predicted for a chemical acting as an estrogen receptor agonist. Dr. Thayer replied that the NTP organized a workshop in 2006 to address the detection of tumors in hormonally responsive tumors (Thayer and Foster 2007). The breakout group that discussed the mammary gland considered perinatal exposure to be an important factor in enhancing the sensitivity of the cancer bioassay to detect mammary gland carcinogens. With respect to whether BPA is acting as an estrogen, Dr. Thayer noted that mammary gland tumors were not detected in female rats in the NTP multigenerational study of ethinyl estradiol, a potent estrogen that is commonly used as a positive control. In addition, although the mammary gland is an estrogen-responsive tissue, mammary gland tumors are not necessarily observed in "low" dose studies with perinatal chronic exposure to positive control estrogens.

Dr. Russell Cattley thought the available data represent "insufficient evidence" to make a conclusion rather than "limited evidence of an adverse effect." Many factors can cause hyperplasia and the specific cause will influence the biological consequences in terms of progression or regression. What is really missing in these studies is evidence of progression.

Dr. Michael Pino was troubled by the lack of a dose-response in Murray *et al.* (2007). Moreover, only the lowest dose had a significant effect at postnatal day 95 [all groups were elevated, but the increase was only significant in the lowest dose group]. Dr. Thayer agreed this factor limits interpretation of the data. This study had a small sample size (n = 4 - 6 litters per group) and this might have contributed to the observed variability of response. Dr. Hammond's concern for the lack of an obvious dose-response relationship was somewhat diminished because the Murray *et al.* (2007) study was considered primarily for hazard identification purposes rather than as a quantitative analysis.

Ms. Rudel thought it appropriate to consider whether the ductal hyperplasia findings are consistent with the larger body of literature on other endocrine active agents, e.g., perfluorooctanoic acid and nonylphenol. A number of these compounds seem to affect mammary gland structure in a manner that relates to the development of breast cancer following developmental exposure. The developmental period of exposure has not been studied sufficiently and the findings with BPA should be considered within the context of this broader literature.

These studies generally investigate the mammary gland using approaches that are not standard in toxicology. She thought there is great need to use these novel types of study designs to address the issue of breast cancer.

2.5 Puberty

Ad hoc reviewer comments: Jorma Toppari, MD, PhD (University of Turku) and Richard Sharpe, PhD (The University of Edinburgh Academic Centre)

Dr. Jorma Toppari said the draft NTP Brief conclusion on puberty is the only one with which he disagreed. He recommended the NTP concur with the expert panel conclusion of "minimal concern" or conclude there are "insufficient data for a conclusion." The interval from vaginal opening to first estrous used in one study is difficult to interpret and not consistent with the other study (Howdeshell *et al.* 1999), which did not report an advancement in age at first estrous. It is also unlikely that the 1-day advancement reported in another study is actually statistically significant (Honma *et al.* 2002). The only really "positive" report of an acceleration in age at first estrous is the Ryan *et al.* (2006) study and the strength of interpreting this finding is limited by the small sample sizes used (n = 4 - 5 litters per group). Moreover, the primary focus of this study was behavior.

Dr. Richard Sharpe agreed with Dr. Toparri's comments for puberty. In addition, he had difficulty understanding the basis for fetal differences in circulating levels of estradiol based on intrauterine position (IUP). He questioned published reports that a female surrounded by two females has higher circulating concentrations of estradiol (vom Saal 1989). Dr. Sharpe was unclear how that outcome might occur given that the female fetuses are not producing estradiol or other steroids that can be converted to estradiol. Dr. Timms added that he has observed that males surrounded by 2 females have higher circulating levels of estradiol and larger prostates than males surrounded by 2 males (Timms *et al.* 1999; Timms *et al.* 2002).

General Discussion

Dr. Jon Mirsalis did not support a conclusion of "some concern" for puberty because no effect was detected in the guideline compliant multigenerational study in mice (Tyl *et al.* 2008). He considered the study by Tyl *et al*. (2008) to be the "gold standard" study and it did not report advancement in age at vaginal opening. Although there may have been some confusion in the literature previously, the Tyl *et al*. (2008) study is definitive and indicates that BPA does not have an effect on puberty. For this reason, he did not believe additional studies on puberty would be particularly helpful.

Dr. Kerkvliet asked whether some of the differences in the studies could be due to differences in route of administration of BPA. Dr. Thayer agreed that differences in response at specific doses could be due to the route of administration. Dr. Thayer added that the CERHR expert panel considered the 1-day acceleration in puberty reported by Honma *et al.* (2002) to be a statistically significant finding. In addition, the authors reported increased duration of estrous cycling at the same dose where an effect on puberty was observed.

2.6 Prostate

Ad hoc reviewer comments: Barry G. Timms, PhD (University of South Dakota) and Robert Cardiff, MD, PhD (University of California - Davis)

Dr. Barry Timms concurred with the NTP conclusion of "some concern" for BPA exposures that occur during development. Fetuses and infants appear to be particularly vulnerable due to differences in metabolic capability and "critical windows of opportunity" for perturbation of the reproductive system during development. Dr. Timms added that BPA was initially tested as a potential synthetic estrogen in 1936 (Dodds and Lawson 1936), then used to produce polycarbonate plastic in 1953. Consequently, lifetime exposures to BPA differ across generations and any health effects due to developmental exposure would not be expected in older generations of people alive today.

Estrogen has been known to affect prostate growth and function for some time. In 1936, Zuckerman proposed that elevated levels of estrogen during development could predispose the prostate to disease later in life (Zuckerman 1936). In addition, high doses of estrogen have been used to treat prostate cancer. Dr. Timms believed the weight of evidence is growing to support the conclusion that BPA can affect the prostate, especially when effects are looked at across studies.

Based on his experience and interpretation of the broader literature, the dorsolateral lobe of the rodent prostate appears to be more sensitive to estrogen than the ventral lobe. This is important for two reasons. First, the dorsolateral region of the rodent prostate is considered to be homologous to the posterior zone in the human prostate. The posterior zone is the region that is most susceptible to the development of human prostate cancer. Second, many studies that did not report an effect of BPA on the prostate focused on the ventral lobe of the rodent prostate, perhaps because it is easier to dissect compared to other lobes such as the dorsolateral lobe.

Dr. Timms noted that the 3-dimensional reconstruction technique he has used to look at the fetal prostate in response to BPA exposure is very time consuming. However, alternative techniques are becoming available that are faster and should prove useful in the study of prostate development and growth and to assess possible effects of BPA. For example, scanning microscopy has been used to assess prostatic epithelial bud formation (Lin *et al.* 2004) and imaging technology has been used to study ductal branching morphogenesis of the prostate (Almahbobi *et al.* 2005). In addition, histopathology assessment is becoming more prevalent.

His morphometric study of the fetal prostate also showed proliferation of basal epithelial cells in BPA-treated animals as well as in animals treated as estrogenic positive controls (Timms *et al.* 2005). Basal cells have been found to contain a subset of stem cells that are considered to have an important role in the normal growth and development of the gland and may play a role in the development of prostate and breast cancers (Wang *et al.* 2006). A recent study showed that BPA can affect basal epithelial cells (Ogura *et al.* 2007). In this study, BPA caused a permanent induction of CK10 expression in basal cells, which is not normally observed. CK10 expression is associated with estrogen-induced squamous metaplasia. The anterior prostate followed by the dorsolateral prostate was the lobe specifically sensitive to these effects.

Other studies using positive controls have also reported effects of BPA on the prostate including prostatic intraepithelial neoplasia (PIN) lesions (Ho *et al.* 2006). PIN lesions in the male mouse have similar histopathology to PIN lesions in men. These lesions in the prostate are indicative of precancerous lesions in humans. Evidence of high grade PIN lesions in men elevates their risk of developing prostate cancer. Increased basal cell proliferation appears to increase the propensity for developing PIN lesions.

A large portion of the literature on BPA and the prostate is based on evaluation of prostatic wet weight. Wet weight is considered to be a very poor measure of prostatic growth. Dr. Timms said his study used ductal volume, which is analogous to a weight measurement, and ductal volume is based on *in situ* methods, which are much more reliable than wet weight. In addition, assessment of prostate wet weight is not likely to be particularly informative for understanding the types of prostatic effects that are being reported recently, e.g., PIN lesions, morphometric changes, or histological effects. Dr. Timms cited a study where administration of an endocrine disruptor altered the early outgrowth of buds in the urogenital sinus and increased branching morphogenesis in the ventral lobe of the prostate indicating that at the molecular level one can observe changes that may not be reflected by prostatic weight changes. In his opinion, future studies should emphasize molecular changes in the development of the prostate (Schlumpf *et al.* 2008). These "low" dose effects manifest at the cellular or molecular level and are interpreted as predisposing the prostate to disease later in life. For the prostate, the concern is that developmental exposure to estrogen may make the gland more sensitive to subsequent estrogenic exposures, such as the higher circulating concentrations of estradiol seen in men as they age.

Because estrogens are known to affect the prostate gland, studies that do not show an effect in positive control treatment groups are difficult to interpret. For example, Tyl *et al*. (2008) did not report an effect on the prostate in the 17β-estradiol positive control group. Similarly, they did not report an effect of BPA on the prostate at any dose. This may be due in part to their use of wet weight and limited histological assessment.

Dr. Cardiff commented that the classification of "low" and "high" grade PIN lesions used by Ho *et al*. (2006) appears to be their own scheme. Dr. Timms agreed this is likely, but noted that PIN lesions in rodent models mimic the appearance of PIN lesions in humans. Dr. Cardiff agreed that PIN lesions in rodents "phenocopy" the lesions that humans tend to develop, but there are certain differences between rodents and humans. For example, in the mouse low grade PIN lesions are associated with progression to invasive disease. However, low grade PIN lesions in humans, e.g., grades 1 and 2, are no longer considered a risk factor for the development of prostatic disease. High grade PIN lesions are of concern.

General Discussion

Dr. Kerkvliet considered the reported effects on the prostate in the context of normal human development. Specifically, she questioned what biological mechanisms exist to "protect" the human male fetus against elevations in maternal estradiol concentrations that occur during pregnancy. Dr. Baum responded that rodents have a high affinity binding protein (alpha-fetoprotein) that binds estradiol to help protect the fetus from elevated blood levels of estrogen

during pregnancy. In humans, the analogous binding protein has a lower affinity and capacity for binding to estrogen.

Dr. Sharpe commented that human male fetuses have prostatic epithelial hyperplasia and these cells are shed following birth. He questioned whether this normal physiological process predisposes the prostate to disease later in life. If not, then there may be reduced concern for BPA-induced effects on the fetal prostate that are not shown to be permanent or clearly linked to adult disease. Dr. Timms verified that human prostates show squamous metaplasia in the prostatic utricle but that no studies have assessed the long-term impact of this process. Of note, he added that African-American women have higher levels of estradiol during pregnancy (Potischman *et al.* 2005) and African-American men have a higher incidence of prostate cancer (Jemal *et al.* 2005).

2.7 General Discussion

Dr. Leeder reiterated that the statements in the draft NTP Brief that relate to the ontogeny of glucuronidation in humans and rodents are accurate. However, he stressed that additional work is needed to improve our ability to extrapolate from the rodent to the human in the specific case of BPA. For example, the specific UGT isoforms that glucuronidate BPA in humans have not been identified. The developmental profiles of individual isoforms differ and this limits our ability to make general statements related to the ontogeny of these enzymes. The draft NTP Brief accurately presents information related to the reduced capacity of the neonate to glucuronidate. He emphasized that the neonate can metabolize BPA and it is likely that a significant variation in the developmental profile, e.g., rate and extent of metabolic capacity, would be observed at the population level.

He suggested the NTP include more discussion on aspects of metabolism that relate to sulfation. Information on the developmental ontogeny for relevant sulfation isoforms in humans is available and should be cited. The overall elimination of BPA in human neonates is likely to be slower compared to older infants and children based on the developmental profile of enzymes catalyzing sulfation and glucuronidation reactions. For example, acetaminophen, another planar phenol that undergoes sulfation and glucuronidation, shows reduced elimination in neonates compared to older age groups. The issue of sulfation is also important given the role of sulfation pathways in regulating endogenous compounds that are involved in controlling the growth and function of some of the reproductive tissues identified as targets of BPA. This raises the possibility that BPA-sulfate conjugates may interfere with estriol biosynthesis during fetal development. Consideration of these types of interactions should be an area for future research.

With respect to sc injection studies in young animals, Dr. Leeder said the study by Taylor *et al.* (2008) reports that the clearance of parent BPA appears to be the same following oral or sc injection to a neonate. This finding argues for similar systemic exposures for the two routes of administration. The draft NTP Brief is accurate in describing this issue. His only reservation with this conclusion relates to the possibility of differences in tissue distribution based on route of administration. Documenting similar tissue distribution would strengthen the conclusion that oral and sc routes of administration in the neonate can be considered equivalent.

Dr. Sharpe overall supported the level of concerns expressed in the draft NTP Brief. He did not support increasing the level of concern for fetuses, infants, and children based on the "low" dose effects and preferred the addition of a qualifier to the descriptor indicating that some residual levels of concern exist and need to be dispelled or confirmed with additional research. A number of observations and opinions form the rationale for his conclusion. First, many of the reported "low" dose effects have not been reproduced, which leads to concerns about the validity of the reported effects as well as their usefulness in a health evaluation. A number of individuals have inappropriately dismissed results based on various suggested explanations that are essentially unproven and untested presumptions. Second, Dr. Sharpe supported the consideration of all available data, including studies that use a non-oral route of administration, although these studies might not be given the same level of consideration as oral administration studies. The suggestion that the non-oral studies lead to higher concentrations of non-conjugated BPA at target tissues needs to be verified. Third, he did not believe the issue of replication could be addressed by merely repeating the same study design. Fourth, future work needs to expand on the reported effects. For example, additional studies should include assessment of progression to adult disease and measurements of unconjugated BPA.

Dr. Sharpe had several suggestions for revising the draft NTP Brief. The NTP Brief should include a discussion of the available information on BPA exposures in pregnant women and fetuses and compare these levels to the low doses administered to test animals. The critical research priority in Dr. Sharpe's opinion is to better characterize the concentrations of unconjugated BPA in humans for the situations for which there is the most concern, i.e., during pregnancy and early infancy. For example, the available data indicate that concentrations of *total* BPA in amniotic fluid are generally low. Concentrations of *unconjugated* BPA are expected to be much lower, which, if true, may decrease our concern for exposures to the fetus during pregnancy. However, to maximize the use of this type of information, concentrations of unconjugated BPA in rodent studies need to be measured at the low doses where effects are reported. This effort may require collaboration of CDC researchers with the researchers who are experts in conducting "low" dose studies. Care must also be taken to avoid contamination from environmental sources of BPA and conversion of BPA-G to BPA.

He considered the "positive" "low" dose BPA studies to be inherently biologically implausible. Advancement of puberty and preneoplastic lesions in the mammary gland and prostate are all classic estrogenic effects, and prostatic lesions are dependent on estrogen receptor alpha (ERα). Numerous *in vitro* and some *in vivo* studies indicate that BPA is 1000- and 10,000-fold less potent than estradiol in binding to the ER. Yet the low dose studies suggest a higher than expected estrogenic potency of BPA. There is currently no clear explanation for this inconsistency. Some have argued that certain dose-response curves for BPA are non-monotonic and it is only at lower doses where effects begin to emerge. However, Dr. Sharpe had trouble accepting this argument because estradiol does not show this type of dose-response. Other explanations for the unexpectedly high biological potency of BPA at low doses focus on mechanisms that do not involve ERα. Yet, in no instance has a non-ER-mediated mechanism been shown to account for a specific "low" dose effect. Thus, the low dose effects remain biologically implausible.

New data showing that BPA interacts with the membrane estrogen receptor (ncmER) affecting calcium signaling, at similar concentrations to diethylstilbestrol is obviously relevant and merits further investigation. The ncmER can be found in pancreatic cells and is involved in the regulation of insulin and glucose. In these studies, both BPA and estradiol cause similar effects and both show a non-monotonic dose-response with BPA being 10-fold less potent (Alonso-Magdalena *et al.* 2005; Nadal *et al.* 2004). In contrast, there is no evidence that the effects on the reproductive system work through a ncmER mechanism. The lack of reproducibility discussed earlier coupled with this inherent biological implausibility limit his confidence in using the low dose findings as the basis for regulatory decisions. The NTP Brief needs to address this biological implausibility.

Dr. Bucher agreed that the NTP Brief could better articulate how the NTP considered the issues raised by Dr. Sharpe. These issues were considered during preparation of the document and are reflected in statements that note the uncertainties associated with the low dose effects.

Dr. Thayer explained why the non-monotonic issue was not addressed in the draft NTP Brief even though it has been a topic of debate for BPA. The critical studies used to support "some concern" did not show a non-monotonic dose response. In fact, a limitation of the low dose literature is that many studies were single dose studies.

Dr. Hammond agreed with Dr. Sharpe that more information is needed for exposure, but that some of the available data are of concern. For example, the blood concentrations of unconjugated BPA in pregnant women are higher than what is predicted. Also, the concentrations of unconjugated BPA in breast milk result in daily intakes for infants in the range of doses that are causing effects in rodents. There is a great need to measure the concentration of BPA in infants and children less than 6 years of age. Finally, she noted an increase in exposure of older children and adults based on the NHANES urine data that show a doubling of median BPA levels and a tripling at the 95^{th} percentile in the last decade.

Dr. McCarver added that the NHANES data would miss certain at-risk populations such as individuals with liver and intestinal disease who may have reduced first-pass metabolism. Often these people spend more time in the hospital where they may potentially be exposed to BPA via medical equipment. Of particular concern are infants in neonatal intensive care who would have underdeveloped first pass metabolism and exposure to heated plastics that may contain BPA, e.g., incubators, oxygen hoods, etc.

With respect to mechanism of action, Dr. Raymond Novak said it is important to remember that intracellular signaling pathways cross-communicate and that cell- or tissue-specific responses may occur. In addition, the role of co-activators and co-repressors in mediating these processes contributes to the complexity of interpreting this literature. Dr. Toparri agreed and thought that the focus on BPA as an estrogen has been misleading. The effects of BPA should be considered on their own regardless of whether they are necessarily consistent with weak estrogenicity. Dr. Toparri thought the draft NTP Brief is clearly written, and this is both a strength and a weakness for such a complicated subject; however, it does not expand on the complexities and weaknesses of the key studies. He reiterated that he agreed with all of the conclusions except for puberty.

Dr. Mirsalis noted that the estimated intakes based on urine concentrations for people ages 6 years and above are much lower than the estimated intakes for infants based on assumptions and aggregating sources of exposures. He thought the most critical research need is to get better exposure data for infants and young children. In addition, he thought it would be unfortunate if any of the beneficial effects associated with breast-feeding were inappropriately attributed to lower BPA intakes. The beneficial effects of breast feeding have been recognized for some time even before the use of polycarbonate baby bottles. Dr. Hammond added that the lower intakes based on back-calculating from urine do not include children younger than 6 and would not represent any exposure that an infant might experience by primarily crawling on the floor. Dr. Thayer said the daily intakes for breast-fed infants are based on breast milk as the only source of exposure and does not account for other sources of exposure, e.g., drinking breast milk from polycarbonate baby bottles.

3. NTP BSC Votes on Draft NTP Conclusions

*Ad hoc reviewers did not vote or make motions.

Peer Review Charge:

To determine whether the scientific information cited in the draft NTP Brief on BPA is technically correct, clearly stated, and supports the NTP's conclusions regarding the potential for BPA to cause adverse reproductive and developmental effects in exposed humans.

1. **NTP concurs with the CERHR Expert Panel that there is *negligible* concern that BPA exposure causes reproductive effects in non-occupationally exposed adults.**

Dr. Kerkvliet moved to accept this conclusion. Dr. Mirsalis seconded the motion. The motion passed unanimously with a vote of 12 yes/0 no/0 abstentions.

2. **The NTP has *negligible* concern that BPA exposure to pregnant women will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring.**

Dr. Mirsalis moved to accept this conclusion. Dr. Pino seconded the motion. The motion passed with a vote of 11 yes/1 no/0 abstentions.

Dr. Hammond voted no because she did not think there is sufficient evidence to reach a conclusion of "negligible" concern.

3. **NTP concurs with the CERHR Expert Panel that there is *minimal* concern for workers exposed to higher levels in occupational settings.**

Dr. Hammond confirmed that the term "minimal" actually indicates more than "negligible" concern even though it sounds rather dismissive. She said "minimal" can be hard to interpret; for example, it can indicate minimal concern for a particular effect. A number of BSC members were unclear on what was the basis for this conclusion. Dr. Shelby clarified that this conclusion was based on (1) higher exposure levels in workers and (2) limited data from several human

studies, including one on workers, showing that BPA is associated with changes in serum hormones.

Dr. Hammond thought that finding an effect in humans could be sufficient justification to express "some" concern for occupational exposures. Dr. Toparri commented that the finding of lower FSH concentrations in exposed men compared to controls may not be significant since the levels in both groups were in the normal range. In addition, for men, high FSH is more of a concern than low FSH. Dr. Thayer added that the conclusion is based primarily on several high dose findings from laboratory animals treated only during adulthood. The doses used in those studies were much greater than the estimated occupational exposures. Although the worker study that reported changes in FSH was well-regarded by the expert panel, it was not clear that this effect should necessarily be considered adverse.

Dr. Pino moved to accept this conclusion. Dr. Novak seconded the motion. The motion passed with a vote of 11 yes/0 no/1 abstention.

Dr. Crump abstained because he did not think there is sufficient information on human exposures in the workplace to reach a conclusion of "minimal" concern.

4. NTP concurs with the conclusion of the CERHR Expert Panel that there is *some* concern for neural and behavioral effects in fetuses, infants, and children.

Dr. Hammond moved to accept this conclusion. Dr. Novak seconded the motion. The motion passed unanimously with a vote of 12 yes/0 no/0 abstentions.

5. NTP also has *some* concern for BPA exposure in these populations based on effects in the prostate gland, mammary gland, and an earlier age for puberty in females.

Dr. Cattley agreed with the conclusion of "some concern," but not with the inclusion of the mammary gland as a basis. The draft NTP Brief conclusion is based on "limited evidence for an adverse effect" and he believed the literature related to effects on the mammary gland is more appropriately characterized as "insufficient evidence." Dr. Pino questioned the inclusion of any of these effects as he believed that much of the evidence was "equivocal." Dr. Keith Soper was concerned about the conclusion for an earlier age for puberty because of an increased risk of detecting false positives when the outcome measures differ from study to study.

Dr. Hammond moved to accept the conclusion presented in the draft NTP Brief as written. Dr. Mirsalis seconded the motion. The motion failed with a vote of 4 yes/8 no/0 abstentions.

Dr. Kerkvliet moved to change the conclusion of "some" to "minimal" concern for BPA exposure in these populations based on effects in the prostate gland, mammary gland, and an earlier age for puberty in females. Dr. Soper seconded the motion. The motion failed with a vote of 3 yes/9 no/0 abstentions.

The BSC proceeded to vote on the endpoints individually.

5a. Prostate

Dr. Hammond moved to accept *some* concern for BPA exposure in these populations based on effects in the prostate gland. Dr. Mirsalis seconded the motion. The motion passed with a vote of 10 yes/2 no/0 abstentions.

Dr. Kerkvliet voted no because she thought there was only evidence of a minimal effect on the prostate. Dr. Cattley voted no because there was no evidence of progression.

5b. Mammary Gland

Dr. Hammond moved to accept *some* concern for BPA exposure in these populations based on effects in the mammary gland. Dr. Novak seconded the motion. The motion failed with a vote of 5 yes/7 no/0 abstentions.

Dr. Kerkvliet moved to accept *minimal* concern for BPA exposure in these populations based on effects in the mammary gland. Dr. Robins seconded the motion. The motion passed with a vote of 7 yes/4 no/1 abstention.

Dr. Crump voted no because what constitutes “minimal” and “some” concern is open to interpretation and he thought “some” is more appropriate for the reported effects on the mammary gland. Mr. Janzen abstained because he was uncertain what distinguished “some” from “minimal” concern. Drs. Bunton, Mirsalis, and Cattley voted no because they believed there is insufficient evidence to reach a conclusion.

5c. Puberty

Dr. Robins moved to accept *minimal* concern for BPA exposure in these populations based on an earlier age of puberty in females. Dr. Hammond seconded the motion. The motion passed with at vote of 7 yes/4 no/1 abstention.

Dr. Mirsalis voted no because he did not think there is any evidence of an effect on puberty. Drs. Cattley, Crump, and Pino voted no because they believed there is insufficient evidence to reach a conclusion. Mr. Janzen abstained because he was uncertain what distinguished “some” from “minimal” concern.

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5. Attendees

NTP Board of Scientific Counselors (BSC) Members
Christopher Bradfield, University of Wisconsin
Tracie Bunton, Eicarte LLC
Russell Cattley, Amgen
Kenny Crump, Louisiana Technical University
Katharine Hammond, University of California Berkeley
William Janzen, Independent Consultant
Nancy Kerkvliet, Oregon State University
Gail McCarver, Medical College of Wisconsin (chair)
Jon Mirsalis, SRI International
Raymond Novak, Wayne State University
Michael Pino, Sanofi-Aventis
Jim Riviere, North Carolina State University (only present during part of the peer review; not present for the voting)
Diane Robins, University of Michigan Medical School
Keith Soper, Merck & Company

NTP BSC Members not in attendance:
Edward Carney, The Dow Chemical Company
George Friedman-Jimenez, New York University School of Medicine
Kenneth Portier, American Cancer Society
David Wegman, University of Massachusetts, Lowell

***ad hoc* Reviewers**
Michael Baum, Boston University
Robert Cardiff, University of California, Davis (via teleconference)
J. Steven Leeder, Children's Mercy Hospitals and Clinics
Ruth Ann Rudel, Silent Sprint Institute
Richard Sharpe, The University of Edinburgh Academic Centre
Barry Timms, The University of South Dakota
Jorma Toppari, University of Turku

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Diane Spencer
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Kristina Thayer
Raymond Tice
Molly Vallant
Suramya Waidyanatha
Nigel Walker

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Ronald Melnick
Retha Newbold
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Dan Doerge, FDA/NCTR
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Andrew Hotchkiss, EPA
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Michelle Twaroski, FDA
Richard Wang, CDC

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Nena Baker, Norton Point Press
Jonathan Brania, Underwriters Laboratories
Sandrine Deglin, Exponent
Sanford Garner, Constella Group
Tom Goldworthy, ILS
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Steven Hengtes, American Chemistry Council
Marc Jackson, ILS
Michelle Lancaster, N.A. Metal Packaging Alliance
Joseph Manuppello, People for the Ethical Treatment of Animals
Leslie Recio, ILS
Neville Shaw, Westend
Shelley Tyl, RTI International