

BPA Consortium comments on the Proposal for harmonised classification and labeling (CLH Report) on Bisphenol A (BPA) prepared by ANSES Version 2.0, dated 17/07/2013

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I. Executive summary of BPA Consortium comments to the CLH Proposal

These comments and attachments are the comments of the Bisphenol A REACH Consortium (BPA Consortium), which represents more than 30 of the main producers, importers and users of BPA in Europe. After careful review of the proposal in the CLH dossier, we have a number of concerns.

- **The case has not been made that BPA merits classification as Category 1B** (presumed reproductive toxicant) under the CLP Regulation. In fact, a review of the relevant studies shows that effects on animal fertility only occur at high doses of BPA and that, rather than being selective reproductive effects, they are merely related to systemic toxicity.
- **The CLH proposal is not consistent with the procedure outlined in ECHA’s “Guidance on the preparation of dossiers for harmonised classification and labeling”** (ECHA 2010) ¹ which directs the use of a weight-of-evidence approach for compounds with a large database, such as BPA. The CLH proposal
 - does not consider *“all available information;”*
 - does not follow the CLP Regulation standard regarding the request that *“Both positive and negative results shall be assembled together in a single weight of evidence determination;”* and
 - fails to follow the CLP Regulation in that *“The quality of the data shall be given appropriate weight.”*
- **The CLH proposal selectively relies only on studies, assessments, and the 1 out of 1.409 self-classifications that supports its proposal and, therefore, portrays an inaccurate and incomplete picture of the state of the science on BPA.**
 - Information is not comprehensive and inconsistent throughout the report.
 - Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased.
 - Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible.
 - Reference of one industry self-classification out of 1.409 is clear evidence of “cherry picking” information and ignoring contrary information.
- **Recent (post December 31, 2012) and important scientific research from government agencies was not considered. These government studies do not support a classification of BPA as a Category 1B Reproductive Toxicant.**

Given the above, the dossier should be rejected as not supporting a classification of BPA as Category 1B reproductive toxic. The CLH proposal does not fulfil the criteria outlined in ECHA’s “Guidance on the preparation of dossiers for harmonised classification and labeling”

¹ EU Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures, the CLP-Regulation, entered into force on 20th January 2009

(ECHA 2010) because it fails to consider the quality of the data and it fails to consider all of the data in a weight of evidence analysis.

As can be seen from the BPA Consortium comments and from assessments of BPA conducted by other government regulators, when all high quality scientific studies on BPA have been considered and a weight of the scientific evidence evaluation is conducted, it will clearly demonstrate that BPA is not a selective reproductive toxicant. In conclusion, there is no basis to change the classification of BPA to Category 1B.

II. BPA Consortium's comments on the CLH proposal

A. Multiple multigeneration studies confirm that BPA is not a reproductive toxicant

Many multigeneration studies on BPA provide ample data to demonstrate that classification of BPA as a Category 1B reproductive toxicant is not supported. Three prior assessments of BPA by European regulators assessed the then available data and determined that BPA was not a selective reproductive toxicant. More recent studies, including an extensive study by US FDA National Center for Toxicological Research (NCTR), simply add to the overwhelming scientific evidence that BPA is not a selective reproductive toxic and that BPA does not meet the criteria for classification as a Category 1B reproductive toxicant.

The history of European regulatory assessments of BPA is instructive. In 2002, after a long and thorough weight of the evidence analysis of the then available data on the potential effects of BPA on animal fertility and development, **BPA was classified by the Member States as reproductive toxicity Category 3 for fertility** (Directive 67/548/EEC; R 62.) The conclusion reflects the Member State's assessment that the reproductive effects from BPA (e.g. reduction of litter size) were only observed when significant toxic effects to the whole body were observed (e.g. influence on body weight and effects on liver and kidneys.) Thus, the Member States working group concluded that the effects on fertility should be regarded as related to systemic toxicity and not as evidence of primary reproductive toxic potential.

Also in 2002, the reproductive toxicity of BPA was evaluated in a **European Risk Assessment (published in 2003)**. It identified a need for further research to resolve uncertainties surrounding the potential for BPA to produce adverse effects on development at low doses. Consequently, **a 2-generation study in mice according to OECD 416** (with some specific modifications) was initiated. The mouse study confirmed that BPA is not a selective reproductive toxicant. The study design and interpretation of the results were supervised by a Steering Group that was chaired by a representative of the European Chemicals Bureau and included experts from several EU Member States; it was published as Tyl et al. (2008a).

With the results of this 2-generation mouse study available, an **updated European Risk Assessment of BPA was finalized in 2008**. A weight of evidence review of the literature, including the 2-generation mouse study, **confirmed the conclusions of the 2002 EU Risk Assessment that BPA is not a reproductive or developmental risk to human health**. The 2002 classification of BPA as Category 3 remained unchanged as the new 2-generation mouse study confirmed that BPA is not a selective reproductive toxicant.

Since 2008, additional robust and comprehensive guideline type studies of regulatory relevance have been concluded. These studies confirm that BPA is not a selective reproductive toxicant; for example:

- In a study on developmental neurotoxicity (OECD 426) BPA was administered from gestation day 0 through lactation day 21 at doses up to 150 mg/kg bw/day: no effect on reproductive outcome were observed (Stump et al. 2010).
- Most importantly, very recently a new study conducted at the US FDA National Center for Toxicological Research (NCTR) became available ([see Annex C for detailed summary](#)). In this study BPA was administered to rat dams by oral gavage from gestation day 6 until parturition and then directly to pups from postnatal day 1 until termination at postnatal day 90 at doses up to 300 mg/kg bw/day. BPA exhibited some adverse effects at high doses (in

females at 100 and 300 mg/kg bw/day and in males at 300 mg/kg), and the authors indicate in the study report that *“the interpretation of the high dose BPA effects are confounded by systemic toxicity”*.

When the results from studies with BPA are compared with the CLP Regulation’s requirements for a substance to be classified as Category 1B, it is clear that BPA should not be classified as Category 1B (*see Annex D for summary of relevant studies*). The CLP Regulation requires that:

- if, based on data from animal studies, there is clear evidence of an adverse effect on sexual function and fertility or on development from exposure to the substance in the absence of other toxic effects, or
- if occurring together with toxic effects, the adverse effect on reproduction is considered not be secondary, non-specific consequence of other toxic effects.

Based on all the available scientific data, BPA does not fulfil the criteria to qualify for Category 1B nor to be considered a selective reproductive toxicant:

- effects on animal fertility only occur at high BPA doses where already significant systemic toxicity (e.g. reduced body weight of dams, effects on liver and kidneys) are seen
- there is no conclusive evidence of adverse primary effects on sexual function, fertility or development.

In addition, based on comprehensive multigeneration reproduction toxicity studies in rodents there is a clear gap between

- the overall No Adverse Effect Level for general systemic toxicity (5 mg/kg bw/day, oral dosing) and
- the doses at which observations on reproduction parameters were seen (500 mg/kg bw/day in rats and 600 mg/kg bw in mice, oral dosing; in the presence of systemic effects).

In summary, BPA is not a selective reproductive toxicant based on guideline studies that cover a very wide dose range, from very low up to high doses. Secondary effects on animal fertility only occur at high doses of BPA that also show clear evidence of systemic toxicity. Consequently, the criteria for classification of BPA as a Category 1B Reproductive Toxic are not met.

B. The CLH proposal fails to engage in a weight of the evidence analysis as required by ECHA’s Guidance

The analysis underlying the CLH proposal is not consistent with the procedure outlined in ECHA’s “Guidance on the preparation of dossiers for harmonised classification and labeling” (ECHA 2010) because it fails to use a weight-of-evidence approach appropriate for compounds, such as BPA, with a large database.²

Specifically, the CLH proposal dossier fails to fulfil criteria outlined in *Section 1.1.1 of Annex I to the CLP Regulation EC1272/2008* (bold type highlight added)³:

*1.1.1.3: “A weight of evidence determination means that **all available information** bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results,*

² Section 1.1.1 of Annex I to the CLP Regulation and Section 1.2 of Annex XI to the REACH Regulation

³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>

*human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well documented case reports and observations. **The quality and consistency of the data shall be given appropriate weight.** Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. **Both positive and negative results shall be assembled together in a single weight of evidence determination.***

1. The CLH proposal does not consider “all available information”

The time period for the literature included in the report is confusing due to inconsistent statements.⁴ However, what is clear is that the CLH proposal omits relevant comprehensive studies published in the literature before December 2012. In particular it omits studies in BPA conducted as part of a comprehensive testing program by the US National Center for Toxicological Research/FDA (e.g. Fischer et al. 2011, Doerge et al. 2011a and b, Doerge et al. 2012 regarding toxicokinetics), as well as an OECD 426 Developmental Neurotoxicity Study (Stump et al. 2010).

2. The CLH proposal does not follow the CLP Regulation Guidance requirement that “Both positive and negative results shall be assembled together in a single weight of evidence determination.”

The CLH proposal discusses only a limited and selected number of studies throughout the report for each endpoint and does not evaluate all positive and negative results in a single weight of evidence determination. For example, the CLH proposal failed to note several studies reported in the literature which investigated sperm parameter. The CLH Proposal provides no rationale for the inclusion/non-inclusion of studies on this topic. A literature review to simply identify sperm parameter studies revealed the following studies that were not collected or analysed considered in the CLH proposal: Aikawa et al. 2004, Toyama et al. 2004, Kubo et al 2003, Wistuba et al 2003, Pecnicova et al 2002, Park et al 2005b, Kubo et al 2001, Cagen et al 1999, vom Saal et al 1998, Ashby et al 1999, Talsness et al 2000, Ema et al 2001 and more recently Kendig et al. 2012, Xie et al. 2010, Zhang et al. 2012b. (Note: In our comments concerning the CLH proposal we have not evaluated these additional studies for quality, but include them as examples of available data that the CLH proposal failed to collect or analyse. *See also Annex A for further details and examples*).

A major flaw in the CLH proposal is its inclusion of studies in which the initial findings could not be reproduced, and its failure to mention studies done in the same laboratory or in different laboratories that demonstrated the non-reproducibility of the original study. There are several cases where studies reporting effects are included, but repeat studies not reporting the effect are not included. For example:

- Hunt et al. 2003 and Susiarjo et al. 2007 - CLH proposal pages 64 and 114; tables 8 and 11.

The CLH proposal cites two in vivo studies (Hunt et al. 2003 and Susiarjo et al. 2007) for the proposition that short-term oral exposure to low doses of BPA in peripubertal or pregnant mice can interfere with meiotic divisions in development of female germ cells (“egg” or

⁴ Page 9 indicates: “This proposal is based on the studies presented in this French report (i.e. considered by the French experts as key studies, irrespective of their publication date) together with all the new data published since 2002 on fertility (bibliographical search stopped 31/12/2012).” However, page 117 refers to another data range “(exhaustive literature search from 2002 to 2011).”

“oocyte”). An increase in hyperploid (aneuploid) metaphase II oocytes was observed. There was not a significant increase in aneuploid embryos.

Not included in the CLH proposal are two subsequent in vivo studies (Pacchierotti et al. 2008, Eichenlaub-Ritter et al. 2008) that attempted – unsuccessfully - to replicate these findings regarding aneuploidy. They detected no significant effects of BPA exposure on the frequency of aneuploidy in “zygotes” (fertilised oocytes) produced from female mice treated before puberty or as adults with a similar range of doses. In addition, Eichenlaub-Ritter et al. (2008) found no effects of BPA exposure on aneuploid oocytes and Pacchierotti et al. (2008) found no increase in aneuploid or diploid sperm following exposure of male mice to BPA. The authors concluded that the aneuploidy predicted by the Hunt group could not be confirmed. This inconsistent picture was noted in the 2008 EU Risk Assessment.

Also not mentioned in the CLH proposal is a further study, Muhlhauser et al. 2009, which was published by the Hunt group, in which the authors could not replicate their own initial findings on “*congression failure*” but report effects on chromosome alignment and/or spindle formation. The authors state: “*After publishing our findings [Hunt et al., 2003], we initiated studies to assess the effect of long term BPA exposure on the growing follicle. To our surprise, levels of BPA that were sufficient to elicit an effect on meiotic chromosome dynamics during the previous two years of study suddenly produced little or no effect. In an analysis of possible changes in experimental protocol, the only change identified was the lot of animal feed.*” (Muhlhauser et al. 2009, page 1066.) The authors report frequencies of abnormal oocytes in the absence and presence of BPA in two different diets (casein based and soy based). The reported frequencies of abnormal oocytes of the BPA/casein group are lower than the background value reported in the soy-based diet.

In conclusion, the initial observations reported by the Hunt laboratory were not reproduced in the same laboratory or in other independent laboratories. The omission of this important information from the CLH proposal fails to accurately represent the state of the science and abrogates the obligation of the CLP Regulation to assemble both positive and negative results in a single weight of evidence determination.

- Sakaue et al. 2001 - CLH proposal page 92 and table 16

In Sakaue et al. 2001⁵, the authors have described how oral exposure of sexually mature male rats to BPA between postnatal days (PND) 91–97 led to a reduction in daily sperm production (DSP) 5 weeks later (18 weeks of age). Activity was observed over the dose range 20 µg/kg – 200 mg/kg BPA, with an absence of activity over the dose range 2 ng/kg – 2 µg/kg BPA. There was no evidence of a dose response relationship over the active dose range (five orders of magnitude range).

But, the CLH proposal does not mention an independent repeat of this study by Ashby et al. 2003 which has been included in other publicly available evaluations of BPA, e.g. EFSA’s November 2006 opinion and CERHR’s 2007 report, published in Birth Defects Research (2008). Ashby conducted a total of four independent studies according to the protocol used by Sakaue et al (2001) and did see any evidence of changes in DSP reported by Sakaue et al.

If the CLH proposal had evaluated both studies in a weight of the evidence evaluation, the conclusion might be similar to CERHR’s which stated: “*These data also strongly suggest that bisphenol A administered orally has no effect on sperm production albeit following only 6 days of administration.*”

⁵ (Note that the data given in table 16 on page 102 do not correspond with the data given on page 92 of the CLH report or the original publication).

- Myers et al. 2009 Commentary – CLH proposal page 95

The CLH proposal also references the Myers *et al.* 2009 commentary criticising the Tyl *et al.* 2008a multi-generation study, but does not mention or evaluate the published responses by Dr. Tyl (Tyl 2009). The omission of Dr. Tyl's response is indicative of a pattern and practice in the CLH proposal to selectively provide only data that supports its proposal.

3. The CLH proposal fails to follow the CLP Regulation requirement that “the consistency of the data shall be given appropriate weight”

Inconsistency in data may indicate that an effect is either transitory, due to normal variation or not a repeatable finding. In many instances, the CLH proposal fails to account for inconsistencies in data. One example is given below (*for further details see Annex A*):

- On page 97, the CLH proposal puts forward its “Conclusion on male reproductive system in animals,” and states that: *“In the animals treated in utero and/or lactation, most of the studies performed in mice or rats found effects on sperm production or quality (Tinwell et al. (2002); Salián et al. (2009c))...”* But this statement is not accurate because there are many additional studies mentioned in the CLH proposal which report no effect on sperm, and the CLH proposal itself recognizes this fact
 - on page 85 *“In contrast to these previous studies, several authors found only limited effect (Tinwell et al., 2002 and Kobayashi et al., 2010 and 2012) and other failed to demonstrate significant effects of BPA exposure on the male reproductive tract, especially at low doses (Howdeshell et al., 2008; LaRocca et al., 2011).”*
 - on page 86: *“It is difficult to find any specific reason explaining those contradictory results with the state of actual knowledge.”*
 - on page 88: *“All BPA groups in which analysis were performed at PND10, 35 and 150 showed normal reproductive parameters (for instance preputial separation, sperm analysis, serum testosterone levels, copulatory and fertility rate, sexual organ weight...”*

Overall, the CLH proposal fails to address inconsistency in the data to reach a weight of evidence determination as required by the CLP Regulation.

4. The CLH proposal fails to follow the CLP Regulation requiring that “The quality of the data shall be given appropriate weight.”

The CLH proposal does not define any quality criteria that it used to evaluate individual studies nor does it provide any explicit criteria for the inclusion or exclusion of studies from the report. Rather than discuss the strengths and weaknesses of individual studies, the CLH proposal merely repeats the data and conclusions of the study authors without further discussion or evaluation of the published data and without comparison with other available data, including historical control data and experience with the test system, and variability. Since no strengths or weaknesses are indicated for individual studies it is not possible to gauge the weight given in the CLH proposal to individual studies. By not evaluating the quality of the data and incorporating the data quality in the weight of the evidence analysis, the CLH proposal fails to meet the basic requirements of ECHA's Guideline.

Only indirect information on the criteria used in the CLH proposal is available. The CLH proposal does cite an ANSES interim report dated 2011. In this interim report a minimum of

six animals was considered sufficient if the effect under investigation displays high variability (hormonal dose, number of sperm per ejaculate), a larger number of animals is necessary. The number of animals, but not the variability of the endpoint, is indicated in tables throughout the CLH proposal. But, there are many studies cited by the CLH proposal that fail to meet the ANSES criteria of a minimum of six animals and are designated as “N ≤ 5” or “no data on the number of animals”. Yet, the CLH proposal does not explain why these studies were considered to be relevant, even though the ANSES interim report in 2011 considers studies with N ≤ 5 as insufficient. By including, without explanation, studies that do not meet its own criteria for data quality, the CLH proposal apparently fails in its fundamental duty to rely only on quality data.

Before relying on the data from any study, the statistical power of an experimental design should be examined for its ability to detect effects of a given magnitude. For example, in neonatal studies the litter should be the statistical unit of comparison, and not the individual offspring. This parameter was identified as an important criterion for study evaluation by other safety assessment panels, for example CERHR⁶ (NTP’s Center For The Evaluation of Risks To Human Reproduction) and by EFSA⁷.

In contrast to the CLH proposal, CERHR used defined criteria to evaluate many studies mentioned in the CLH proposal and considered the studies as either inadequate or adequate but with limitations. EFSA’s 2008 Opinion followed a similar approach which included rationale, results, statistical issues, strengths and weaknesses of each study, and consequently the reasoning for EFSA to include or not include the individual study into their assessment. Neither of these assessments nor their concerns with the studies was mentioned in the CLH proposal.

A detailed commentary concerning the studies on which the CLH proposal relies and which track the sections of the CLH proposal can be found in Annex A. A brief summary of the CERHR Reports assessment of studies mentioned in the CLH proposal in the chapter “*Summary and discussion of reproductive toxicity*” is provided here as an illustration of the CLH proposal’s failure to consider study quality and the consequent reliance on inadequate or inappropriate studies for its proposal:

Aikawa et al. 2004: “Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate and not useful based on small sample sizes and inadequate presentation of statistical methods of analysis.”

Akingbemi et al. 2004: “Utility (Adequacy) for CERHR Evaluation Process: “...Experiment 2 is inadequate for consideration due to inappropriate statistics that failed to account for litter effects.”

Al-Hiyasat et al. 2004: ” Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate for the evaluation based on small sample size.”

Berger et al. 2007: “Utility (Adequacy) for CERHR Evaluation Process: Due to the absence of key information and faulty methodology, this study is inadequate for evaluation process.”

Chitra 2003: “A weakness includes the marginal sample size. Utility (Adequacy) for CERHR Evaluation Process: This study is adequate for inclusion but of limited utility based on small group size.”

⁶ U.S. Department of Health and Human Services, National Toxicology Program, Center For The Evaluation of Risks To Human Reproduction, *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A*, September 2008, NIH Publication No. 08 – 5994, available on the web at: <http://cerhr.niehs.nih.gov/evals/bisphenol/bisphenol.pdf>

⁷ <http://www.efsa.europa.eu/de/efsajournal/pub/428.htm>

Evans et al. 2004: "The unique animal model and the use of LH pulsatile response are uncommon but interesting. The high-dose level via i.m. injection is a weakness as are small sample sizes (n 5 6). The statistical tests for LH trends did not appear to take into account the repeated nature of the sampling leading to over stating the significance of trend effects. Utility (Adequacy) for CERHR Evaluation Process: This study is adequate for inclusion but of limited utility for the evaluation process."

Herath et al. 2004: "Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate and not useful for the evaluation process primarily due to the significant inconsistencies in the hormone data from control animals."

Honma et al. 2002: "The lack of AGD measurement at birth and difficulty of measurement at PND 60 are weaknesses. The Expert Panel was unable to confirm the statistical significance of the effects shown in Table 2 of the manuscript. Utility (Adequacy) for CERHR Evaluation Process: The study is adequate for inclusion but of limited utility due to statistical questions about body weight and AGD and subcutaneous route of exposure."

Howdeshell 1999: "The omission of a description of husbandry conditions and lack of clarity of statistical procedures are weaknesses. Use of only a single dose is a weakness. Further, the use of time from vaginal opening to first estrus is not a standard endpoint for assessing puberty in mice and is of questionable biological significance. Utility (Adequacy) for CERHR Evaluation Process: This study is adequate for the evaluation process but utility is limited due to uncertainties in data analyses."

lida et al. 2002: "Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate for the evaluation process based on methodology."

Kabuto et al. 2004: "Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate for the evaluation process due to inappropriate statistical procedures and small sample size."

Nikaido et al. 2004: " Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate for the evaluation process."

Rubin et al. 2001: "Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate for the evaluation process, based on a lack of adequate control for litter effects"

Savabieasfahani et al. 2006: "Weaknesses are the use of a single dose level and the relatively small sample size. The single time point for bisphenol A plasma determination at an unknown time relative to s.c. injection is a weakness. Utility (Adequacy) for CERHR Evaluation Process: This study is adequate though of limited utility."

Takahaski and Oshi 2003: "Weaknesses include use of single high doses administered for different durations across groups using minimal sample sizes. Utility (Adequacy) for CERHR Evaluation Process: This study is adequate but of limited utility."

Toyama and Yuasa 2004: "Utility (Adequacy) for CERHR Evaluation Process: This study is inadequate and not useful due to critically small sample size, route of administration, lack of clarity of design, and inappropriate statistical procedures."

The CERHR Report's criticisms of fundamental study aspects, such as sample size, inappropriate statistical procedures, and even methodology, highlights the lack of quality in the studies relied on for the conclusions of the CLH proposal. Its example of robust quality analysis also highlights the failures of the CLH proposal to meet the requirements of the CLP Regulation to define quality criteria for individual studies, evaluate studies for quality, and perform a transparent weight-of-evidence evaluation.

5. The information on reproductive endpoints reported in the CLH proposal is inconsistent throughout the proposal

In studies that investigate potential reprotoxic effects, the animal can be treated and/or monitored for effects in various different stages of life: the dam, during gestation, pregnancy immediately after giving birth, during lactation, during mating and in the offspring as neonatals, pups, in puberty, and during mating phase... The period of observation can be a few hours up to several generations of animals etc. The doses applied, the frequency, route and duration of application add another multiplying factor. In order to avoid comparing "apples with pears" in data from such a variety of study designs it is important to be very transparent and specific in selecting and describing the endpoints and related parameters that form the basis of a report and related conclusions.

However, throughout the CLH proposal,

- the allocation of studies to the specific treatment intervals is incorrect and not consistent.
- The scientific rationale for the chosen differentiation of intervals is missing.
- No scientific reasoning is given for the exclusion of multigeneration studies from the assessment of defined intervals, although other study results within the dosing scheme of the multigeneration studies are included.

OECD test guidelines as well as the globally followed testing protocols are based on the assumption that a study result is relevant for the interval of dosing that is covered.

In a study which covered several dosing intervals (e.g. from birth until next pregnancy) it is possible that an adverse effect might be revealed. It might then be worthwhile to further investigate the specific interval in which the adverse effect was induced. However, in cases where a study with a large dosing interval does **not** reveal an adverse effect, there is no need to examine specific intervals or to exclude the large interval studies from the assessment of a specific interval.

In a proper weight of evidence approach, it is not acceptable to exclude studies which showed no effect and only include studies that did show an effect, neither is it appropriate to exclude the results of such studies with respect to a specific interval only because it showed no effect. No effect is also a result. However: this is the approach the CLH proposal takes.

6. Differences in strain sensitivity are mentioned throughout the CLH proposal, but the statements are contradictory, and relevant information on strain sensitivity is not included.

The CLH proposal makes contradictory statements regarding Sprague-Dawley (SD) rats:

- page 53: They are "*insensitive*" to endocrine mediated toxicity
- page 60: have "*low sensitivity*" to estrogenic compounds
- page 60: "*are found responders*" to estradiol

Also with mice a statement on strain sensitivity is included in the CLH proposal:

- C57BL/6N mouse “was estrogen-sensitive” whereas “ICR mice were found insensitive” (page 93)

The proposal also takes an inconsistent approach to strain sensitivity in its summary tables: The proposal summarizes effects on different endpoints in tables, but included in general only information on positive findings (showing an effect) and did not indicate information on endpoints with no observed effect in these tables. There are several studies mentioned in these tables which investigated SD rats or ICR mice.

- The following studies in SD rats were considered relevant in the CLH proposal: Rubin et al. 2001, Takagi et al. 2004, Fernandez et al. 2009, Fernandez et al. 2010, Schönfelder et al. 2004, Tyl et al. 2002 (page 53 of the CLH proposal); whereas the following studies were considered not relevant based on strain sensitivity: Ema et al. 2001, Tyl et al. 2002, Kwon et al. 2000.
- There is a similar inconsistency for studies in ICR mice. Although discussed as insensitive based on the Nagao et al. 2002 study the following studies utilizing ICR mice which found effects are considered relevant by the CLH proposal: Fernandez et al. 2010, Hiyama et al. 2011, Honma et al. 2002, Nah et al. 2011, Nikaido et al. 2005.

Overall, the CLH proposal does not reconcile how strain sensitivity in SD rats or ICR mice is not relevant when observations are reported, but is relevant in no-effect studies using the same strains.

Nor does the CLH proposal reconcile the omission of highly relevant information (e.g. EFSA 2010, CERHR 2008) and studies (e.g. Tyl et al. 2006, Gray et al. 2010, Tyl et al. 2008b and 2009) that address potential species and strain differences; specifically:

- CERHR 2008 conclusions of potential differences in strain sensitivity: *“The differences in outcomes cannot be attributed to the use of an insensitive strain or stock because a variety of rat models were used in the “negative” studies: Sprague-Dawley, Wistar, Wistar-Furth rats, Wistar-derived Alderley Park, CD, and Donryu. Moreover, three of the “negative” rat puberty studies reported other “low” dose effects (53, 122, 173).”*
- The 2010 EFSA conclusion on strain sensitivities, which is not included in the CLH proposal, said that: *“...low dose effects of BPA in rodents have not been demonstrated with the sufficient certainty to serve as pivotal studies for risk assessment. The more recent observations of species differences in toxicokinetics of BPA between primates, including humans, and rodents, and in particular the low bioavailability of BPA (free systemic BPA) in primates, further weaken the relevance of observations of low-dose effects of BPA in sensitive strains of rodents for human health risk assessment.”*
- Gray et al. 2010, stated in a rebuttal to previous criticism: *“The LE and SD rat strains also are excellent animal models for the study of the effects of EE2 and other environmental estrogens because the sensitivity of these rat strains is very similar to the sensitivity of humans to EE2.”*
- The CLH proposal also references the Myers et al. 2009 commentary criticising the Tyl et al. 2008 multi-generation study, but does not mention or evaluate the published responses by Dr. Tyl (Tyl 2009). Tyl commented as follows on claims by Myers et al. 2009: *“We identified the same BPA systemic and reproductive/developmental NOAELs (and sensitivity comparable to similar dietary E2 intakes) in rats and mice,*

with no BPA effects on the prostate weight or histopathology. Strain differences in response to estrogens in rats (and mice) vary across tissues, so no strain can be considered more sensitive than another (Howdeshell et al. 2008). E2 activities via estrogen receptor- α in the reproductive tract did not display major strain differences in OECD multilaboratory rat uterotrophic assay validation studies; oral BPA was only a weak partial agonist at 400–600 mg/kg/day (Kanno et al. 2003)."

Based on the additional information and taking also into account the most recent NCTR sub-chronic toxicity study in SD rats (which included EE2 positive control groups), the contrary conclusion is correct: there is no solid scientific evidence that SD rats are insensitive to estrogenic compounds, and in general no strain can be considered more sensitive than another.

7. The CLH proposal inappropriately rejects the results of guideline studies based on validated protocols, yet accepts without question the results of exploratory studies

The statement in the CLH proposal that data derived in guideline studies do not confirm the data derived from some exploratory studies is correct. The lack of conformity should raise questions about the results of the non-guideline studies, not, as the CLH proposal suggests, raise questions about the results of the guideline studies. Guideline studies are conducted according to methods that have been validated by repeated testing and found to be reliable; they also specify sample size and other parameters that contribute to the reliability of the results. It is for these reasons that guideline are broadly accepted as reliable methods. Therefore, the statements in the CLH proposal "*The guideline studies contradict the other studies reported without straightforward explanation of this discrepancy*" (page 42) and "*The authors do not explain this difference.*" (page 65) inappropriately reject without explanation results from studies conducted in accordance with internationally validated, approved and accepted test guidelines. Indeed, it is the exploratory studies with limited study design that require quality review to confirm that the study design, sample size and statistical power are sufficient for their data to be considered reliable, reproducible, robust and relevant.

The CLH proposal, as discussed above, has not provided a review of the quality of the exploratory studies and many have been found inadequate in prior government reviews, such as CERHR, EFSA and the EU RAR. Those same reviews by CERHR, EFSA and the EU RAR also reviewed the quality of the guideline studies and found them to be of extremely high quality, reliable and consistent; in particular, across the guideline studies there was consistently no adverse effects on reproductive or developmental endpoints that would support a classification of BPA as category 1B reproductive toxicant.

8. Epidemiological studies referenced in the CLH proposal provide no evidence to support stricter classification of BPA

The epidemiological studies referenced in the CLH proposal to support its argumentation are incapable of providing any meaningful evidence of causation because of their methodological approach (cross-sectional, single-spot sample measurement). In these studies, health effect and chemical exposure data are collected at the same point in time, which means there is no way to know, based on the data evaluated, if the exposure preceded the disease. Without this temporal information, statistical associations between exposure and health effects may be derived, but it is not possible to establish any causal relationship between any observed disease and BPA-exposure, because the respective information to assess such a relationship is not available in these studies.

Most of the epidemiological studies referenced in the CLH proposal are of cross-sectional design, and they base their finding on one single blood or urine sample. Recent studies have shown that, for investigating substances with a short half-life, cross-sectional studies, such as the US CDC's NHANES data set, are particularly inappropriate (LaKind *et al.* 2012)⁸. BPA has a very short half-life of only a few hours. Studies have shown that BPA levels in urine are highly variable even within one day. It is therefore impossible to draw conclusions from a single BPA measurement about any potential human disease which needs months or years to develop (e.g. Townsend *et al.* 2013, Valvi *et al.* 2013, Philippat *et al.* 2013). Several of the authors note themselves that their findings need further investigation, and a number of the studies display significant methodological flaws. About one third of the included studies report no effect at all (*see Annex E for review of epidemiological studies used in the proposal*). Overall, the cross-sectional epidemiological studies relied on in the CLH proposal are inappropriate to provide any meaningful information as to potential effects of BPA in humans.

C. Statements about the multigeneration animal studies upon which regulators have relied (Tyl *et al.* 2002 and 2008a) are inconsistent, incorrect and contrary to evaluations of these studies

The Tyl *et al.* (2002 and 2008a) multi-generational studies of BPA in rodents are widely regarded as authoritative research on BPA reproductive effects. These studies have been repeatedly relied upon by governmental regulators in assessing the risks and hazards of BPA. Tyl *et al.* (2002 and 2008a) have been credited for their statistical power, wide range of doses and adherence to established guideline protocols. The 2008 European Risk Assessment Report said:

*"...We consider this investigation by Tyl *et al.* (2007) as the gold-standard, definitive study of the reproductive toxicity of BPA (for the endpoints examined)...."*⁹

Likewise, the FAO/WHO report said that:

*"Typically, a dose of 5 mg/kg bw per day has been identified as a NOAEL in assessments conducted for regulatory or health-based guidance value setting purposes, based on consideration of two multigeneration studies in rats and mice conducted by Tyl *et al.* (2002, 2008a). These studies are generally considered to be statistically and methodologically sound for the end-points investigated and have sufficient dose groups to support dose–response modeling."*¹⁰

Tyl 2002 was described by NTP as *"arguably the most comprehensive of the studies we evaluated."*¹¹

⁸ LaKind JS, Goodman M, Naiman DQ (2012) Use of NHANES Data to Link Chemical Exposures to Chronic Diseases: A Cautionary Tale. PLoS ONE 7(12):e51086. Available at <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0051086>

⁹ European Commission, Joint Research Centre, Institute for Health and Consumer Protection, *Updated Risk Assessment of 4, 4 Isopropylendephenol (Bisphenol-A), Human Health Addendum*, April 2008, p. 87.

¹⁰ Food and Agriculture Organization of the United Nations, the World Health Organization, *Joint Expert Meeting to Review Toxicological and Health Aspects of Bisphenol A: Summary Report*, November 1-5, 2010, available on the web at: ftp://ftp.fao.org/ag/agn/agns/BPA_Summary_Report.pdf, p. 28.

¹¹ National Toxicology Program, *Report of the Endocrine Disruptors Low Dose Peer Review*, page 1-11, August 2001.

The CLH proposal mischaracterized important elements of the multigenerational reproductive studies on rats (Tyl *et al.* 2002) and mice (Tyl *et al.* 2008a), as *described in detail in Annex B* and in summary below.

- The CLH proposal mistakenly claims that fertility effects were observed in Tyl *et al.* 2008a when the study authors did not identify fertility effects from the data. The interpretation by the study authors is supported by the European RAR, which stated that: *“In the mouse 2-generation study, using dose levels of 0.003-600 mg/kg/day, no effects on fertility, reproductive organ weights and histopathology or sperm production were observed.”*¹²
- The CLH proposal likewise claims that BPA caused pituitary effects in Tyl *et al.* 2008a. Study data (discussed in Annex B) show isolated increases in pituitary weight and pituitary relative weight in males only. These data points do not support a plausible dose response, and do not suggest a treatment related effect. Neither the authors nor the European RAR identify treatment related pituitary effects.
- The CLH proposal cites Tyl *et al.* 2008a as supporting claims of extended estrus. The data do not show a clear pattern of extended estrus among treated females. There were no statistically significant findings in the number of F0 or F1 females in estrus at any dose when compared to controls. The authors concluded that *“stage of estrus at demise was unaffected in mice.”*
- The CLH proposal also claims that extended periods of diestrus were observed in Tyl *et al.* 2008a. In fact, the percentage of F0 and F1 females in diestrus was notably consistent across the range of doses. The data in Tyl *et al.* 2008a does not support the CLH proposal’s statement on extended period of diestrus.
- The CLH proposal contends that CD-1 mice and SD rats are insensitive to estrogenic compounds, suggesting this may account for the lack of reproductive effects observed in the Tyl studies. As discussed in Section B(6) of these Comments (above), the data do not support strain in sensitivity. In fact, Tyl *et al.* (2008a and 2008b) included a concurrent positive control of 17 β -Estradiol which clearly demonstrated the responsiveness of this mouse model to estrogenic substances. Similarly, the U.S. Food and Drug Administration sub-chronic study on SD rats utilized a concurrent positive control (EE2) which showed clear indications of estrogenic response. The CLH proposal’s claims of estrogenic insensitivity of CD-1 mice and SD rats are refuted by substantial data as recognized by CERHR (2008), EFSA (2010) and Gray *et al.* 2010.
- The CLH proposal characterizes the renal tubular degeneration and chronic hepatic inflammation observed in Tyl *et al.* 2002 as *“strong and direct effect of BPA on these organs.”* In fact, these effects, at the relatively high doses of 50 mg/kg/bw and 500 mg/kg/bw, were judged by the author and by the European RAR to be products of systemic toxicity.
- The CLH proposal contends that delayed puberty is observable in Tyl *et al.* 2002 at the 50 mg/kg/bw and 500 mg/kg/bw doses. This statement is not correct. Tyl *et al.* 2002, Fig 7 shows no significant effect at 50 mg/kg.
- The CLH proposal claims that effects on sperm concentration and accessory sex organs occurred in Tyl *et al.* 2002. Because the data on sperm are not consistent across the generations, they were not considered by the study authors to be treatment related. Further, Tyl *et al.* 2002 found no treatment-related gross or

¹² European Commission, Joint Research Centre, Institute for Health and Consumer Protection, *Updated Risk Assessment of 4, 4 Isopropylendephenol (Bisphenol-A), Human Health Addendum*, April 2008, p. 128.

microscopic findings on reproductive organs for F0, F1, F2, or F3 adult males or females.

The criticisms in the CLH proposal about these multigeneration studies are neither supported by the study data themselves, nor by other independent reviewers such as the EU RAR or the US-CERHR Report both of which confirmed the high quality of the design of the Tyl studies and the validity of their results. The Tyl studies do not provide a basis for concluding that BPA is a selective reproductive toxicant and do not support a classification of BPA as category 1B reproductive toxicant.

D. Recent and important information available on a new study conducted at the US FDA National Center for Toxicological Research (NCTR) is not included in the CLH proposal

Very recently, findings from a new study conducted at the US FDA National Center for Toxicological Research (NCTR) became available (*see Annex C for further details*). In this study BPA was administered to rat dams by oral gavage from gestation day 6 until parturition and then directly to pups from postnatal day 1 until termination at postnatal day 90 at doses up to 300 mg/kg bw/day. In this robust study, which features a comprehensive range of dose levels and wide array of health endpoints, BPA exhibited some adverse effects in females only at the high dose levels of 100 and 300 mg/kg bw/day and in males at 300 mg/kg. The authors note that *“the interpretation of the high dose BPA effects are confounded by systemic toxicity”*. Thus, the study supports earlier research and European Risk Assessments concluding that BPA produces adverse effects only at high doses associated with systemic toxicity. Overall the data in this comprehensive study do not support the premise that BPA is a selective reproductive toxicant. This recent research further confirms that more stringent classification of BPA as Category 1B is not warranted.

E. The CLH proposal is not comprehensive in considering the available toxicokinetics data

The CLH proposal is based on an interim report by ANSES dated 2011. In that report ANSES indicated: *“A detailed analysis of the toxicokinetic data of BPA by species and route of exposure is in progress with a view to establishing correlations between the various studies and the exposure levels in humans.”* The now available CLH proposal does not mention such a human PB-PK model (species-specific physiology-based pharmacokinetic), but nevertheless justifies the inclusion of many studies – if not the majority - using the parenteral route of administration, thereby disregarding route-dependent pharmacokinetics of BPA.

It is well established that the primary route of exposure to BPA is oral.¹³ Also well characterized is the toxicokinetic profile of BPA (i.e. the fate of the substance in the body: its absorption, distribution, metabolism, elimination) in mice, rats, monkey and human volunteers. In humans and other primates, multiple studies show that orally ingested BPA is rapidly transformed to BPA-glucuronide during first pass metabolism in the gut wall and the liver and that BPA-glucuronide does not have any endocrine activity. Both BPA and BPA-glucuronide are rapidly excreted via the urine, with an elimination half-life of less than 6 hours. Thus, there is very low bioavailability of the parent substance, BPA, in humans and other primates (EU Risk Assessment 2008, Volkel *et al.* 2002 and 2005, Teeguarden *et al.*, 2011 and 2013).

¹³ (US FDA and EFSA 2006a, 2008; EFSA Panel 424 on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2010, as well as DRAFT Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs – Part: exposure assessment (2013))

In humans, due to rapid biotransformation, excretion and plasma protein binding, peak BPA-concentrations after dietary exposures to BPA are predicted to be very low even in worst case exposure scenarios. In rats, orally administered BPA also predominantly undergoes glucuronidation, but the BPA-glucuronide is excreted from the liver into the gut in the bile. In the gut, BPA-glucuronide is then cleared into BPA and glucuronic acid and BPA is reabsorbed as such into the blood stream. This enterohepatic recirculation results in slower elimination of BPA in rodents (BPA half-life in rodents 19-78h) (EFSA 2006, Hengstler *et al.* 2011).

Non-human primates internal exposure to BPA is remarkably similar from birth through adulthood and consistently lower than rodents during the neonatal phase. The results of the recent NCTR work indicates that if BPA doses causing adverse effects in rodent models were attributable to discrete neonatal development windows, such effects should be less likely for comparable neonatal primate exposures on the basis of internal dosimetry. (EU Risk Assessment 2008, Hengstler *et al.* 2011, Doerge *et al.* 2010a and b).

Toxicokinetic information is available for oral and parenteral dosing in rodents and monkeys from multiple recent studies by the US FDA/NCTR¹⁴. The data on toxicokinetics and metabolism revealed substantially lower internal exposure to BPA after oral dosing compared to parenteral dosing for rat and monkeys at all time points investigated (newborn to adulthood) and in mice from juvenile to adulthood. Based on these data it can be concluded, that parenteral routes of administration as s.c, i.m. injection or osmotic pumps will lead to substantially higher internal doses of BPA. In particular high parenteral doses of BPA should be regarded as unreliable based on EU Regulation 1272/2008 chapter 3.7.2.5.6:

“Studies involving routes of administration such as intravenous or intraperitoneal injection, which result in exposure of the reproductive organs to unrealistically high levels of the test substance, ..., must be interpreted with extreme caution and on their own are not normally the basis for classification.”

As a review and analysis of the studies show, BPA exposure is primarily oral and it is rapidly metabolized in the gut which means that BPA-concentrations after dietary exposures to BPA are predicted to be very low even in worst case exposure scenarios. In light of the toxicokinetic profile, the CLH proposal's heavy reliance on studies with parenteral routes of exposure leads to unrealistically high levels of exposure which is not an appropriate basis for classification.

F. Reference to baby bottles as source of exposure is outdated

On page 23, with reference to an ANSES report of 2010, the CLH proposal mentions polycarbonate bottle feeding and/or infant formula feeding as a source of direct infant exposure to BPA. Such exposure is no longer existing, as since 1 June 2011, the sale of BPA-based polycarbonate baby bottles is no longer permitted under European law.

The decision was taken after the market for polycarbonate baby bottles in Europe had virtually disappeared. This decision was not a consequence of any evidence of adverse effects from BPA, but rather a highly precautionary approach by the EU. Not one

¹⁴ Doerge *et al.*, 2010a, 2010 b, 2010 c, Twaddle *et al.*, 2010; Doerge *et al.*, 2011; Fisher *et al.*; 2011, Doerge *et al.*, 2012, Yang *et al.*, 2013, Patterson *et al.*, 2013.

governmental authority in the world has identified any health risk for adults, children or newborns from the trace levels of BPA that they might be exposed to through contact with the certain food contact products.

G. The CLH proposal refers to an incorrect industry self-classification in chapter 1.7 “Current self-classification and labelling”

From the 1,410 entries in the C&L inventory¹⁵ of industry self-classifications, the CLH proposal relies on the only one industry self-classification that supports the proposed classification. (Unfortunately, it was not possible for the BPA REACH Consortium to identify the company behind the classification that deviated from the overall industry consensus.)

The single self-classification is irrelevant. The only relevant inquiry in determining how BPA should be classified is: “what classification is supported by the scientific data?” As discussed above and in 2002 Classification and Labelling decision (Directive 67/548/EEC; R 62), the 2002 European Risk Assessment and the 2008 European Risk Assessment, BPA does not have an adverse effect on reproduction and development and, therefore, should not be classified as a Category 1B reproductive toxicant.

The scientific evidence does not support a change to the classification proposed in 1,409 self-classifications, which is:

Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Pictograms, Signal Word Code(s)
Skin Sens. 1	H 317	H 317	GHS07 GHS09 GHS05 GHS08 Dgr
Eye Dam. 1	H 318	H 318	
STOT SE 3	H 335	H 335	
Repr. 2	H 361	H 361	
Aquatic Chronic 2	H 411	H 411	

¹⁵ It should be noted that **the CL inventory has no regulatory status**: ECHA accepts no responsibility or liability whatsoever with regard to the information on this website. “**Companies have provided this information in their C&L notifications or registration dossiers. ECHA maintains the Inventory, but does not review or verify the accuracy of the information.**” <http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory>

III OVERALL CONCLUSION

The CLH proposal prepared by ANSES to justify the proposal to re-classify BPA builds its arguments on incomplete, inconsistent and selective use of data rather than on a sound and comprehensive weight-of-evidence approach as dictated by good science and by ECHA's "Guidance on the preparation of dossiers for harmonised classification and labelling".

The CLH dossier fundamentally fails to comply with ECHA's Guidance because it:

- does not consider *all available information, but leaves out significant studies on toxicokinetics and inappropriately relies on parenteral exposure studies*;
- does not assemble *both positive and negative results together in a single weight of evidence determination* and in fact fails to acknowledge that replicates of some studies on which the proposal relies failed to show the same effects and fails to address inconsistencies between the guideline studies and the exploratory studies;
- does not give the "*the consistency of the data*" appropriate weight because it fails to consider whether inconsistent data on male sperm production may indicate that an effect is either transitory, due to normal variation or not a repeatable finding; and
- does not give the *quality of the data appropriate weight* which results in the reliance of the CLH proposal on many studies found to be inadequate in CERHR's detailed assessment of study quality;

The CLH dossier inexplicably rejects the regulatory guideline studies, which have been characterized by others as "the gold standard" in favour of taking at face value the findings of small exploratory studies that have been deemed inadequate by other government reviewers.

In trying to justify its approach, the CLH proposal attempts to undermine the guideline studies with unfounded criticism of strain insensitivity and erroneous statements about findings of reproductive effects. In fact, the guideline studies, which consistently show that BPA does not cause reproductive or developmental effects are highly reliable due to their size, statistical power, broad range of doses, appropriate route of exposure and use of a validated protocol. Individually and on a weight of evidence base these studies shows that BPA is not a reproductive toxicant.

Given the above, the dossier should be rejected. It does not fulfil the criteria outlined in ECHA's "Guidance on the preparation of dossiers for harmonised classification and labeling" (ECHA 2010).

The proposal to reclassify BPA as a Category 1B reproductive toxicant is not supported by scientific argumentation. As can be seen from the BPA Consortium comments and from assessments of BPA conducted by other government regulators, when all high quality scientific studies on BPA have been considered and a weight of the scientific evidence evaluation is conducted, it will clearly demonstrate that BPA is not a selective reproductive toxicant. In conclusion, there is no basis to change the classification of BPA to Category 1B.

IV Annexes

Annex A	CLH proposal contains inconsistent and incorrect information on male and female endpoints
Annex B	CLH proposal contains inconsistent and incorrect information on Tyl et al. (2002 and 2008)
Annex C	“NCTR Evaluation of the toxicity of Bisphenol A (BPA) in Male and Female Sprague-Dawley Rats Exposed Orally from Gestation Day 6 through Postnatal Day 90”
Annex D	Overview of relevant studies for classification of Bisphenol A (BPA)
Annex E	Review of the epidemiology studies described in the ANSES 2013 report on harmonized classification and labeling of Bisphenol A

V References

- Ashby, J., Owens, W., Odum, J., and Tinwell, H. 2003. The intact immature rodent uterotrophic bioassay: Possible effects on assay sensitivity of vomeronasal signals from male rodents and strain differences. *Environmental Health Perspectives*. 111:1568-1570.
- CERHR 2008. Center for the Evaluation of Risks to Human Reproduction, NTP-CERHR monograph on the potential human reproductive and developmental effects of bisphenol A. Shelby MD., NIEHS, Research Triangle Park, NC 27709, USA. NTP CERHR MON. 2008 Sep;(22); alternatively: U.S. Department of Health and Human Services, National Toxicology Program, Center For The Evaluation of Risks To Human Reproduction, NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, September 2008, NIH Publication No. 08 – 5994, available on the web at: <http://cerhr.niehs.nih.gov/evals/bisphenol/bisphenol.pdf>
- Doerge et al. 2010c. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. *Toxicol. Appl. Pharmacol.* 247, 158-165.
- Doerge et al. 2011a. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. *Toxicology and Applied Pharmacology* 255, 261-270.
- Doerge et al 2011b.: Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. *Toxicology Letters* 207, 298-305.
- Doerge et al. 2012. *Toxicology Letters* 211, Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice. 114-119.
- ECHA 2010; Guidance on the preparation of dossiers for harmonised classification and labeling. http://echa.europa.eu/documents/10162/13626/clh_en.pdf
- EFSA 2010. European Food Safety Authority, Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A. *EFSA Journal* 2010; 8(9):1829. <http://www.efsa.europa.eu/de/efsajournal/pub/428.htm>
- Eichenlaub-Ritter, U., Vogt, E., Cukurcam, S., Sun, F., Pacchierotti, F., and Parry, J. 2008. Exposure of mouse oocytes to bisphenol A causes meiotic arrest but not aneuploidy. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*. 651(1-2):82-92.
- EU Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures, the CLP-Regulation, entered into force on 20th January 2009
- EU Risk Assessment 2008. European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Updated Risk Assessment of 4, 4 Isopropylenedephenol (Bisphenol-A), Human Health Addendum, April 2008. http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/bisphenolareport325.pdf
- Fisher et al. 2011. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. *Toxicology Applied Pharmacology* 257, 122-136,
- Gray et al.: Rebuttal of "Flawed Experimental Design Reveals the Need for Guidelines Requiring Appropriate Positive Controls in Endocrine Disruption Research" by (Vom Saa1 2010). *Toxicological Sciences* 115, 614-620, 2010
- Hengstler, J. G., Foth, H., Gebel, T., Kramer, P.-J., Lilienblum, W., Schweinfurth, H., Völkel, W., Wollin, K.-M., and Gundert-Remy, U. 2011. Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. *Critical Reviews in Toxicology*. 41(4):263-291.

- LaKind JS, Goodman M, Naiman DQ (2012) Use of NHANES Data to Link Chemical Exposures to Chronic Diseases: A Cautionary Tale. *PLoS ONE* 7(12):e51086. Available at <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0051086>
- Muhlhauser, A., Susiarjo, M., Rubio, C., Griswold, J., Gorence, G., Hassold, T., and Hunt, P. 2009. Bisphenol A effects on the growing mouse oocyte are influenced by diet. *Biology of Reproduction*. 80(5):1066-1071.
- NCTR Evaluation of the toxicity of Bisphenol A (BPA) in Male and Female Sprague-Dawley Rats Exposed Orally from Gestation Day 6 through Postnatal Day 90" conducted by the US National Center for Toxicological Research (NCTR); Jefferson, AR; Study director Barry Delcos; Report Number: 2176.01; dated March 4, 2013
- Pacchierotti, F., Ranaldi, R., Eichenlaub-Ritter, U., Attia, S., and Adler, I.-D. 2008. Evaluation of aneugenic effects of bisphenol A in somatic and germ cells of the mouse. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*. 651(1-2):64-70.
- Patterson, T.A., N.C. Twaddle, C.S. Roegge, R.J. Callicott, J.W. Fisher and D.R. Doerge: Concurrent determination of bisphenol A pharmacokinetics in maternal and fetal rhesus monkeys. *Toxicol. Appl. Pharmacol.* 267: 41-48, 2013
- Philippat C; Wolff MS; Calafat AM; Ye X; Bausell R; Meadows M; Stone J; Slama R; Engel SM. 2013. Prenatal Exposure to Environmental Phenols: Concentrations in Amniotic Fluid and Variability in Urinary Concentrations during Pregnancy. *Environmental Health Perspectives*; online /
- Stump et al.: Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. *Toxicological Sciences* 115, 167-182, 2010
- Teeguarden, J., Hanson-Drury, S., Fisher, J.W., Doerge, D.R., Are Typical Human Serum BPA Concentrations Measureable and Sufficient to be Estrogenic in the General Population?, *Food and Chemical Toxicology*, doi: <http://dx.doi.org/10.1016/j.fct.2013.08.001>
- Townsend MK; Franke AA; Li X; Hu FB; Eliassen AH. 2013. Within-person reproducibility of urinary bisphenol A and phthalate metabolites over a 1 to 3 year period among women in the Nurses' Health Studies: a prospective cohort study. *Environmental Health*, 12:80
- Twaddle et al.: Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry., *Rapid Communications in Mass Spectrometry* 24, 3011-3020, 2010
- Tyl RW, Myers CB, Marr MC, Castillo NP, Veselica MM, Joiner RL, et al. 2008a. One-generation reproductive toxicity study of dietary 17 β -estradiol (E2; CAS No. 50-28-2) in CD-1[®] (Swiss) mice. *Reproductive Toxicology*. 25(2):144-160.
- Tyl, R. W., Myers, C. B., Marr, M. C., Sloan, C. S., Castillo, N. P., Veselica, M. M., Seely, J. C., Dimond, S. S., Van Miller, J. P., Shiotsuka, R. S., Stropp, G. D., Waechter, J. M., and Hentges, S. G. 2008b. Two-generation reproductive toxicity evaluation of dietary 17 β -estradiol (E2; CAS No. 50-28-2) in CD-1[®] (Swiss) mice. *Toxicological Sciences*. 102(2):392-412.
- Tyl, R. W. 2009. Basic exploratory research versus guideline-compliant studies used for hazard evaluation and risk assessment: bisphenol A as a case study. *Environmental Health Perspectives*. 117(11):1644-1651.
- Valvi D; Casas M; Mendez MA; Ballesteros-Gómez A; Luque N; Rubio S; Sunyer J; Vrijheid M. 2013. Prenatal Bisphenol A Urine Concentrations and Early Rapid Growth and Overweight Risk in the Offspring. *Epidemiology*. 24: 00-00
- Yang et al.: Prediction and evaluation of route dependent dosimetry of BPA in rats at different life stages using a physiologically based pharmacokinetic model. *Toxicology and Applied Pharmacology* 2013,