Health Group: Comments:

Ursula Gundert-Remy, 07.04.2009:

„…anbei habe ich meine Änderungen im Änderungsmodus eingetragen. Ich habe nur zeitweilig am Meeting teilgenommen, daher kann ich mich nur zu diesem teil äußern.
Mit freundlichen Grüßen
Ursula Gundert-Remy.

Human Exposure: Conclusions

There are data showing free BPA in newborns in neonatal intensive care unit.
Physiologically based modelling of blood concentrations resulted in 3 (modelling of both excretion pathways, sulfation and glucuronidation) to 11 times (modelling of glucuronidation excretion pathway only) higher concentration in newborns as compared with adults resulting from the identical external dose.
There are data showing free BPA levels in human blood (more than 12 studies…showing reproducibility) at normal environmental exposures whereas exposure to an experimental dose of 5 mg did not result in blood concentrations above 2.3 µg/L (lack of consensus about the accuracy of the measurements).
We do not know all the sources of BPA exposure… data may indicate there must be more than oral exposure.
Pbpk model based on high newborn exposure produces data that does not match published data.
If human exposure is as high as many data suggest, recalculation should be performed using higher exposure levels.

Human Exposure: Conclusions

Rodents and humans similarly exposed will have comparable internal levels of free BPA.
We should not focus on enterohepatic recirculation (EHC) as a reason for dismissing rodent data as relevant to human data.

The pbpk model should be applied to other published data sets.

Kommentar [G1]: The sentence is physiologically not true. In modelling exercises, we do not use rat data without appropriate scaling.

• Need more data on BPA kinetics in newborns and adults.

• Need internal measurements of free and conjugated BPA in serum and urine of rodent models and humans (more than one time point) especially pregnant mothers and newborns via cord blood.

Kommentar [G2]: I do not understand what the word with means

André Conrad, 07.04.2009:

"Is there something different about BPA that results in low dose studies or is it a more general phenomenon? (Folie 7)
Mir ist nicht ganz klar, was damit genau gemeint ist. Wenn möglich, sollte dieser Punkt klarer formuliert werden.
Bestand Einigkeit, dass diese Frage zukünftig untersucht werden sollte?

Should we apply precautionary principle… (Folie 8)
Auch dieser Punkt sollte umformuliert werden, um Missverständnisse zu vermeiden.
z.B.: Application of precautionary principle remains to be discussed."

Earl Gray, 08.04.2009:

"there are several sections of the "consensus" statement that I plan to address. some of it I do not agree with as being a "consensus" and there are some major and important issues that were presented by speakers that are not covered. I feel that the meeting was excellent but there was not enough time to reach a consensus on many issues, if this is possible.

Since there was no press at the meeting I assumed that this would not be released to the press until these issues had been resolved, but we already are getting contacts from some journalists in the US asking us about the consensus statement, which I consider an early draft.

I would request that the consensus statement not be released to the press until it is discussed and either represents a true consensus or a minority opinion is included.

Thank you

Earl Gray"

Earl Gray, 09.04.2009:

"this is the press contact that I was referring to:

To: Earl Gray
From: Susanne Rust
Date: 04/08/2009 06:13PM
cc: "Meg Kissinger"
Subject: Germany

Dear Dr. Gray,

We've been in touch with several scientists who were at the German meeting last week.

It is our understanding that there were several lines of consensus that came out of this meeting, including issues about the usefulness of rodent models for making estimates

about BPA exposure; the use of non-GLP studies in informing regulatory policy; and an acknowledgement that infants and newborns have three to 11 times as much free BPA in their blood than adults.

We were wondering if you could confirm this, or elaborate on it – or tell us where you believed consensus had been made.

Thank you for your time and consideration,

Susanne Rust and Meg Kissinger ”

Laura N. Vandenberg, 09.04.2009:

“The file available online is the exact file presented at the meeting that we “agreed” to. Based on my notes from the meeting, we can provide Uba comments to these “summary statements” but they do not plan to open the consensus statements.

LNV”

Andreas Gies, 09.04.2009:

“Dear all,
just to remind you what we all decided on the conference:
The slides presented by Mark and Jerry summarize the consensus of the workshop in general.
Participants are invited to comment (the request was sent out by Andreas Naulin). If these comments are clarifications, they will be included in the workshop summary. Any other comments will be regarded as personal comments to the summary.
On the basis of the slides and the clarifying comments the chairs will produce a summary. This summary will be published by UBA. This summary will not contain any statements beyond those summarized on the original slides.

UBA did not inform press. UBA will inform the public on the basis of the summary document as soon as this is finalized.
Thank you again for your participation in this workshop. Without everyone of you discussions would not have been as fruitful as they were on the conference.

Best regards from Berlin
Yours
Andreas”

Fred vom Saal, 09.04.2009:

"There were comments in the meeting summary that were indicated to have not represented a consensus. The other comments could have been contested at the meeting but were not. The perspective of the Beyer representative who spoke first at the meeting was that any statements would be unwelcomed and unacceptable – the issue was "closed". I assume that an employee of the US-EPA would understand that in the post-Bush USA this era had ended – the German people are lucky in that they did not have to experience first hand that 8-year assault on science.

Individual post-meeting comments regarding the Berlin meeting should be taken as only the views of that individual. Earl made his views very clear at the meeting, so his post-meeting comments are predictable. As everyone at the meeting clearly observed, I believe that Earl Gray is seriously confused about these issues and that his one experiment with BPA was flawed as revealed by the marked insensitivity of his rat strain to the positive control estrogen ethinylestradiol for the outcomes he examined – anyone who looks at the data in his paper in relation to the sensitivity of women to ethinylestradiol can confirm this conclusion. That I disagree with Earl or anyone else at the meeting is of no consequence with regard to the accuracy of the meeting summary. Of course, post-meeting comments concerning the meeting summary are anyone's right to make to the UBA or in whatever forum an individual chooses to pursue, but the notes from the meeting are an accurate record of what occurred at the meeting and should not be changed based on the post-meeting comments of any individual. I assume that the UBA officials will not waste their time responding to comments from Earl, me or anyone else who wants to alter the meeting summary for their own purposes. If post-meeting comments were to be posted on the conference web site as views of an individual, I am sure they would lead to a lively exchange that could go on for years. This tactic is, of course, intended to delay decision making. Hopefully, that will not occur.

Fred vom Saal"

Andrea Edginton, 13.04.2009:

"Please find below my changes:

1/ 'There are data showing free BPA in newborns in neonatal intensive care unit' should read '10% of BPA found in urine in newborns in neonatal intensive care unit was unbound'

2/ physiologically based modelling of blood concentrations resulted in 3 (modelling of both excretion pathways, sulfation and glucuronidation) to 11 times (modelling of glucuronidation excretion pathway only) higher concentration in newborns as compared with adults resulting from the identical external dose.

3/ PBPK model based on high newborn exposure produces data that does not match published data.

4/ If human exposure is as high as many data suggest, recalculation should be performed using higher exposure levels.

Take care,
Andrea"

Rochelle W. Tyl, 13.04.2009 :

"… I received these questions from two reporters from the Milwaukee Journal Sentinel on April 7, 2009. My written responses are in red. Please note that the questions are, in most cases, exactly related to the summary points as written in our draft consensus statement. How did they get the document, even before it was on the Share Point? The reporters subsequently wrote an article published in the Greensboro (NC) Sunday paper (yesterday), and likely elsewhere, which was woefully biased and inaccurate; I'll send you a copy as soon as I figure out how to scan it into an email. Thank you again for the opportunity to visit Berlin and participate in your important Workshop. Regards, Shelley Tyl (Rochelle W. Tyl)

From: Tyl, Rochelle W.
Sent: Wednesday, April 08, 2009 5:52 PM
To: 'Meg Kissinger'
Cc: Myers, Christina B.; Marr, Melissa C.
Subject: My responses to your questions

We understand that there was general consensus on the following points:

1. Newborns have 3 to 11 times the level of bpa in their blood than adults

This statement is correct but incomplete. Both newborns and adults have greater than 90% (adults 95%) of the BPA in the blood as the BPA glucuronide, which is not estrogenically active. It is then excreted exclusively via the urine in humans. So both newborn and adult humans have very little free (biologically active) BPA in their bloodstream.

2. Rodents and humans similarly exposed will have comparable internal levels of free bpa. Scientists should not focus on enterohepatic recirculation as a reason for dismissing rodent as relevant to human data. Therefore, rodent data are appropriate for modeling human data.

Enterohepatic recirculation in rodents creates cycles of free BPA and BPA glucuronide as they shuttle between the gut and the liver, resulting in much higher levels (for longer time periods) of free BPA in the rodent than in the human. That said, rodent data are used (with caveats) to model human data.

3. There should be one data set that includes GLP and non-GLP studies. There was no consensus at the meeting on this statement.

We also wanted to address the following concerns about your 2008 studies.

1. Your study did not sufficiently address neural and behavioral and prostate health.

Our studies were not designed to evaluate neurobehavioral toxicity; there are specialized EPA and OECD guideline neurotoxicity and developmental neurotoxicity study designs; these types of studies are being planned or are in progress under these governmental testing guidelines and GLPs by FDA and industry. For "prostate health", we weighed them from parental and offspring males (for both rats and mice) by lobe, examined them grossly and veterinary histopathologists examined them microscopically.

2. There was a concern about using estradiol as opposed to ethinyl estradiol.

Ethinyl estradiol (EE) is a synthetic estrogen, designed to provide significantly greater oral bioavailability, so it was not viewed as an appropriate positive control. 17B-estradiol (E2) was used to confirm the sensitivity of the mouse model to an estrogen and for comparison of any mouse effects from BPA, since E2 is an endogenous estrogen. The selected dietary concentration (0.5 ppm) and dose (80-100 ug/kg/day) was based on two mouse dietary E2 studies (one-generation and two-generation studies) we performed prior to the mouse BPA study.

3. The way the animals were exposed to BPA and the positive control – i.e. on the food

The major route of human exposure is oral during episodic feeding and drinking. The BPA or E2 was not "on" the feed but thoroughly mixed into the feed, with homogeneity, stability and dose level verification performed for both studies; dose level verification was done on every dose level for every formulation for both studies.

There is concern that a positive control wasn't run at the same time as the test. Your concern is totally unfounded. The positive control group, the two negative control groups and the six BPA groups were run at EXACTLY the same time, in the same rooms, by the same staff, who were "blind for dose" throughout the study (only Rx number codes and color codes were used to prevent any inadvertent bias).

4. You've given three different ages for the mice. What was the actual age and can you say why this has been such a problem to report?

Our mice were at different ages at termination depending on whether they were the initial parents (F0), or offspring adults (F1), and depending on the lengths of the studies. The youngest animals in our studies were approximately 3 months at termination and the oldest ones were approximately 5 to 5½ months at termination.

5. Concern that your lab was contaminated by a fire in august 2001. What is your response?
   The fire in our Animal Research Facility occurred on August 25, 2001. The BPA rat study was completed on February 1, 2000 (last necropsy day; before the fire) and the BPA mouse study began on March 2, 2005 (just under 4 years after the fire). Immediately after the fire we implemented a monitoring program for the animals, including analyses of hair, feces, broncholavage of sentinel animals in the facility prior to the fire, at the time of the fire and afterward to examine the alveolar macrophages in the lavage which are there to trap particulates (to determine whether or not there was exposure, and if so, to what extent), necropsy and histopathology of exposed animals, use of sentinels, analysis of air, dust, feed and bedding, complete renovation of the fire-damaged area with extensive remediation where warranted. We also convened an Independent Expert Panel who reviewed all our samples, analyses and data and concluded in a written report:
   a. That neither the animals nor the studies in the ARF at the time of the fire were compromised.
   b. That the animals brought into the facility after the fire have not been compromised, and that the integrity of these new studies is being maintained.
   c. The panel determined that the animal research facility was an excellent one prior to the fire and is improved as a result of the remediation actions.
   d. The panel determined that the staff of RTI acted in a timely and appropriate fashion to deal with this event. The actions taken to preserve existing studies, to collect and analyze appropriate samples, to remediate the damage and to prevent any impact of the remediation on the studies were exemplary.
6. Why wasn't blood collected to validate the level of bpa the animals were exposed to. We measured the feed consumed in the individually housed animals weekly; we weighed the

animals weekly (more often during pregnancy and lactation), and we knew the concentration of test chemical in the feed, so we could (and did) calculate, and report, the amount of BPA ingested for each interval on a mg/animal/day and mg/kg body weight/day basis. Blood sampling in mice would require additional satellite animals in every group and generation; one cannot repeatedly bleed these small mammals, especially when pregnant and/or nursing.

We're interested in any thoughts or observations you have about this meeting. I attended, by invitation, to participate in a discussion on how to reconcile the disparate results from the small exploratory studies versus the large guideline-compliant studies.
We see these studies are funded by the Plastics Council. Are all of your studies underwritten by industry?
RTI International is funded approximately 85% by governmental grants and contracts, and 15% by commercial entities. My group is funded approximately 50% by government and 50% by industry, but it varies over time. My staff and I have been performing reproductive and developmental toxicology studies in animal models for governmental and commercial clients for over 40 years.
What are your thoughts on being the author of the only two studies that FDA is relying on to proclaim that BPA is safe. Our guideline studies do not claim that BPA is safe. Our studies conclude that there are no reproductive effects caused by low dose oral exposure to BPA in rats or mice. There are other studies which also indicate that BPA does not cause reproductive toxicity at low oral doses: Ema et al. 2001, funded by the Japanese Government, Cagen et al. (1999) and Ashby et al. (1999), funded by industry and others. It is NOT who funds the study, it is the study design which is important. The industry-funded studies are very big, long term, utilize regulatory guideline study designs, validated endpoints, perform them under Good Laboratory Practice principles and regulations, and are under independent Quality Assurance oversight; all data are reported and retained. A number of weight-of-the-evidence evaluations on BPA have also come to the same conclusion.
Is it your opinion that the agency needs to expand its universe of studies? CERHR, EFSA, FDA, OECD, etc. all examined all of the BPA studies and selected the ones which, they felt, were appropriate to use for safety/risk assessment. Formal Safety/Risk Assessments require guideline studies, use of validated endpoints, appropriate routes of exposure, adequate numbers of dose groups, adequate numbers of animals per group, appropriate statistical methods, analytical verification of dosing formulations, etc.

If you have further questions, do not hesitate to let me know.
Regards, Shelley Tyl"

Earl Gray, 13.04.2009:
[An/To: Tyl, Rochelle W.]

Betreff: Re: FW: My responses to your questions
This is a copy of the article that appeared in the Mil Journal Sentinel that Dr Tyl was referring to.
In particular reference to ques 1, below, this is a part of the consensus that we agreed at the meeting would be clarified and the facilitator indicated that it would be done "later". the levels reported in the single study that this comes from is reporting total BPA (free and metabolized) and the BPAg accounted for about 90% of the total. In addition, we agreed at the meeting that we would clarify that this was from a highly exposed NICU population and the general public, as the newspaper implies.

I also stated in the meeting that there were issues in the consensus that I do not think we had reached consensus on and that I did not agree with and there also were important issues that we discussed that were not included. Will there be a summary or minutes of the meeting (talks and all issues discussed) in the report released along with the consensus statement? that would be useful.
Thanks
Earl Gray

Rochelle W. Tyl, 14.04.2009:

"Here are the articles on BPA I referred to in my previous email. Now I'm getting emails about the articles… Shelley Tyl (Rochelle W. Tyl)"

Consortium rejects FDA claim of BPA's safety

Scientists say 2 studies used by U.S. agency overlooked dangers

By Meg Kissinger And Susanne Rust

Posted: Apr. 11, 2009

An international consortium of industry, academic and government scientists has rejected as incomplete and unreliable the U.S. Food and Drug Administration's case that a chemical found in food containers and other household products is safe.

The group, which met last month in Germany, is working to release a consensus statement in the next few weeks. The meeting was closed to the public, but the Journal Sentinel has interviewed many scientists who attended the meeting and has seen several working versions of their agreement.

The group raises questions about the two studies that the FDA has used as its foundation to declare that bisphenol A is safe in food and beverage containers. It calls for a much broader look at the chemical than the FDA has given.

Speakers at the conference included Rochelle Tyl, the author of the two studies that are being used as the FDA's benchmarks. Both of Tyl's studies were paid for by the American Chemistry Council, a trade association for BPA makers.

According to scientists at the meeting, Tyl conceded that there were errors and inconsistencies in the 2008 report that the FDA used as the foundation for its findings.

"It is becoming undeniable that BPA is dangerous," said Laura Vandenberg, a developmental biologist at Tufts University, one of 58 scientists from around the world invited to the conference in Germany. "The FDA's standard for safety is reasonable certainty. It is no longer reasonable to say that BPA is safe."

The group's conclusions also call into question the European Food Safety Authority's assessment of BPA. The authority, which also relies on Tyl's studies, sets policy for all countries in the European Union.

The scientists' consensus statement will contradict claims by industry spokesmen who have been citing the FDA and European assessments as proof that BPA is safe.

Tyl told the Journal Sentinel in an e-mail that her studies do not claim that BPA is safe. Her studies were not designed to cover all aspects of the chemical's effects. They simply show no effects to the reproductive system of rats and mice that were exposed to the chemical at low doses, she said.

She has previously acknowledged inconsistencies in her data, particularly the age of some animals that were examined in the 2008 study for effects on the prostate.

While Tyl answered several questions by e-mail, she declined to be interviewed.

John Vandenbergh, a biologist at North Carolina State University who attended the conference in Germany, said the FDA risks losing credibility by relying on such flimsy evidence.

"We desperately need good judgment at the FDA," Vandenbergh said. "For years, they did a superb job looking out for food safety. I hate to see something like this jeopardize all that."

The conference, held in late March, was called to reassess the safety of BPA for German regulators. But the agreements that were forged there are being closely watched by those worldwide with a stake in the future of the chemical, including BPA-makers, regulators and advocates who consider the chemical to be dangerous.

The group agreed that Tyl's studies were too limited in their scope to be considered benchmarks.

The group found that Tyl's studies failed to consider serious dangers posed by BPA. They include effects on behavior and the development of the brain and prostate. Those problems were identified in a National Toxicology Program report published last year. FDA administrators promise to address those issues more thoroughly now.

Ruling protested

Despite concerns raised by other regulatory agencies, the FDA declared BPA to be safe last August. It cited Tyl's two studies, which were released in 2001 and 2008. Several BPA experts and health advocates protested the ruling, saying that the agency was too quick to ignore hundreds of other studies that found the chemical caused harm. The agency's Science Board agreed and recommended that the FDA reopen its assessment of the chemical.

Laura Tarantino, director of the FDA's Office of Food Additive Safety, said Tyl's studies followed proper protocol. But she acknowledged some uncertainties about whether Tyl's studies addressed all concerns about the chemical. Neither Tarantino nor any FDA scientists were invited to the meeting.

Tarantino said her agency would now look at other studies that raise concerns about BPA.

BPA, developed more than 100 years ago as a synthetic estrogen, is used in thousands of household products to make hard, clear plastic for things such as baby bottles and food containers. It also is used in many dental

sealants and to line most food and beverage cans. The chemical has been found in the urine of 93% of Americans tested.
Tests conducted last year for the Journal Sentinel found that toxic levels of the chemical leached from 10 different product containers when heated, including those marked "microwave safe." Although the levels that leached from the containers were low, the Journal Sentinel identified several peer-reviewed studies that found health risks in laboratory animals at similar levels.
Scientists began studying the chemical more than 10 years ago after laboratory animals were found to be developing health problems suspected of being caused by their polycarbonate cages. These problems included heart disease, obesity, diabetes, some forms of cancers and reproductive failures.
Recent studies have linked the chemical to heart disease and diabetes. It has been found to interfere with chemotherapy for breast cancer patients. Concern is especially keen for its effects on fetuses and newborns, whose development are most affected by exposure to the chemical.
Canada declared BPA to be a toxin and has banned its use in baby bottles. Earlier this year, the six major baby bottle makers promised to stop using BPA. Sunoco, one of five BPA makers, now requires companies buying its BPA to sign a promise that they will not use it to make products for children younger than 3.
The government is expanding its look at the chemical, and last month the National Institute of Environmental Health Sciences announced it was investing $5 million in BPA research. Last month, bills were introduced in both houses of Congress to ban BPA from all food and beverage containers.

Different accounts
The German conference did not reject Tyl's studies but had questions regarding her methodology and accuracy.
In the past seven months, Tyl has given three different accounts of the ages of the animals that she used to study BPA's effects on prostate size. Scientists who attended the conference in Germany say that the discrepancies are significant because prostate size varies greatly depending on age. A larger-than-normal prostate could indicate cell change caused by BPA.
Tyl said in her 2008 paper that the animals were younger than 14 weeks, or around 3 months old. Critics questioned this at an FDA hearing in September. They noted that Tyl's data showed the mice to have abnormally large prostates for animals that were 3 months old. They said that could indicate that either the animals were diseased or that a lab technician had bungled the data.
Tyl said then that the paper erred. The animals were 6 months old, she said. FDA administrators were at the hearing, but there is no record of the discrepancy on the FDA's Web site, which lists the studies for the public to review.
Last month in Germany, when questioned again, Tyl said the paper was wrong. The animals actually were 5 months old.
"How could this mistake be made and not caught," said Laura Vandenberg, the Tufts scientist. "Now that this issue has been brought to light, have the other data been verified and validated, and by whom?"
FDA spokesman Michael Herndon said Friday that he was not certain if the agency had made note of the discrepancy.
"She is in *big* trouble over the age issue," said Fred vom Saal, biologist at the University of Missouri and one of the most vocal critics of the FDA's assessment. Vom Saal was also at the meeting in Germany.
Vandenbergh, the BPA expert from North Carolina State, said the discrepancies "significantly weaken" Tyl's 2008 study.
"I wouldn't use it as a benchmark study," Vandenbergh said.

Lab fire
Scientists who attended the conference said they also were concerned about a fire that broke out in Tyl's North Carolina laboratory that was never reported to the FDA.
The fire occurred on Aug. 25, 2001, about a year after her first paper had been written and some three years before work began on the second study.
Eighteen polycarbonate cages, made with BPA, burned in the fire. Scientists at the conference say the lingering effects of the fire may have compromised future experiments. The chemical could have gotten into the heating ducts or the feed, exposing the animals to much higher doses than reported in the study.
Tyl's company, RTI International, investigated the fire - which appeared to be arson. An independent firm analyzed the lab and reported that it had been sufficiently cleaned. The group declared that the animals were not compromised and that Tyl's lab "was, and continues to be, an excellent facility."
But scientists at the conference, when told of the fire by the Journal Sentinel, said they would not trust that assessment. BPA is a sensitive chemical that acts at extremely low levels, and the group that analyzed the lab did not test for the chemical at those levels, they said.
Vandenbergh, of North Carolina State, who examined the reports on the fire and the laboratory's investigation for the Journal Sentinel, said he would have conducted the experiments at a different lab.
"In hindsight, this is too important of an issue to leave open these questions," Vandenbergh said.
Herndon, the FDA spokesman, said the agency was unaware of the fire and has no plans to discount the studies.
"It appears that sufficient corrective action was taken at the laboratory regarding the fire, the incident and its impact on the animals is not relevant to the studies reviewed regarding BPA," Herndon said.

Scores of studies
The scientists at the German conference also agreed that government regulators need to greatly expand the universe of studies that they consider.
Scores of studies have linked BPA to behavioral problems in animals, such as aggression, anxiety and hyperactivity. Other studies have found changes to the prostate gland that have been shown to lead to cancer. But the FDA discounted them because they did not adhere to the Good Laboratory Practices designation. The

internationally recognized designation is considered by some to be biased toward industry because it requires more animals to be tested than many academic institutions can afford or are willing to test.
The March conference was the first time that scientists from all perspectives reached a consensus on several key aspects of human exposure to the chemical.
Though representatives of European industries attended the conference, scientists from the American Chemistry Council, which represents American BPA-makers, were not invited.
Steven Hentges, the industry spokesman on BPA, deflected worries that this new position would threaten previous safety assessments of BPA.
"Within the last year, the European Union, European Food Safety Authority, German Federal Institute for Risk Assessment, Danish Environmental Protection Agency, French Food Safety Authority and the Swiss health authorities have all evaluated BPA and concluded that BPA in food contact applications is not a human health risk," Hentges said.
These agencies also relied largely on Tyl's work and several premises that are about to be discounted, a review of those assessments show.
For years, scientists from industry and many regulatory agencies have said that BPA is not a health risk because people - including infants and children - are exposed to such low levels of the chemical. But the group in Germany acknowledged that children and infants have levels of BPA in their urine that are three to 11 times higher than adults.
The FDA also discounted studies that used rodents to gauge human exposure to BPA. But the German group found that humans and animals treated with comparable doses end up with similar levels even though they metabolize it differently.
The group also urged regulators to look at studies that examined how BPA acts at low doses, an area of research that many regulating bodies were reluctant to consider.
A growing number of scientists say that because BPA acts like a hormone, its effects are seen at extremely low levels, even if no damage is found at higher doses.
Tarantino of the FDA says the agency will expand its look to include low-dose effects.

http://www.jsonline.com/watchdog/watchdogreports/42858862.html

Babies carry more BPA, scientists group agrees
By Susanne Rust of the Journal Sentinel
Posted: Apr. 11, 2009

Scientists from industry, academia and government met in Germany last month to reassess concerns about bisphenol A, also known as BPA.
They agreed on several key and controversial aspects about how people are exposed to the chemical, how they metabolize it, how to test for it, and kinds of data regulators should be reviewing.
The following is a partial list of some of those consensus statements, according to preliminary drafts reviewed by the Journal Sentinel:
•Newborns have between three and 11 times more BPA in their system than adults.
•Although scientists know that people are exposed to BPA by ingesting it through food and drink, they also know that they must be exposed to the chemical by other means as well. The levels detected in people are too high to be the result of ingestion only.
•Rodents and humans receiving similar exposure to BPA will have comparable internal levels of biologically active BPA. Therefore, scientists should not dismiss rodent studies on the grounds that mice and rats metabolize the chemical differently than people. These findings suggest that rodent data are suitable for modeling human data.
•The National Toxicology Program expressed some concern for neurobehavioral effects at low doses of BPA. The program also expressed some concern about precancerous lesions on the prostates of fetuses exposed to the chemical. This level of concern means that regulatory agencies should pay attention to this data, and try to collect more.
•A pivotal study used by the FDA to declare that BPA was safe for use in food and drink containers was authored by Rochelle Tyl and a team of industry scientists in 2008. That study, according to the German group, collected only minimal data on behavior, and no data on the precancerous lesions the National Toxicology Program is concerned about.
•Regulators should look at one data set when making assessments about the safety of BPA, and that should include not only studies with the stamp of Good Laboratory Practices, but others as well. In addition, studies that don't adhere to Good Laboratory Practices should use more documentation in their experiments.
•The panel then concluded that there is controversy concerning how people are exposed to BPA and by how much.

Antonia Calafat, 14.04.2009:

"… I am sorry about the delay in responding to your message. I was on vacation last week and away from e-mail…

For the first slide, I have some text I would like to add (in bold red and capital letters); the comments (in parentheses) are to explain why I believe the text is needed. The additional text, in my opinion, does not change the conclusions, but only make the points more reflective of the actual research they describe. During the discussion in Berlin, it was so clear to me the research the bullets reflect that I didn't even realize then that some statements were somewhat incomplete. However, after having read the statements now several times, I believe that these additional clarifications may be needed and also useful particularly for people who are not as familiar as many of the workshop attendees are with BPA research. I am sending these comments now only to you and Andreas Naulin because I am not sure how you would like to proceed. If you want me to forward them to the "human exposure" group, please let me know and I will gladly do so.

Also, please note that ALL report/manuscript/document/etc. with a CDC researcher as a coauthor must be cleared for publication at CDC. Therefore, if the summary to be published by UBA lists me, among the other participants, as an author, the final document must be cleared at the CDC before it can be published. Because clearance takes time (several weeks and sometimes months), and BPA is now a controversial topic worldwide, I will need to know as soon as possible how you plan to disseminate the workshop conclusions so we can determine the best way to proceed at CDC.

FIRST SLIDE

- There are data showing free **AND CONJUGATED** BPA in **THE URINE OF** newborns in neonatal intensive care unit**S**.
- Newborns **UNDERGOING MEDICAL TREATMENT IN NEONATAL INTENSIVE CARE UNITS** have 3-11 times adult blood levels. **(We did not measure BPA in the blood of these premature neonates, only in the urine, so the statement may have referred to adult urine rather than adult blood levels?)**
- There are data showing free BPA levels in human blood (more than 12 studies…showing reproducibility) (lack of consensus).
- We do not know all the sources of BPA exposure… data indicate there must be more than oral exposure.
- Pbpk model based on very low newborn exposure produces data that does not match actual data **ON PREMATURE INFANTS UNDERGOING MEDICAL TREATMENT IN NEONATAL INTENSIVE CARE UNITS (To my knowledge, no BPA data for neonates other than these premature infants exist).**
- If human exposure is as high as many data suggest, the model needs to be recalculated based on higher exposure levels.

Let me know if you have any questions.

Thanks,

Antonia"

Andreas Gies, 15.04.2009:

"Dear Antonia,
Thank you for your mail that I cc to to Birger and Jerry from the Human Health Working Group.
Thank you also for your useful comments. It should be clarified that the information we have about free bisphenol in blood is mainly from cord blood and that your ICU data for urine should be compared to other data from urine.
About the further process: The slides are open for comment until April 17th. We received a number of comments and some of them are beyond that what we discussed at the workshop. We do not aim to produce a consensus statement (though some American newspapers stated that). What we want is a report of the chairs and rapporteurs about this workshop on the basis of an improved (but not substantially changed) notes of the meeting that were presented in the final slides. Along with that I would not mind to put any further comment on the net, but well separated from the final report.
The final report will serve as an policy and scientific advice to decision makers to help them distinguish between information that is agreed and uncertainties in the debate about bisphenol.
I hope this will be o.K. for you as the report by the chairs would neither bind you nor CDC.
I am also open to produce an author's paper to continue the discussion process at the workshop as I felt that we made substantial progress in this difficult field - thanks to all of the paticipants.
Dear Antonia, any further comment of you is welcome as I really appreciate your constructive role in the workshop. Thank you again for coming to Berlin. We will keep you informed about every further step.
Best regards
Yours Andreas"

Antonia Calafat, 15.04.2009:

"Dear Andreas,

Thank you very much for your prompt reply and for your commitment to keep me updated. Also, I want to tank you for having invited me to attend the workshop. It was indeed a pleasure coming to Berlin.

Because of the ongoing controversy around BPA and its widespread media coverage, it may be best that I submit the chairs' report to CDC clearance, so CDC is 1) aware of the upcoming release of such report (even though will not a binding document either for me or for CDC) and 2) knows that one of the CDC researchers (me) attended the workshop. Would this be OK with you? If so, I would need a draft of the report (as close as possible to its final form) and an e-mail from you giving me permission to submit it to CDC clearance.

Best regards,

Antonia"

Birger Heinzow, 16.04.2009:

"Sehr hilfreiche Kommentare durch Antonia,

Ich habe keine Bedenken diese Ergänzungen in die Slides aufzunehmen, da Sie der Erläuterung der Statements dienen und deshalb sinnvoll und sogar notwendig sind.
Statements, die die Aussagen erweitern oder verändern würde ich -wie vorgeschlagen- getrennt behandeln. …."

Rochelle W. Tyl, 16.04.2009:

„… Thank you again for the opportunity to attend the BPA workshop (and to once again visit beautiful Berlin). My comments on the Consensus Statement are as follows:

1. Under Human Exposure: Conclusions (page 1)
    A. First bullet: Although the statement in correct, it is incomplete; Dr. Calafat's work indicated that even in hospitalized premature babies (in the Newborn Intensive Care Unit), greater than 90% of the BPA in their urine sample was, in fact, glucuronidated.
    B. Second bullet: Again, the statement is accurate but incomplete without a frame of reference, which should include the actual levels of BPA and BPA-glucuronide in the blood. Domoradzki et al. (2003) reported that 99+% of BPA in neonatal rats was glucuronidated, and Inoue et al. (2001;2003) reported that oral BPA is almost completely (>95%) glucuronidated in the intestine and/or liver before it enters the general circulation.
2. Under Human Exposure: Conclusions (page 2)
    A. First three bullets (related): Enterohepatic recirculation in rodents (but not in humans) will result in prolonged systemic exposure to BPA and BPA glucuronide in the blood as these molecules cycle between the liver and intestine, undergoing addition of and removal of the monoglucuronide from BPA. It is naïve to assume that humans and rodents would have comparable internal levels of free BPA from similar exposures. That said, rodent data are being used to model human BPA exposures, but they must be used with caution.
3. Under Animal Studies: (page 1)
    A. Third bullet: The Earl Gray study with BPA and EE positive control was a careful, thorough evaluation. The EE results indicated the responsivity of the model; perhaps there were no BPA effects observed because there were no BPA effects.
    B. Fourth bullet: There is clear indication from the literature that strain differences in response to estrogens varies across tissues, so no one rat strain can be considered more or less sensitive than another. E2 activities via the ER alpha in the reproductive tract did not display major strain differences in the multi-laboratory OECD

uterotrophic assay validation, and BPA was only a weak partial agonist at 400-600 mg/kg/day.

C. Fifth bullet: Tyl's studies were multigeneration reproductive toxicity studies performed according to EPA (rat) and OECD (mouse) testing guidelines and GLPs. They were not neurobehavioral studies; there are specific EPA and OECD testing guidelines for adult and developmental neurotoxicity assessments. The veterinary pathologist on Tyl's studies examined the prostate sections histopathologically and did not find any evidence of treatment-related effects.
D. Sixth bullet: The use of dietary E2 as Tyl's positive control for her mouse BPA study was based on results from her one- and two-generation E2 dietary studies in mice, and the literature, which confirm the sensitivity of the mice to dietary E2.

4. Under Animal Studies ctd: (page 2
   A. Second bullet: Tyl's studies looked for effects from oral BPA over a huge range of doses, many of which were in the environmentally relevant range, and found no effects on any parameter below 5 mg/kg/day in either rats or mice. The positive control (E2) confirmed the sensitivity of the animal model to an endogenous estrogen. Tyl knows of no published studies (exploratory or guideline) which measured BPA or BPA glucuronide in the blood or urine (It is a good idea for future work); why single out her studies?
   B. Third bullet: Combining GLP and non-GLP studies in one dataset ignores the fact that they are different. That is not to say that they should not both be evaluated for possible use in safety/risk assessments, and they are, but the small non-GLP studies with non-validated endpoints, few animals/group, few groups, etc. are typically considered inappropriate for such use.
   C. Fourth bullet: I strongly concur with this suggestion!

Thank you for the opportunity to provide my comments on the BPA Workshop Consensus Document.

Sincerely, Rochelle (Shelley) W. Tyl"

Gisela Stropp, 16.04.2009:

"die Folien aus der Health Discussion Group stellen eine während der Veranstaltung durch den Protokollanten erstellte Sammlung von Diskussionspunkten dar. Die einzelnen Aspekte sind nicht im Detail ausformuliert und die Diskussion dazu ist nicht dargelegt (was in Anbetracht der Kürze der Zeit während der Veranstaltung bzw. zwischen der Diskussion in der Health Discussion Group und der Vorstellung der Folien in der Joint Discussion Group auch nicht anders möglich war). Auch sind die einzelnen Aussagen und Diskussionspunkte nicht gewichtet. Die Folien geben daher zwar einen gewissen Einblick in die diskutierten Aspekte, ohne jedoch die komplexen Diskussionen transparent und nachvollziehbar machen zu können. Viele der mit kurzen Anstrichen dargelegten Aussagen sind ohne den Kontext der Veranstaltung und ohne die Diskussion miterlebt zu haben nicht verständlich und können sogar zu Missverständnissen beim Leser führen. Um ein Beispiel zu nennen: auf der 2. Folie im 2. Anstrich wird gesagt „Newborns have 3-11 times adult blood levels".

Einem Teilnehmer der Diskussion, nicht aber einem sonstigen Leser der Folien, ist bekannt, dass PBPK-Modellierungen und nicht konkrete Messwerte die Grundlage dieser Aussage bilden und dass im Verlauf der Diskussion deutlich wurde, dass die Studie, die zu dem Wert 11 führte einen Teilaspekt der Verstoffwechselung nicht mit berücksichtigt hatte. Ein anderes Beispiel: das Thema Precautionary Principle wurde zwar andiskutiert, aber es wurde keine Schlussfolgerung dazu gezogen, so dass die Darstellung im letzten Satz der letzten Folie nicht verständlich ist und auch Verlauf und Ausgang der Diskussion nicht widerspiegelt.

Somit lässt sich aus meiner Sicht aus den Folien ohne umfangreiche Überarbeitung keine für ein breiteres Publikum geeignete Zusammenfassung der Diskussion ableiten.

Ein aktueller Zeitungsartikel in den USA (http://www.jsonline.com/watchdog/watchdogreports/42858807.html) zeigt wie groß das Potential für Missverständnisse in diesem Zusammenhang ist.

Ich hoffe, diese Kommentare sind hilfreich und stehe für Rückfragen gerne zur Verfügung.

Freundliche Grüße / Best Regards

Gisela Stropp"

Andreas Luch, 17.04.2009:

„…die Folien 6 und 8 im "Summary Public Health" wurden von BfR-Seite aus leicht modifiziert (Änderungen in Rot markiert; siehe Anhang).
Ich bitte um Beachtung.

Mit freundlichen Grüßen, A. Luch

Slide #6:
Animal Studies ctd.

- Mechanism of BPA in animals unclear…ER alpha or Beta or membrane ER?
- No reasons developed to explain why Tyl studies did not find BPA effects: prostate wts inconsistent with literature? No internal BPA measurements.
- There should be one data set…GLP and non GLP studies. However, quality criteria have to be met by study in order to be considered (e.g., reproducibility, plausibility, relevant exposure routes, ...)
- Non-GLP studies should make use of some GLP principles (→Documentation).

Slide #8:
Human Exposure: Conclusions

There is controversy concerning the levels and sources of human exposures to BPA:

Need to clarify exposure sources in addition to food intake (which is reflected in the EFSA report).

Should we apply precautionary principle ? (no consensus)…

Earl Gray, 18.04.2009:

"I have attached my comments on the consensus document here in pdf format.

Thank you for the opportunity to comment on this and to particpate in the BPA Workshop in Berlin earlier this month.

Please let me know if I can be of any further assistance.

Sincerely

Dr Leon Earl Gray Jr

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
National Health and Environmental Effects Research Laboratory
Reproductive Toxicology Division
Research Triangle Park, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

April 18, 2009

Dear Sirs,

I would like to comment on the consensus statement from our meeting, but first, let me thank the organizing committee for the opportunity to participate in this meeting. I hope that the lively debate will facilitate a clear understanding of the unresolved scientific issues surrounding the chemical bisphenol A and facilitate scientific regulatory progress in resolving the controversy after consideration of all the high quality scientific information.

As indicated during the discussion of the consensus statement, I stated specifically that there items in the consensus document that was presented that I did not agree with and did not feel that we had achieved complete consensus on and that there were several important issues presented by multiple speakers at the meeting that we not listed in the document. It was for this reason that I asked if we were going to be able to comment on the consensus statement after the meeting.

The comments that follow will

- Address the original consensus document slides with points of clarification.
- List issues that were presented the several speakers that were not included in the consensus document.
- Included a copy of the text from one US newspaper article and the first two paragraphs of another on our consensus statement that claim to be based on "**several working versions of their agreement"** that were reportedly given to the reporters by workshop participants. I included this because there are many statements in these articles that are

very misleading about the consensus of all the participants at the workshop, although they reflect the opinion of a few of the participants.

- Provide here one definition of "consensus" to support my feeling that a "consensus" is not supposed to be based only upon the opinions of the most vocal, most outspoken and most assertive members of a workshop and it certainly is not the interpretation of newspaper reporters of what was discussed at the workshop.

  http://en.wikipedia.org/wiki/Consensus

  Definition: "Consensus has two common meanings. One is a general agreement among the members of a given group or community, each of which exercises some discretion in decision making and follow-up action. The other is as a theory and practice of getting such agreements (for information on the *practice* of achieving formal consensus, *see* **consensus decision-making**). Achieving consensus requires serious treatment of every group member's considered opinion. Once a decision is made it is important to trust in members' discretion in follow-up action. In the ideal case, those who wish to take up some action want to hear those who oppose it, because they count on the fact that the ensuing debate will improve the consensus. In theory, action without resolution of considered opposition will be rare and done with attention to minimize damage to relationships."

Comments on the Consensus document presented at the Workshop

The unedited text from the slides in bold in quotation marks and my comments follow un-bolded.

"Berlin Workshop on BPA Health Discussion Group Report

Human Exposure: Conclusions"

• There are data showing free BPA in newborns in neonatal intensive care unit."

Provide the reference to the paper and merge the following bullet with this statement. As indicated at the workshop during the discussion of the following point, the higher levels of total BPA in newborns is not reflective of levels in the general population but rather are levels in newborns from the NICU

"• Newborns have 3-11 times adult blood levels."

Merge with above bullet and clarify that the NICU babies were able to metabolize about 90% of the free BPA to inactive form BPA-G, as concluded in the paper.

"•There are data showing free BPA levels in human blood (more than 12 studies…showing reproducibility) (lack of consensus)."

Comment, higher quality data are needed.

"•We do not know all the sources of BPA exposure… data indicates there must be more than oral exposure."

Comment. The discrepancies among data on BPA exposures on a microgram/kg body weight per from biomonitoring studies versus estimates of exposure from food, dust, water and etc are quite large and unexplained. However, scientists have much greater faith in biomonitoring estimates than external exposure estimates which indicate that exposures to free BPA are very low from all sources and routes of exposure.

• Pbpk model based on very low newborn exposure produces data that does not match actual data.

Research is needed to improve the models based upon hypothesis driven high determinations of free BPA levels (not just total BPA levels) in tissues.

"•If human exposure is as high as many data suggest, the model needs to be recalculated based on higher exposure levels."

Comment. This definitely needs to be reworded to accurately reflect the discussions at the workshop. We did not agree that BPA levels are "high as many data suggest". What was discussed that the measured BPA levels were higher (not high) than the models estimated. Without further research we do not know which is in error: the model or the chemical determinations of BPA levels.

"Human Exposure: Conclusions

•Rodents and humans similarly exposed will have comparable internal levels of free BPA."

Comment, I do not agree that we can conclude this. We hypothesized that this might be the case, but there are not sufficient data to conclude this. More data are needed before a final conclusion is warranted.

"•We should not focus on enterohepatic recirculation (EHC) as a reason for dismissing rodent data as relevant to human data."

Comment. The response to this bullet provided at the meeting was that no one had dismissed rodent data from risk assessments for this reason. So it is moot point. Data were dismissed from risk assessments for valid scientific reasons, but not for this reason.

"•These findings suggest that rodent data are appropriate for modeling human exposure to BPA."

Comment. I would conclude that "these findings suggest that rodent data may be appropriate" not that the "are appropriate".

"•There are state of the art technologies for measurement of BPA, hplc and tandem mass spec with isotope dilution. QC is critical!"

Comment. True, and many of the data in the literature are not valid having used less reliable and specific methods.

"• Elisa assays for BPA should not be used as they are not specific."

Comment. Very True.

"Human Exposure Data Needs

•The pbpk model should be applied to other published data sets.

• Need more data on BPA kinetics in newborns and adults.

•Need internal measurements of free and conjugated BPA in serum and urine of rodent models and humans (more than one time point) especially pregnant mothers and newborns with cord blood."

Comment. Agreed that more high quality data will be very useful.

"•Need to determine all sources of exposure to BPA in addition to oral route…obvious there must be more routes of exposure."

Comment. Agree that we should determine all routes of exposure, but definitely do NOT agree that is obvious that there are more routes of exposure for the general population. This is a hypothesis, not a proven fact.

"•Need blood samples free of BPA for use in assays…analytical quality control important."

Comment. This is a rather minor point.

"Animal Studies

•NTP some concern for neurobehavioral effects at low doses of BPA (pattern-masculinization of females 8-20 studies) and prostate pin lesions.

Comment. The NTP monograph does conclude that there is some concern for low dose effects of BPA on neural-behavioral outcomes. It did NOT conclude that there was a pattern of masculinization of females from 8-20 studies. Since this refers to the NTP monograph, it should accurately reflect the conclusions of the NTP and are not subject to modification in our consensus and the attributed to the NTP. Also, I do NOT agree that there are 8-20 studies showing masculinization of females by BPA. I clearly stated this in my presentation and this opinion was offered by one other participant but there was no further discussion of this and no

consensus was reached. This is an exaggeration of the NTP conclusions and the consensus of our workshop about the consistency of the low dose effect of BPA on neural behavioral endpoints. A detailed review of this issue is available in the NTP BPA expert panel report, and several peer-reviewed publications.

"**• Some concern regulatory agencies should pay attention to these data and also more data needed."**

Comment. There was not a consensus on what "some concern" meant from the two former members of the NTP CERHR BPA Expert Panel. But, neither a "high level of concern", nor the next level of concern "concern" were not expressed by any member of the NTP CERHR BPA Expert Panel or in the NTP monograph.

"•Earl Gray study with EE positive control no BPA effects- discussion on sensitivity of model, no consensus.

•No consensus on strain differences in sensitivity to BPA."

Comment. The statement that there was "no consensus" is misleading. I presented information on the cellular and molecular basis for tissue-specific estrogen-mediated effects in several different strains of rats in response to a single question about the sensitivity of our rat strain. We also have published this in two peer-reviewed papers. I explained that no rat strain is more or less sensitive than another to all the effects of estrogens, there are tissue specific strain responses. The genes are on different chromosomes from one another and for this reason, they do not segregate with one another. Following this, the response was that the individual posing the question agreed with my explanation. So, to say "no consensus" implies that there was widespread disagreement when in fact; there was a single question about our model, an explanation and no further discussion about this issue. There was no attempt to reach consensus.

"•Tyl study minimal behavioral endpoints, no prostate pin endpoints. "

Comment. These were comments by a few individuals and not agreed upon as part of the consensus. It has no place in a consensus document. The Tyl study was well designed and executed (as determined by several Agencies and expert panels) and very comprehensive and

robust. However, no single study is going to measure everything or address all the hypotheses about this chemical. If we are going to include this then one would need to list every endpoint that was not measured in every one of the BPA studies. This is not a worthwhile task. Delete this since it appears to be a criticism of the study, when in fact it is no more than an aside.

"•Discussion on use of estradiol as positive control in Tyl studies …not effective orally…no consensus.

Comment. The study used a positive control that was effective. The dose was carefully selected from a previous E2 dose response study."

"• Mechanism of BPA in animals unclear…ER alpha or Beta or membrane ER? "

Comment. To date there is no biologically plausible mechanism that explains why one should expect BPA to produce effects at low levels. There are new hypotheses about membrane ERs, but the role of these in vivo is uncertain and, to date, have not yet been shown in vivo to be relevant to the effects of estrogens on reproductive function. At the moment, we have no proven mechanism of action.

"•No reasons developed to explain why Tyl studies did not find BPA effects: prostate wts inconsistent with literature? No internal BPA measurements."

Comment. The reason that Tyl et al, and many other robust multigenerational studies (in several strains of rats (Wistar, SD, F344, LE, Alderly-Park, etc) and mice (CD-1, CH 3, etc) did not find low dose effects of BPA may well be that there are no reproducible low dose effects of BPA on prostate weight. The most of the mouse studies and all rat studies have not found that BPA or the positive estrogen controls increased prostate weights in male offspring.

An additional criticism of the Tyl mouse study verbalized at the meeting and in one of the following press articles on the meeting was related to comments errors in ages of the animals at necropsy made by Dr Tyl should invalidate the use of the study for risk assessment. However, this criticism is not valid. There are no errors about the ages at necropsy of the mice in this study. These are clearly described in Dr Tyl's peer-reviewed publication and in the raw data

provided to groups like the NTP CERHR BPA Expert Panel and the FDA. If one is unclear about how this and other multigenerational studies are executed and the ages at which animals in different generations and sexes are necropsied they need to carefully read the paper.

"•There should be one data set…GLP and non GLP studies. "

Comment. But the data set can only include high quality studies that meet minimum criteria for use in risk assessment. EFSA, NTP and FDA all have rejected many of the low dose studies for very valid scientific reasons. I did present the criteria used by the NTP CERHR BPA Expert Panel in my presentation. This is critical. Some low dose studies were deemed inadequate for not having concurrent control groups, invalid experimental designs, incorrect statistical analysis (some were reanalyzed by NIEHS statisticians and results could not be repeated), direct injection of the chemical into neural tissues, and etc. Furthermore, some of these studies have had to retract the original level of BPA given to the dam having incorrectly reported it by 1000 fold.

Non-GLP studies should make use of some GLP principles (.Documentation).

Comment. They also should be willing to make their raw data, SOPs, histology slides and statistical analyses available to regulatory bodies if they want the published data to be used in risk assessment.

Animal Studies Needed

"•Need additional behavioral studies, focused to clearly define sexually dimorphic behavioral changes or repeat studies-link to estrogenic effects.

•Need internal dose in animal studies.

•Demonstrate mode and mechanism for in vivo effects."

Comment. First, we need to find a robust low dose effect that scientists can actually replicate before we can study the mode and mechanism of action. Currently, we have no reproducible effects and no proven mechanism for the low dose effects of BPA.

"•Is there something different about BPA that results in low dose studies or is it a more general phenomenon? "

Comment. What is different about BPA is that there has been 10's of millions of dollars of funding; this is what results in low dose studies being done. However, I am not clear on what this statement is actually trying to say. Until there are robust, reproducible low dose effects we cannot conclude anything about whether it is "different" or "a more general phenomenon. There is nothing unique about controversy in science, however.

"Human Exposure: Conclusions

There is controversy concerning the levels and sources of human exposures to BPA: these controversies are not reflected in the EFSA report.

Should we apply precautionary principle…"

Comment. The last sentence was removed from the consensus during the discussion, by consensus, and it should remain deleted.

Some key issues presented by speakers not covered in the consensus document.

Several speakers reported that risk assessment agencies and expert panels conducted under US FACA guidelines (to eliminate the possibility of special interest groups from biasing official recommendations to governmental agencies, and to allow for public comment and peer review) had rejected or declared as "inadequate" a significant percentage of the low dose studies. The bases for these decisions were presented and there was no debate on the issue that only high quality studies can be used in the risk assessment process.

The criteria used by the NTP CERHR BPA Expert Panel were presented. In addition, the levels of concern for low dose effects determined by the Expert Panel and subsequently by the NTP in its Monograph were presented. The potential low dose effects on endpoints such as obesity, early puberty, mammary gland effects, hormonal alterations, fertility, cancer, fetal or neonatal mortality, birth defects, reduced birth weight, and effects on adults, were all of minimal or negligible concern.
(NTP Monograph on BPA, p 38-39). The overall conclusion by the NTP (page 8, Figure 2 b) was that there is "limited evidence of adverse effects" from low doses of BPA.

Some of the problems with studies that led to the determination that they were inadequate for further consideration in the NTP CERHR BPA expert panel were published and include the following

1. Invalid experimental designs that precluded reanalysis of the data.
    a. Lack of concurrent controls
    b. Cross fostering after in utero exposure in a manner that eliminated the ability to track the prenatal litter effects
    c. All the pups in a dose group were from a single litter
2. Inappropriate statistical analyses.
    a. Failure to account for litter effects in the data analysis
    b. Failure to account for repeated measures in the analysis

3. Unusual routes of administration (e.g. injected directly into neural tissues)
4. Studies previously identified as having statistical problems by statisticians at an NIEHS Low Dose Workshop. (Reanalysis of the data could not repeat the same statistical outcome).

Comments on the newspaper Article reporting on the Workshop consensus.

The items in the following article in bolded text are comments that I feel inaccurately are attributed to the consensus of all the participants at the workshop. While they may reflect the opinion of a few participants, they were not agreed upon by group and ignore the opinions of other participants at the workshop. As indicated in the definition of "consensus" listed above, "**Achieving consensus requires serious treatment of every group member's considered opinion**." and clearly every group member's opinion is not presented here.

The article, unedited except for bolded text which reflects claims that I do not agree are part of our workshop consensus and I deleted the names of the reporters.

"Consortium rejects FDA claim of BPA's safety

Scientists say 2 studies used by U.S. agency overlooked dangers
By (reporter's names deleted) Posted: Apr. 11, 2009

An international consortium of industry, academic and government scientists has rejected as incomplete and unreliable the U.S. Food and Drug Administration's case that a chemical found in food containers and other household products is safe. The group, which met last month in Germany, is working to release a consensus statement in the next few weeks. The meeting was closed to the public, but the Journal Sentinel has interviewed many scientists who attended the meeting **and has seen several working versions of their agreement**. The **group raises questions about the two studies that the FDA has used as its foundation to declare that bisphenol A is safe** in food and beverage containers. It calls for a much broader look at the chemical than the FDA has given. Speakers at the conference included Rochelle Tyl, the author of the two studies that are being used as the FDA's benchmarks. Both of Tyl's studies were paid for by the American Chemistry Council, a trade association for BPA makers. **According to scientists at the meeting, Tyl conceded that there were errors and inconsistencies in the 2008 report that the FDA used as the foundation for its findings.** "It is becoming undeniable that BPA is dangerous," said Laura Vandenberg, a developmental biologist at Tufts University, one of 58 scientists from around the world invited to the conference in Germany. "The FDA's standard for safety is reasonable certainty. It is no longer reasonable to say that BPA is safe." **The group's conclusions also call into question the European Food Safety Authority's assessment of BPA.** The authority, which also relies on Tyl's studies, sets policy for all countries in the European Union. **The scientists' consensus statement will contradict claims**

by industry spokesmen who have been citing the FDA and European assessments as proof that BPA is safe. Tyl told the Journal Sentinel in an e-mail that her studies do not claim that BPA is safe. Her studies were not designed to cover all aspects of the chemical's effects. They simply show no effects to the reproductive system of rats and mice that were exposed to the chemical at low doses, she said. She has previously acknowledged inconsistencies in her data, particularly the age of some animals that were examined in the 2008 study for effects on the prostate. While Tyl answered several questions by e-mail, she declined to be interviewed. John Vandenbergh, a biologist at North Carolina State University who attended the conference in Germany, said the FDA risks losing credibility by relying on such flimsy evidence. "We desperately need good judgment at the FDA," Vandenbergh said. "For years, they did a superb job looking out for food safety. I hate to see something like this jeopardize all that." The conference, held in late March, was called to reassess the safety of BPA for German regulators. But the agreements that were forged there are being closely watched by those worldwide with a stake in the future of the chemical, including BPA-makers, regulators and advocates who consider the chemical to be dangerous. **The group agreed that Tyl's studies were too limited in their scope to be considered benchmarks. The group found that Tyl's studies failed to consider serious dangers posed by BPA.** They include effects on behavior and the development of the brain and prostate. Those problems were identified in a National Toxicology Program report published last year. FDA administrators promise to address those issues more thoroughly now.

Ruling protested

Despite concerns raised by other regulatory agencies, the FDA declared BPA to be safe last August. It cited Tyl's two studies, which were released in 2001 and 2008. Several BPA experts and health advocates protested the ruling, **saying that the agency was too quick to ignore hundreds of other studies that found the chemical caused harm.** The agency's Science Board agreed and recommended that the FDA reopen its assessment of the chemical. Laura Tarantino, director of the FDA's Office of Food Additive Safety, said Tyl's studies followed proper protocol. But she acknowledged some uncertainties about whether Tyl's studies addressed all concerns about the chemical. Neither Tarantino nor any FDA scientists were invited to the meeting. Tarantino said her agency would now look at other studies that raise concerns about BPA. BPA, developed more than 100 years ago as a synthetic estrogen, is used in thousands of household products to make hard, clear plastic for things such as baby bottles and food containers. It also is used in many dental sealants and to line most food and beverage cans. The chemical has been found in the urine of 93% of Americans tested. Tests conducted last year for the Journal Sentinel found that toxic levels of the chemical leached from 10 different product containers when heated, including those marked "microwave safe." Although the levels that leached from the containers were low, the Journal Sentinel identified several peer-reviewed studies that found health risks in laboratory animals at similar levels. Scientists began studying the chemical more than 10 years ago after laboratory animals were found to be developing health problems suspected of being caused by their polycarbonate cages. These problems included heart

disease, obesity, diabetes, some forms of cancers and reproductive failures. Recent studies have linked the chemical to heart disease and diabetes. It has been found to interfere with chemotherapy for breast cancer patients. Concern is especially keen for its effects on fetuses and newborns, whose development are most affected by exposure to the chemical. Canada declared BPA to be a toxin and has banned its use in baby bottles. Earlier this year, the six major baby bottle makers promised to stop using BPA. Sunoco, one of five BPA makers, now requires companies buying its BPA to sign a promise that they will not use it to make products for children younger than 3. The government is expanding its look at the chemical, and last month the National Institute of Environmental Health Sciences announced it was investing $5 million in BPA research. Last month, bills were introduced in both houses of Congress to ban BPA from all food and beverage containers.

Different accounts

The German conference did not reject Tyl's studies but had questions regarding her methodology and accuracy. **In the past seven months, Tyl has given three different accounts of the ages of the animals that she used to study BPA's effects on prostate size.** Scientists who attended the conference in Germany say that the discrepancies are significant because prostate size varies greatly depending on age. A larger-than-normal prostate could indicate cell change caused by BPA. Tyl said in her 2008 paper that the animals were younger than 14 weeks, or around 3 months old. Critics questioned this at an FDA hearing in September. They noted that Tyl's data showed the mice to have abnormally large prostates for animals that were 3 months old. They said that could indicate that either the animals were diseased or that a lab technician had bungled the data. Tyl said then that the paper erred. The animals were 6 months old, she said. FDA administrators were at the hearing, but there is no record of the discrepancy on the FDA's Web site, which lists the studies for the public to review. Last month in Germany, when questioned again, Tyl said the paper was wrong. The animals actually were 5 months old. "How could this mistake be made and not caught," said Laura Vandenberg, the Tufts scientist. "Now that this issue has been brought to light, have the other data been verified and validated, and by whom?" FDA spokesman Michael Herndon said Friday that he was not certain if the agency had made note of the discrepancy. "She is in big trouble over the age issue," said Fred vom Saal, biologist at the University of Missouri and one of the most vocal critics of the FDA's assessment. Vom Saal was also at the meeting in Germany. Vandenbergh, the BPA expert from North Carolina State, said the discrepancies "significantly weaken" Tyl's 2008 study. "I wouldn't use it as a benchmark study," Vandenbergh said.

Lab fire

Scientists who attended the conference said they also were concerned about a fire that broke out in Tyl's North Carolina laboratory that was never reported to the FDA. The fire occurred on Aug. 25, 2001, about a year after her first paper had been written and some three years before work began on the second study. Eighteen polycarbonate cages, made with BPA, burned in the fire. Scientists at the conference say the lingering effects of the fire may have compromised future experiments. The chemical could have gotten into the heating ducts or the

feed, exposing the animals to much higher doses than reported in the study. Tyl's company, RTI International, investigated the fire - which appeared to be arson. An independent firm analyzed the lab and reported that it had been sufficiently cleaned. The group declared that the animals were not compromised and that Tyl's lab "was, and continues to be, an excellent facility." But scientists at the conference, when told of the fire by the Journal Sentinel, said they would not trust that assessment. BPA is a sensitive chemical that acts at extremely low levels, and the group that analyzed the lab did not test for the chemical at those levels, they said. Vandenbergh, of North Carolina State, who examined the reports on the fire and the laboratory's investigation for the Journal Sentinel, said he would have conducted the experiments at a different lab. "In hindsight, this is too important of an issue to leave open these questions," Vandenbergh said. Herndon, the FDA spokesman, said the agency was unaware of the fire and has no plans to discount the studies. "It appears that sufficient corrective action was taken at the laboratory regarding the fire, the incident and its impact on the animals is not relevant to the studies reviewed regarding BPA," Herndon said.

Scores of studies

The scientists at the German conference also agreed that government regulators need to greatly expand the universe of studies that they consider. Scores of studies have linked BPA to behavioral problems in animals, such as aggression, anxiety and hyperactivity. Other studies have found changes to the prostate gland that have been shown to lead to cancer. But the FDA discounted them because they did not adhere to the Good Laboratory Practices designation. The internationally recognized designation is considered by some to be biased toward industry because it requires more animals to be tested than many academic institutions can afford or are willing to test. The March conference was the first time that scientists from all perspectives reached a consensus on several key aspects of human exposure to the chemical. Though representatives of European industries attended the conference, scientists from the American Chemistry Council, which represents American BPA-makers, were not invited. Steven Hentges, the industry spokesman on BPA, deflected worries that this new position would threaten previous safety assessments of BPA. "Within the last year, the European Union, European Food Safety Authority, German Federal Institute for Risk Assessment, Danish Environmental Protection Agency, French Food Safety Authority and the Swiss health authorities have all evaluated BPA and concluded that BPA in food contact applications is not a human health risk," Hentges said. These agencies also relied largely on Tyl's work and several premises that are about to be discounted, a review of those assessments show. For years, scientists from industry and many regulatory agencies have said that BPA is not a health risk because people - including infants and children - are exposed to such low levels of the chemical. But the group in Germany acknowledged that children and infants have levels of BPA in their urine that are three to 11 times higher than adults. The FDA also discounted studies that used rodents to gauge human exposure to BPA. But the German group found that humans and animals treated with comparable doses end up with similar levels even though they metabolize it differently. The group also urged regulators to look at studies that examined how BPA acts at low doses, an area of research that many regulating bodies were reluctant to consider. A growing number of scientists say that

because BPA acts like a hormone, its effects are seen at extremely low levels, even if no damage is found at higher doses. Tarantino of the FDA says the agency will expand its look to include low-dose effects.

Second newspaper article (first two paragraphs only)

Scientists Rebuff FDA's Claim that BPA is Safe
Date Published: Monday, April 13th, 2009

A group of experts from around the globe, including 58 scientists in industry, academia, and government, have rejected the U.S. Food and Drug Administration's (FDA) long-maintained claims that the chemical bisphenol A (BPA) is safe. The "international consortium," said ContraCostaTimes met in Germany in March and is collaborating on a "consensus statement" to be released in the next "few weeks."

Although the meeting was closed to the public, McClatchy Newspapers—parent of the Contra Costa Times—interviewed a number of the scientists in attendance and has seen, it said, "several working versions of their agreement."

Sincerely

Leon Earl Gray Jr, PhD
Senior Research Biologist,
gray.earl@epa.gov

MD-72, Reproductive Toxicology Branch, Toxicological Assessment Division, National Health and Ecological Effects Research Laboratory, Office of Research and Development, United States Environmental Protection Agency
Research Triangle Park, NC 27711

Wolfgang Dekant, 21.04.2009:

"…wir haben eine Kopie auf die Sharepoint-website eingestellt, hier ist auch noch mal eine Kopie angehaengt.

wd"

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Lehrstuhl für Toxikologie
(Vorstand Prof. Dr. W.K. Lutz)

Institut für Toxikologie, Versbacher Str. 9, 97078 Würzburg, Germany

Prof. Dr. W. Dekant
TEL: +49-931-20148449
FAX: +49-931-20148865
E-mail: dekant@toxi.uni-wuerzburg.de

Würzburg, 20.07.2009

Dear all,

I would like to comment on the points regarding the health discussion group report.

In my opinion, the points and conclusions do not sufficiently present the disagreements and use a highly imprecise and unscientific language, which needs to be corrected. After all, it was intended as a scientific discussion. A point by point discussion follows with bullets in boldface:

- **There are data showing free BPA in newborns in neonatal intensive care unit.**

COMMENT: This observation is not relevant for the general public, since, most likely, non-oral exposures are involved. Moreover, the data show that even at significantly higher exposures than those expected for the general populations, newborns have significant capacity to metabolize BPA to a large extend. Bullet should be removed or the authors caveats should be included.

- **Newborns have 3-11 times adult blood levels.**

COMMENT: This statement is not correct because nobody has ever measured this. The correct statement is “PBPK models predict that peak concentrations of BPA in human neonates after oral exposures may be 3 – 11 times higher than those of adults”. It also needs to be included that PBPK modeling (supported by UBA) has predicted free BPA concentrations in blood in older children and adults to be between 3 and 4 pmoles/L (600 - 800 pg/L). It remains to be determined if an increase even by 10-fold to a few ng/L may present a health risk. Moreover, the 10-fold increase is based on a PBPK model which did not include a major biotransformation pathway, sulfation. These facts should be integrated.

- **There are data showing free BPA levels in human blood (more than 12 studies…showing reproducibility) (lack of consensus).**

COMMENT: Many of these studies using ELISAs have been agreed to be unreliable. Of the other studies, Schönfelder and Padmanabhan have major problems. While the analytical part of Schönfelder looks ok and may be suitable to analyze BPA in water, a number of issues including presence of background, no information on background variability, and presentation of totally inconsistent data in tables and chromatograms significantly reduce reliability. In the Padmanabhan publication, the chromatography is strange since BPA is only eluted when the gradient is reversed and the retention time

cannot be reproduced. Kuroda et al., likely determine total BPA because strongly acidic media are used in the derivatization process. These are expected to cleave BPA-conjugates. Moreover, the Kuroda-data are 10 fold lower than those of Schönfelder and Padmanabhan. No consensus.

- **We do not know all the sources of BPA exposure… data indicates there must be more than oral exposure.**

COMMENTS: The data indicating this should be clearly mentioned. Assessment of non-food exposures were made by the ECB using their routine approach and by Wilson et al. Both papers suggest that food is a major source for BPA. The conclusions that non-food exposures are high are not based on a rigorous analysis of the available data and do not consider the many studies on biomonitoring of BPA using urinary concentrations, which is much more suitable for exposure assessment of rapidly metabolizing compounds. Urinary concentrations of BPA show that exposures are much lower then those predicted by using concentrations of BPA in food and/or leaching rates. Imprecise statement, no consensus.

- **Pbpk model based on very low newborn exposure produces data that does not match actual data.**

COMMENTS: The exposures used in the PBPK models are the conservative estimates derived by several regulatory agencies. They do not mach the measured data reported in publications with major methodological problems. The bulled should be removed.

- **If human exposure is as high as many data suggest, the model needs to be recalculated based on higher exposure levels.**

COMMENTS: Bullet should be removed, models cannot be recalculated, they only can integrate higher exposure levels to predict peak blood levels under such conditions.

- **Rodents and humans similarly exposed will have comparable internal levels of free BPA.**

COMMENT: There was no agreement. Rats excrete free BPA in significant amounts in urine, therefore EFSA concluded that free BPA levels may be higher. No consensus.

- **We should not focus on enterohepatic recirculation (EHC) as a reason for dismissing rodent data as relevant to human data.**

COMMENT: This bullet can be removed because nobody has done that. The next bullet, "**These findings suggest that rodent data are appropriate for modeling human exposure to BPA**" therefore can also be removed. It should be mentioned that biotransformation of BPA in the mouse is widely different from that in rats and humans.

- **There are state of the art technologies for measurement of BPA, hplc and tandem mass spec with isotope dilution. QC is critical!**
- **Elisa assays for BPA should not be used as they are not specific.**

Total agreement

- **The pbpk model should be applied to other published data sets.**

COMMENT: This is unclear, what data sets? Exposures? In this case, bullet can be removed since this is covered above.

- **Need more data on BPA kinetics in newborns and adults.**

COMMENT: Kinetic data in newborns may be very useful but a controlled study cannot be performed due to justified ethical concerns. Regarding data in adults, there are a number of human studies and several studies in primates all showing the same outcome. Therefore, there is no need for such studies. No consensus.

- **Need internal measurements of free and conjugated BPA in serum and urine of rodent models and humans (more than one time point) especially pregnant mothers and newborns with cord blood.**

COMMENT: Fine, but with adequate quality control only.

- **Need to determine all sources of exposure to BPA in addition to oral route…obvious there must be more routes of exposure.**

COMMENT: see above. No consensus.

- **Need blood samples free of BPA for use in assays…analytical quality control important.**

COMMENT: Full agreement

- **NTP some concern for neurobehavioral effects at low doses of BPA (pattern-masculinization of females 8-20 studies) and prostate pin lesions.**

COMMENT: It should be made clear that NTP is the only organization coming to this conclusion. All regulatory agencies have evaluated the data and have made very clear statements regarding reliability. In addition, this statement does not correctly reflect the NTP-position.

- **Some concern=regulatory agencies should pay attention to these data and also more data needed.**
- **Earl Gray study with EE positive control no BPA effects- discussion on sensitivity of model, no consensus.**
- **No consensus on strain differences in sensitivity to BPA.**
- **Tyl study minimal behavioral endpoints, no prostate pin endpoints.**
- **Discussion on use of estradiol as positive control in Tyl studies …not effective orally…no consensus.**

COMMENTS: Agree with “no consensus”

- **Mechanism of BPA in animals unclear…ER alpha or Beta or membrane ER?**

COMMENTS: Agreement

- **No reasons developed to explain why Tyl studies did not find BPA effects: prostate wts inconsistent with literature? No internal BPA measurements.**

COMMENT: The point “no internal BPA-measurements” should be removed because none of the toxicity studies on BPA, either under GLP or non-GLP, have made such measurements. Not including such measurements does not disqualify a study.

- **There should be one data set…GLP and non GLP studies.**

COMMENTS: All published data on BPA and all original reports describing BPA toxicity studies under GLP have been considered by regulatory agencies. The studies and the conclusions are clearly described both in EFSA and ECB-documents. The bullet, therefore, is not needed.

- **Non-GLP studies should make use of some GLP principles (Documentation).**

COMMENT: Agreement

- **Need additional behavioral studies, focused to clearly define sexually dimorphic behavioral changes or repeat studies-link to estrogenic effects.**

COMMENT: Such studies should be performed under GLP using appropriate OECD and US-EPA guidelines.

- **Need internal dose in animal studies.**

COMMENT: Agreement, but satellite groups to be used for kinetics will greatly inflate all toxicity studies and may therefore not be feasible, especially for non-contract research laboratories with limited resources.

- **Demonstrate mode and mechanism for in vivo effects.**

COMMENT: Mode-of-Action alone is sufficient in the bullet.

- **Is there something different about BPA that results in low dose studies or is it a more general phenomenon?**

COMMENT: The wording needs to be changed and “studies” has to be replaced by “effects”. However, only studies with appropriate study design should be funded.

There is controversy concerning the levels and sources of human exposures to BPA: these controversies are not reflected in the EFSA report.

COMMENT: EFSA only addressed exposures with food, the ECB document is very concise regarding assessments. Therefore, the reference to the EFSA report should be removed. No consensus.

- **Should we apply precautionary principle…**

COMMENT: No consensus, but see the response of the French Food Safety Agency to questions raised in the French Parliament regarding application of the Precautionary Principle to regulate BPA.

I had hoped that we could come to conclusions on minimal needs for study designs, data reporting, and use of statistics in study evaluation. This could have been a useful result of a workshop and could have served as a basis for funding agencies to evaluate research proposal. Unfortunately, we have not moved form the opposite positions.