

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Substance name: bisphenol A;4,4'-isopropylidenediphenol

CAS number: 80-05-7

EC number: 201-245-8

Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Netherlands		MemberState	1
Comment received				
<p>[all comments are also submitted in a seperate document, for easier reading]</p> <ul style="list-style-type: none">• For many of the studies summarized in the proposal, it is not clear whether the studies are well performed and/or reported (how many animals were used, which analyses were performed, if GLP or guidelines were followed etc) and therefore how reliable these studies are. In addition, in most cases the quantity of effects and historical control range is not included, making it difficult to conclude whether observed effects are toxicologically relevant.• Some of the studies included in the CLH proposal have used very high dose levels (sometimes at 6% in diet corresponding with 68 mg/mouse according to Berger et al, 2007, but 180-240 mg/mouse according to our calculation corresponding with approximately 9000 mg/kg bw). It should be discussed whether effects observed only at these dose levels would warrant classification as described in paragraph 3.7.2.5.7 of Annex I of CLP.• Many studies were performed using subcutaneous injection or implanted time release pellets (bypassing the first pass effect). The relevance of these studies compared to humans and/or animal studies using relevant routes of exposure should be discussed based on the available toxicokinetic data in line with paragraph 3.7.2.5.6 of CLP. This should determine whether these studies can be used to support the proposed classification. The current chapter on toxicokinetic does not address this important question and in most studies using this exposure route, it is not or only very limited justified. Therefore, the relevance of these routes should be justified before using them for classification. The relevance could be dose dependent as sometimes a high dose is used subcutaneously which could result in very high exposure levels which may not be relevant as discussed under the previous bullet. The provided summaries focus mainly on the observed effects on development or fertility. However, information on maternal / other toxicity is often lacking. It is considered important to assess whether the observed reproductive effects are a direct effect of BPA or a secondary non-specific consequence of other toxicity. Further, it is unclear whether additional parameters have been determined in the studies which were not affected. This information is important for assessing the consistency between studies of effects observed in other studies.• For all effects, it can be discussed whether these are effects on fertility or effects on development. Basically, effects on fertility (or the reproductive system) that are caused by developmental changes of the fertility system are primarily caused by an altered development and should therefore be seen as developmental effects. When fertility effects (or changes in the reproductive system) are observed in animals that are only exposed in utero, it can be concluded that these effects have arisen during development. If they are considered relevant for classification, they are relevant for classification for developmental				

effects, not fertility effects. Effects induced by post-natal exposure would not justify classification for development as described in Chapter 3.7.1.4 of the criteria. However, they could be considered as reprotoxic effects in general without differentiation as allowed in 3.7.1.1. It is suggested to first discuss which window of exposure would contribute to which differentiation of the classification for reproductive toxicity. Then the available studies could be split into those windows of exposure as a start before discussing the classification.

(ECHA note: The following attachment was provided - same content as in the comment above:

"Comments on the proposal for harmonized classification and labeling of Bisphenol A." [Attachment 9])

Date	Country	Organisation	Type of Organisation	Comment number
04.10.2013	United States	Can Manufacturers Institute	Industry or trade association	2

Comment received

The Can Manufacturers Institute (CMI) is the US national trade association of the metal can manufacturing industry and its suppliers in the United States. The can industry accounts for the annual domestic production of approximately 124 billion food, beverage and other metal cans; which employs more than 28,000 people. A BPA warning label would convey a threat to human health that is unsupported by sound scientific evidence and is not found by conclusions drawn by FDA and most international public health regulatory bodies. Such an erroneous warning on packaged food could scare consumers away from these vital and affordable sources of nutrition. Our members are committed to providing safe, nutritious and refreshing canned food and beverages to consumers.

CMI is opposed to the proposal to reclassify bisphenol A (BPA) as a reproductive toxicant Category 1B under Regulation (EC) No. 1272/2008. According to the Classification, Labeling and Packaging (CLP) regulations, substances to be classified as reproductive toxicant, Category 1B, must have clear evidence of an adverse effect in the absence of other toxic effects OR if other effects are seen, the reproductive toxicity effect must be the origin of the other toxic effects and not be a secondary, non-specific consequence. That is not the case with BPA. In studies where reproductive toxicity effects were observed, those effects occurred at dose levels above those where systemic toxicity effects. Thus, the criteria are not met and the reclassification proposal should not be accepted.

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2013	United Kingdom		Individual	3

Comment received

This substance must be better regulated and population better protected.

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	United States	North American Metal Packaging Alliance, Inc.	Industry or trade association	4

Comment received

North American Metal Packaging Alliance, Inc.

Comments on French Government Dossier
Proposing Harmonised Classification and Labelling of BPA

October 11, 2013

The North American Metal Packaging Alliance, Inc. (NAMPA) submits these comments to the European Chemicals Agency (ECHA) in response to the July 2013 proposal from the French government for harmonized classification and labeling based on Regulation (EC) No. 1272/2008 for bisphenol A (BPA). NAMPA is a not-for-profit U.S. corporation committed to protecting health through the safety of metal packaging and metal packaged foods. NAMPA's membership includes companies and associations representing various sectors along the supply chain for the food and beverage packaging industry. Our members actively engage in worldwide trade and, as such, have a vested interest in the outcome of regulatory requirements within Europe. As discussed below, the French government proposal to reclassify BPA should not be adopted because it is not scientifically justified. NAMPA fully supports and incorporates by reference the comments submitted by the Bisphenol A REACH Consortium.

Background

BPA is currently classified as Category 2, defined as "substances which should be regarded as if they impair fertility in humans" under the Classification, Labeling and Packaging (CLP) regulation nomenclature. The French government has proposed that BPA be reclassified as Category 1B, which is defined as "presumed reproductive toxicant." According to the CLP regulations, a substance that is classified as Category 1B should have

- 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, alternatively,
- if toxic effects and the adverse effect on reproduction are both observed, the latter must not be a secondary, non-specific consequence of other toxic effects, but the origin of the effect.

BPA Data Do Not Support a "1B" Classification

The extensive available data on BPA do not support a "1B" classification. The generally recognized No Observed Adverse Effect Level (NOAEL) for general system toxicity for BPA is 5 mg/kg/day. The doses at which reproductive toxicity effects were observed were far higher than 5 mg/kg/day. A comprehensive review of applicable studies is included with the Bisphenol A REACH Consortium comments. As shown in that review, in those studies where animal fertility effects were observed, they occurred only at high dose levels at which other significant systemic toxicity effects were also observed. This clearly does not meet the Category 1B criteria and, as such, the proposal from the French government must be rejected.

The French Government Proposal Did Not Follow ECHA Procedures

As more fully articulated in the Bisphenol A REACH Consortium comments, the classification proposal from the French government did not follow specific procedures outlined in ECHA guidance. The proposal did not follow a weight of evidence approach, which is the specified approach for chemicals with large databases such as that supporting BPA. The BPA database is very large, and, as such, it is imperative that evaluations of available information be comprehensive and consider all pertinent data. It appears that the French government proposal included certain studies in its supporting documentation, deselected

others for no apparent reason, and failed to integrate information on all studies, including numerous studies that showed no adverse effects. Likewise, several studies that the French government proposal cited as supportive to the reclassification were previously reviewed by the National Toxicology Program (NTP) and the European Food Safety Authority (EFSA) and found to be scientifically inadequate. This bias in a purported scientific evaluation is very concerning and raises credibility questions with the goal of the French government proposal.

Finally, NAMPA notes that the proposal does not include more recent study data (post 2012), including an important research project from the U.S. Food and Drug Administration (FDA) National Center for Toxicological Research (NCTR). NAMPA urges that this study (Delclos 2013; "Relating Internal BPA Doses to Adverse Effects in Rodent Toxicity Studies"), which was specifically designed to address specific data gaps and lingering scientific questions on BPA, be carefully considered before any decision on classification is made.

For these reasons, the French government proposal to reclassify BPA should not be adopted because it is not scientifically justified, reflects an inappropriate bias, and does not consider all relevant and available scientific studies.

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	Germany	Bayer MaterialScience AG	Company-Manufacturer	5

Comment received

Executive summary of
BPA Consortium comments to the CLH Proposal

These comments and attachments are the comments of Bayer MaterialSciene AG and 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
 - o does not consider "all available information;"
 - o 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
 - o 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.
 - o Information is not comprehensive and inconsistent throughout the report.
 - o Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased.
 - o Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible.
 - o 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"

(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.

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	Belgium	ReachCentrum BPA Consortium	Industry or trade association	6

Comment received

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
 - o does not consider "all available information;"
 - o 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
 - o 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.
 - o Information is not comprehensive and inconsistent throughout the report.
 - o Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased.
 - o Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible.
 - o 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"

(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.

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	United Kingdom	Public Health England	National Authority	7

Comment received

This is a summary of the data collected on bisphenol A which attempts to explain the large inconsistencies in the outcomes of many of the studies undertaken on the potential toxicity of bisphenol A. Despite these inconsistencies, it is proposed that there is sufficient weight of evidence to classify as Repr. 1B-H360F or even Repr. 1A; H360F. The latter is inappropriate as there is no evidence for a direct effect of BPA in human reproductive toxicity. Data presented from human investigations shows correlation but not causation of effects. BPA is found in food contact material and there is no clear evidence that the human studies are not merely a representation of a poor diet having an effect upon fertility. Likewise there are a number of other inadequacies in the human data that make classification as Repr.1B suspect and Repr. 2 more appropriate (some evidence in humans but some deficiencies in the studies).

It should be noted that the document requires some editorial review.

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	Sweden	ChemSec	International NGO	8

Comment received

ChemSec welcomes the French Proposal for a Harmonised Classification and Labelling (CLH) of Bisphenol A (BPA).

Overall the CLH report prepared is robust in order to justify an additional classification entry of BPA as Repr 1B H360F according to Annex VI of the CLP Regulation (Toxicity to reproduction – fertility Cat. 2; R60 according to the Dangerous Substances Directive).

However after our assessment of the available data, BPA should instead be classified as a Reproductive toxicant, Category 1A, as it is a known human reproductive toxicant based on evidence from humans.

BPA is associated with reproductive dysfunction, increased cancer risk, including breast and prostate, and a range of other chronic or irreversible health problems, often from very low levels of exposure. Both animal and human studies confirm these effects of very high concern. BPA is commonly detected in humans.

We therefore support this additional classification entry as Repro 1B (360F) but suggest that a classification entry as Repro 1A is more justified for this substance.

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2013	United Kingdom	Exponent	International NGO	9

Comment received

With respect to regulation EC 1272/2008 Table 3.7.1(a) " Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans" it is concluded based on the review of the human data that no such evidence is forthcoming and therefore the placing of BPA in Category 1 is inappropriate and unsupported.

(ECHA note: The following attachment was provided:

"Review of the epidemiology studies described in the ANSES 2013 report on harmonized classification and labeling of Bisphenol A" [Attachment 13])

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2013	Germany		MemberState	10

Comment received

A classification of Bisphenol A as Repro 1B H360F is not supported by DE. In order to support Cat 1 B the criteria require that clear evidence on the adverse effect should be given. Instead, some evidence and inconsistencies across effects and discrepancies between studies confirms the present classification as Cat 2.

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Switzerland	Dow Europe GmbH	Company-Manufacturer	11

Comment received

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. The Dow Chemical Company endorses the positions taken in the BPA Consortium comments. The Dow Chemical Company possesses notable technical expertise in toxicology, especially in the area of reproductive toxicology. It also has considerable expertise in the areas of hazard and risk assessment. Finally, the Dow Chemical Company has been and is a significant stakeholder in the area of classification since it has promoted and contributed a great deal of the critical scientific information relevant to the classification issue at hand.

After a 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
 - o does not consider “all available information;”
 - o 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
 - o 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.
 - o Information is not comprehensive and inconsistent throughout the report.
 - o Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased.
 - o Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible.
 - o 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” (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.

Date	Country	Organisation	Type of Organisation	Comment number
04.10.2013	Norway		MemberState	12
Comment received				
Norway would like to thank France for the proposal for harmonised classification and labeling of Bisphenol A (BPA), CAS- no. 80-05-7.				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Sweden		MemberState	13
Comment received				
The SE CA supports classification of bisphenol A (Cas No 80-05-07) as specified in the proposal. SE agrees with the rationale for the classification into the proposed hazard class and differentiation.				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Belgium	European Environmental Bureau (EEB)	International NGO	14

Comment received

There is a review of ninety-one studies that links Bisphenol A (BPA) to health effects in humans that should be taken into account.

A comprehensive review conducted by TEDX's Johanna Rochester, PhD, was recently accepted for publication in Reproductive Toxicology. Associations were revealed between Bisphenol A exposure and adverse perinatal, childhood and adult health outcomes in humans, including reproductive and developmental effects, metabolic disease and other health outcomes, particularly behavioral effects in children. These studies, over half of which were published in the last year, confirm that BPA can be harmful to humans at levels experienced by the general population, and well below levels considered safe by the EPA.

Abstract: There is growing evidence that bisphenol A (BPA) may adversely affect humans. BPA is an endocrine disruptor that has been shown to be harmful in laboratory animal studies. Until recently, there were relatively few epidemiological studies examining the relationship between BPA and health effects in humans. However, in the last year, the number of these studies has more than doubled. A comprehensive literature search found 91 studies linking BPA to human health; 53 published within the last year. This review outlines this body of literature, showing associations between BPA exposure and adverse perinatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types. While it is difficult to make causal links with epidemiological studies, the growing human literature correlating environmental BPA exposure to adverse effects in humans, along with laboratory studies in many species including primates, provides increasing support that environmental BPA exposure can be harmful to humans, especially in regards to behavioral and other effects in children.

Link to the study: <http://www.sciencedirect.com/science/article/pii/S0890623813003456>

(ECHA note: The following confidential attachment was provided: "Bisphenol A and Human Health: A review of the literature" [Attachment 14])

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Netherlands		MemberState	15

Comment received

Effects on oocytes

- Effects on chromosome segregation could be considered induction of genetically based heritable effects on the offspring. According to chapter 3.7.1.1 it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

Effects on the male reproductive tract

- When adult male rats were exposed to BPA, via gavage or subcutaneously, a decreased sperm count and an increased ventral prostate weight were observed. This might decrease reproductive performance and may be considered as an effect on sexual function. This

effect was however not reported in the multigeneration studies. Because of the short study descriptions, it is not clear whether the studies that report these effects can be considered as reliable.

- The summary of the study by Sakaue et al, 2001 contains an error as fertility was not determined in this study.

Effects on reproductive performance

- The reduced number of litters/pups in the 3-generation study in rats without an effect on resorptions (also in F0) and the reduced number of litters/pups in the continuous breeding study in mice suggests an adverse effect on fertility. This effect is observed in two species and in multiple studies (i.e. the secondary effect of reduced litters/pups). However, summaries of the available developmental studies could further substantiate whether this is an effect on fertility or development. No reductions in offspring were observed in the developmental studies by Stump (2010) and Ryan (2010). This further justifies that the effects in the multigenerational studies are due to an effect on fertility instead of post-implantation loss.

Human data

- Two epidemiological studies suggest a relationship between BPA and endometriosis. However, both studies have a poor methodology and are therefore not reliable.
- Some epidemiological studies indicate that higher urinary or plasma BPA concentrations are related to reduced implantation, increased miscarriages, premature birth or ovarian response following ovary stimulation. Also these studies have serious methodological flaws with regard to confounders, population size etc. Because human exposure to BPA largely comes via food intake and spot urine samples only reflect the last meal (Teegarden et al, 2011), caloric intake should be included as confounder to exclude the possibility that the correlation is due to higher BPA intake due to higher food intake, in particular higher food intake via canned food (e.g. soft-drinks or beer). Only in some incidental epidemiological studies this possible confounding is mentioned but even in these few studies, the influence of this confounder was not taken into account.
- The methodology of the human data is insufficient, therefore these studies cannot be used for classification purposes. Not even as supportive evidence.

(ECHA note: The following attachment was provided - same content as in the comment above:

"Comments on the proposal for harmonized classification and labeling of Bisphenol A." [Attachment 9])

Date	Country	Organisation	Type of Organisation	Comment number
11/10/2013	Italy		MemberState	16

Comment received

(ECHA note: The comment below was submitted as a separate attachment with the name "Bisphenol classification" [Attachment 7])

We support that classification of Bisphenol A for reproductive effects has to be reconsidered, since numerous studies have been produced in the recent years.

Under this respect, we consider that the studies performed by sub-cutaneous administration or other parenteral routes (intramuscular, i.p.) may serve as proof-of-principle, i.e., to show the potential of bishenol A to act as a reproductive toxicant and the main targets of its reproductive effects. However, for classification and labelling purposes, priority has to be given to studies using treatment routes relevant to consumer's exposure, such as oral,

diet, drinking water, inhalation.

We support the classification proposal as 1b for reproductive toxicity (R60), based on the consistent observation of reproductive impairment at oral/dietary dose levels. Considering only studies performed after 2000 using oral (gavage, diet, drinking water) routes:

Female reproduction

- increased ovarian meiotic abnormalities upon prepubertal exposure in mice (Hunt et al., 2003)
- increased resorption rate in mice exposed since mating (Al-Hiyasat et al., 2004)
- dose-related delayed puberty (two-generation study in rats; Tyl et al., 2002)
- endometrial proliferation (increased thickness of uterine epithelia and stroma, less apoptotic cells) with reduced ER- α expression in rats exposed to 1.2 mg/kg bw in utero and during lactation (Mendoza-Rodriguez et al., 2011); at much higher in utero exposure (50 mg/kg) the thickness of the uterine epithelium is reduced with altered expression of estrogen receptors (Schönfelder et al., 2004)
- irregular estrous cycle upon developmental (pre- and neonatal) exposure (Rubin et al., 2001; Mendoza-Rodriguez et al., 2011)

Male reproduction

- Impaired spermatogenesis upon in utero exposure in rats (Tinwell et al., 2002; Iida et al., 2002) also with demonstrated impaired reproductive ability (Salian et al., 2009)
- Reduced testis and seminal vesicles weight, with reduced Leydig cells testosterone production in rats exposed in utero and neonatally (Akingbemi et al., 2004)
- Reduced testosterone (Akingbemi et al., 2004; Della Seta et al., 2006) and LH (Akingbemi et al., 2004) serum levels in rat exposed during prepubertal phase (Akingbemi et al., 2004); reduced reproductive performance also observed (Della Seta et al., 2006)
- Delayed puberty in rats exposed in the prepubertal phase (Tan et al., 2003)
- Impaired spermatogenesis with reduced testis and epididymal weight and increased prostate weight in adult rats (Chitra et al., 2003)

Apparently the above effects were observed in the absence of other toxic effects that may cause reproductive impairment as a secondary consequence. Thus, the overall picture of BPA effects on fertility/reproductive function fulfills the criteria for classification as **1b**.

The data available hint to some further observations:

- The effects of BPA are more complex than being simply "estrogenic" and hint to modes of action modulated by dose, sex and lifestage; species- and strain-related susceptibility have been observed, mice appearing as less susceptible. This interplay among factors modulating BPA effects may partly explain why some studies contradict the majority of findings as no effects are shown; this aspect is surely worth investigating for a refined risk assessment. However, the overall the overall weight of evidence points to clearly point to an impaired reproductive function in both sexes, encompassing several endocrine, morphological and functional parameters and with enhanced sensitive of the prenatal and also prepubertal stages. Thus, for classification purposes BPA should be considered as a chemical capable to elicit clear-cut reproductive effects in both sexes through relevant exposure routes.
- Reproductive effects were apparently less evident in the two-generation studies, however these were not entirely absent as shown by the dose-related delayed puberty seen also at the intermediate dose in the rat two-generation study by (Tyl et al., 2002). This is another finding definitely worth investigating: data may suggest that the repeated pulse exposure related to gavage is much more effective than continuous low-level exposure elicited by the long term dietary administration.

One might speculate that the aggregate, multiple way exposure of humans is more similar to the repeated pulse scenario, whereas a continuous dietary exposure might be more

relevant to cumulative chemicals.

Again, this issue is definitely worth investigating for risk assessment, but it bears little weight for classification purposes, that currently rely on rather stringent, hazard-based criteria

Moreover, consideration should be given to available human data:

- Biomonitoring data in humans indicate a continuous aggregate exposure, with a prolonged presence of detectable internal levels
- Humans may have more efficient detoxification mechanisms than rodents; however, many differences exist within the human population, related to genetics, sex and lifestage
- Epidemiological investigations suggest a relationship between BPA levels and increased risk of reproductive disorders in women (infertility, recurrent miscarriage, impaired IVF), while in males correlations with impaired spermatogenesis and altered endocrine balance (steroid hormones, FSH, Inhibin B) have been observed.

Overall human data are not robust enough to support a 1a classification; however, these studies support the evidence provided by the animal studies pointing out that bisphenol A should be classified as 1b for reproductive toxicity.

--- End of attachment ----

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2013	United Kingdom		Individual	17

Comment received

It is known that effects exist on certain species of animals but this is not enough publicised, probably because the topic is very specific and not'sexy' enough to attract a wide press coverage.

Date	Country	Organisation	Type of Organisation	Comment number
04.10.2013	United States	Can Manufacturers Institute	Industry or trade association	18

Comment received

CMI is opposed to the proposal to reclassify bisphenol A (BPA) as a reproductive toxicant Category 1B under Regulation (EC) No. 1272/2008. According to the Classification, Labeling and Packaging (CLP) regulations, substances to be classified as reproductive toxicant, Category 1B, must have clear evidence of an adverse effect in the absence of other toxic effects OR if other effects are seen, the reproductive toxicity effect must be the origin of the other toxic effects and not be a secondary, non-specific consequence. That is not the case with BPA. In studies where reproductive toxicity effects were observed, those effects occurred at dose levels above those where systemic toxicity effects. Thus, the criteria are not met and the reclassification proposal should not be accepted.

Date	Country	Organisation	Type of Organisation	Comment number
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10.10.2013	Netherlands	Momentive Specialty Chemicals B.V.	Company-Manufacturer	19
Comment received				
<p>Executive summary of BPA Consortium comments to the CLH Proposal</p> <p>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.</p> <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> o does not consider "all available information;" o 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 o 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. <ul style="list-style-type: none"> o Information is not comprehensive and inconsistent throughout the report. o Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased. o Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible. o 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. <p>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" (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.</p> <p>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.</p> <p>Please see for more details in the public attachment</p> <p><i>(ECHA note: The following attachments were provided: "Annex A - BPA REACH Consortium CLH male and female endpoints 10-10-2013" "Annex B - BPA REACH Consortium CLH information on Tyl 10-10-2013"</i></p>				

"Annex C - BPA REACH Consortium CLH summary NCTR-2013 10-10-2013"
 "Annex D - BPA REACH Consortium CLH overview relevant studies for BPA classification 10-10-2013"
 "Annex E - BPA REACH Consortium CLH review epidemiology studies described in the CLH proposal 10-10-2013"
 "BPA REACH Consortium comment on CLH proposal on BPA prepared by ANSES 10-10-2013_final"
 [Attachments 1-6])

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	Germany	Bayer MaterialScience AG	Company-Manufacturer	20

Comment received

Executive summary of
 BPA Consortium comments to the CLH Proposal

These comments and attachments are the comments of Bayer MaterialScience AG and 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
 - o does not consider "all available information;"
 - o 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
 - o 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.
 - o Information is not comprehensive and inconsistent throughout the report.
 - o Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased.
 - o Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible.
 - o 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"

(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.

see public attachments

(ECHA note: The following attachments were provided:

"Annex A - BPA REACH Consortium CLH male and female endpoints 10-10-2013"

"Annex B - BPA REACH Consortium CLH information on Tyl 10-10-2013"

"Annex C - BPA REACH Consortium CLH summary NCTR-2013 10-10-2013"

"Annex D - BPA REACH Consortium CLH overview relevant studies for BPA classification 10-10-2013"

"Annex E - BPA REACH Consortium CLH review epidemiology studies described in the CLH proposal 10-10-2013"

"BPA REACH Consortium comment on CLH proposal on BPA prepared by ANSES 10-10-2013_final"

[Attachments 1-6])

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	Belgium	ReachCentrum BPA Consortium	Industry or trade association	21

Comment received

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
 - o does not consider "all available information;"
 - o 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
 - o 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.
 - o Information is not comprehensive and inconsistent throughout the report.
 - o Statements related to the value of regulatory guideline studies compared to the value of exploratory studies are biased.

- o Statements on multigeneration animal studies upon which regulators have relied (Tyl et al 2002 and 2008a) are inconsistent, incorrect and incomprehensible.
- o 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”

(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.

see public attachments

(ECHA note: The following attachments were provided:

"Annex A - BPA REACH Consortium CLH male and female endpoints 10-10-2013"

"Annex B - BPA REACH Consortium CLH information on Tyl 10-10-2013"

"Annex C - BPA REACH Consortium CLH summary NCTR-2013 10-10-2013"

"Annex D - BPA REACH Consortium CLH overview relevant studies for BPA classification 10-10-2013"

"Annex E - BPA REACH Consortium CLH review epidemiology studies described in the CLH proposal 10-10-2013"

"BPA REACH Consortium comment on CLH proposal on BPA prepared by ANSES 10-10-2013_final"

[Attachments 1-6])

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	Denmark		MemberState	22

Comment received

The Danish CA welcomes this thorough evaluation of the reproductive effects of BPA. Based on the total weight of evidence we agree that classification in Cat. 1B is warranted as adverse effects on fertility and the reproductive systems have been demonstrated in several studies in mice. These findings furthermore confirm the data obtained from various human studies, which i.e. indicate that exposure to BPA is associated with impact on sperm parameter and sexual dysfunction in males and effects on the reproductive organs in women. However, we are uncertain as to whether the human data are strong enough to justify a Cat. 1A classification.

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2013	United Kingdom	Public Health England	National Authority	23

Comment received

Part A1

A critical aspect of identifying an EDC especially at the high doses utilised in the majority of

these studies is that the observed effects should be observed in the absence of systemic effects. The absence of any data on the acute oral toxicity or repeated dose toxicity for bisphenol A makes this data difficult to interpret.

Part B2

Final section is incomplete 'Out of many sources, the general public might be exposed via thermal paper; in articles made of PVC....'

The major source of BPA exposure is ingestion via use of BPA in food contact materials or in infants by mouthing behaviour of PVC-containing items. This is important information as the evidence presented later in the dossier shows conflicting data dependent upon whether BPA is dosed orally or injected subcutaneously.

Part B4.1

BPA intake of 13ug/kg quoted. This is out of date and the current EFSA opinion under public consultation estimates daily exposure at <1ug/kg/day for all age categories.

In metabolism section (4.1.3) it is stated that the enterohepatic circulation of BPA in rats has little consequence on clearance however, what is important is the reformation of the parent 'active' BPA from the inactive conjugates which makes the rat a more susceptible species than man. Also, the possibility of β -glucuronidase activity in placenta increasing exposure to the foetus is described despite the studies of Patterson et al 2010 showing that in primates, placenta contributes an increase in glucuronidation.

The very low proportion of aglycone in body fluids including breast milk highlight the facts that high dose levels by routes other than oral that avoid first pass effect are not representative of the risks to humans and wildlife.

Section 4.11.

Several different animal models have been utilised to investigate the effects of BPA. Many of the effects observed in these studies occur spontaneously in different animal strains eg ovarian cysts. Where these have been presented data should be referenced to the range of expected spontaneous incidence in that species.

If a weight of evidence approach is being used, less weighting should be given to studies using inappropriate routes of dosing.

4.11.1.1.5 Multigenerational exposure

In the continuous breeding study weight loss is observed in the female mice in the treated groups suggestive of systemic toxicity which may affect the small declines in fertility of these animals.

Tyl et al 2008 saw no reprotoxicity except at the highest dose (where the authors report systemic toxicity) in CD-1 mice. Organ specific toxicities were observed for kidney and liver at 300 ppm (50 mg/Kg, Fo) and 0.018 ppm (3ug/kg, F1, F2) suggest the Repro. Tox is a secondary effect and that classification based upon repeated dose toxicity is more appropriate.

Likewise the same authors reported renal tubular degeneration and chronic hepatic inflammation in SD rats exposed to 750 and 7500 ppm but only observed reprotoxic effects at the highest dose (7500 ppm)

4.11.1.1.6 Transgenerational exposure

Hiyama study, all doses are in excess of the doses inducing organ toxicity (Tyl et al)

4.11.1.1.7

No effects on meiosis and oocyte development were observed in the 4 guideline studies. The spontaneous incidence of ovarian cysts is well documented in CD-1 mouse strain. It should be made clear whether the test groups described here fall within the range of spontaneous incidence or not especially as this was the only significant finding in these studies.

Hoxa10 and Hoxa 11 expression data are contradictory in two studies therefore little can be inferred from the data at this time.

Several of the mechanistic studies take place in ovariectomised animals and therefore the studies should be given less weight as they are not in intact animals.

Effects on the female reproductive capacities

Effects are only observed when BPA is dosed by subcutaneous injection. Oral dosing eg cabaton et al, Tyl et al induced no effects

The authors make reference to publications for the lack of sensitivity of SD rats to estrogens. This evidence needs to be made clearer as the research referenced as Nagao et al and Kwon et al 2000 demonstrate that SD rats respond to DES or estradiol benzoate but not BPA. Without this the intent of the authors to allow less emphasis on the negative studies conducted in SD rats is unfounded.

Is it correct that the doses in the Berger study are 3375 mg/day and 10,125 mg/day? Is this even possible? If so, was a full toxicological evaluation conducted? Were any other organ toxicities observed?

Conclusion on female reproductive system in animals

The increased incidence of ovarian cysts in CD-1 mice needs to be confirmed as significantly greater than the well documented spontaneous occurrence rate if this effect is to be proven to be attributed to BPA.

There is significant inconsistency between studies with uncertainties associated with strain and species differences, studies showing no toxicity (particularly those using OECD guideline tests), use of ovariectomised animals, routes of exposure and hepatic and renal toxicity at concentrations lower than those inducing reproductive effects. As such, a categorisation of BPA as Repr. 2 is appropriate.

4.11.1.2 Human information

4.11.1.2.2 Effects during pregnancy

No significant well conducted studies are presented here.

In addition to the criticisms of these studies by the authors; the case-control study of Sugiura-Ogasawara is also suspect as non-pregnant women are used as controls for women with recurrent miscarriage. The correct control would have been first trimester women with no history of miscarriage. Inoue et al (2005 Drug Metab Dispos) demonstrated that in rats biliary excretion of BPA glucuronide is decreased in pregnant rats and circulating BPA glucuronide is increase. ELISA will not differentiate between parent and glucuronide and so in this study an increased BPA level in the pregnant women with a history of miscarriage is to be expected.

4.11.1.2.3 Effects on Ovary

Data are contradictory between studies for the effects of obesity for example BPA is increased in obese women in Tekeuchi et al but not Kandaraki et al. and data is questionable because of the use of ELISA and urinary BPA levels negatively correlate with oocytes collected (Mok-Lin et al) but not between serum BPA and oocytes collected (Bloom et al).

4.11.2 Effects on male reproductive tract

4.11.2.1.1 in utero and lactation exposure

Strain differences

Some studies show effects on prostate others don't. Some studies show effects on male reproductive tissues others no not. Majority of the more recent studies were negative

4.11.2.1.2 neonatal exposure

The study of Salian et al shows no dose response but a consistent post-implantation loss of around 25% for doses 400, 800 and 1600ug/kg bw/d. How does this vary compared with the natural variability in Holzman rats? There is a dose dependent effect on sperm count and motility however these effects wouldn't cause infertility as counts are still within the normal range of a fertile animal.

In the description of the study of Aikawa et al there is inconsistency in reporting the dose ug or mg?

No effects on sperm count seen in this study despite comparable doses to Salian et al study?

Toyama and Yuasa (2004b) and Kato et al (2006) suggest that BPA dosing of neonates has no effect on fertility.

4.11.2.1.3 Prepubertal exposure

There is no consistency across these studies with respect to effects on oestradiol or testosterone levels. Some studies show an alteration of LH but there are no signs of adversity in any of the studies with respect to reproduction.

Akingbemi et al , no dose response with significant effects only observed at one dose and no indications of adversity.

Nakamura et al 2010 only demonstrate effects on testis weight and reduced epididymis and seminal vesicles at doses responsible for weight loss and therefore potential systemic toxicity.

Tan et al showed little significant effect whereas Takahashi and Oishi did show toxicity in Wistar rats but only when dosed ip or sc and no toxicity when dosed via the oral route.

4.11.2.1.4 Adult exposure

Consistent transitory effects of adult exposure on sperm parameters following prolonged, high dose exposures, using an inappropriate route of exposure in rat only suggesting a Repr. Tox 2 categorisation.

4.11.2.1.5 Multiple Exposure

No consistent significant effects

4.11.2.1.6 Multigenerational exposure

No evidence of any multigenerational effects even at very high doses.

No clear reproductive toxicity is seen in these mouse studies. Effect on reproductive organ weight in the continuous study is accompanied by a marked increase in liver and kidney weights. It is not clear from the report which characteristic toxicity response (liver, kidney, reproductive organs) happens at the lowest dose and therefore is the key/primary target organ in this study and consequently whether BPA should be classed as a repro, hepatic or renal toxicant.

In rat (Emma et al), no statistically significant changes to AGD or sperm statistics nor any dose-response for seminal vesicle weight and no morphological changes and therefore no adversity. Likewise the study of Tyl et al 2002 only demonstrated effects at the highest dose which was accompanied by body weight loss suggesting toxicity at other sites

4.11.2.1.7 Transgenerational exposure

The study of Salian et al demonstrates a transgenerational effect of BPA with some dose response and indication of adversity (post-implantation loss). This is inconsistent with the multigenerational studies described above and is the only study of its type further highlighting the large unexplained discrepancies between studies.

Conclusions on male reproduction

The authors state that oral studies may elicit more effects than sub-cutaneous studies which isn't supported by the data. For example Tan et al showed limited toxicity by sc route and non by the oral route.

It is apparent that many studies are conducted in SD rats which require 100- to 400-fold higher doses of estrogens to observe an effect which is a shortfall. However, doses used in many of these studies are 1000-fold or higher than expected human exposures and so some effects would still be expected to be observed.

Additional information

Although this section is of interest, the effects observed on various proteins do not demonstrate adversity

4.11.2.2 Human information

There is marked inconsistency between studies. No consistent association between urinary BPA and adverse semen parameters in Mendiola et al (2010). Where correlations exist this is not evidence of a causal relationship. BPA exposure will be higher in people consuming a processed food diet rich in sugary, carbonated drinks. This group is more likely to have dietary insufficiencies, to be overweight and have high blood glucose levels which are all associated with lowered fertility/sperm counts. It is very difficult to prove causality and the concentrations of BPA found in biofluids of humans are orders of magnitude lower than those expected to occur in the animal models at the effective doses of BPA in vivo.

The marked significant decrease in AGD in boys whose mothers ($P=0.003$) but not fathers ($p=0.15$) were exposed to BPA is an important finding but it shows no adversity and BPA levels in cord blood were not significantly different between cryptorchid boys and controls
Conclusions in humans (men)

It is wrong for the authors to state that 'all point out a correlation between higher BPA levels and different sexual parameters' as not all studies in men do and the observations of Meeker et al (2010a) and Mendiola et al (2010) report inconsistent relations between urinary BPA and FSH. What these studies do consistently show is the very low (single digit ng/ml or lower) plasma levels of BPA in the human population which are inconsistent doses employed inducing any detrimental effects observed in animal models.

4.11.5. Summary...

The authors state 'the significance of the positive trend between BPA and testosterone was not reached' for three studies in humans. This suggests that BPA causes an increase in testosterone which would be expected to cause an increase in sperm count. This is inconsistent with proposed effects on sperm populations and AGD in rodents in vivo. Most consistent effect is ovarian cyst occurrence but this is observed in CD1 mice which have a predisposition for ovarian cysts.

'...to show that the hazard demonstrated in animals can be observed as a risk in humans.'

This is not a truly accurate statement. Although more work on measuring tissue and biofluid levels in animals during these experiments should be conducted to verify concentrations of BPA in circulation it is very likely that the doses of BPA employed to achieve the low ng/ml levels seen in patients consistently show no detrimental effects in vivo. This is emphasised more when it is considered that rats demonstrate significant enterohepatic circulation of BPA that humans do not.

4.11.6 Comparison with criteria

Category 2. The data provided in this dossier provides some evidence from humans but this is limited to correlations and has a lack of consistency and lots of inconsistent studies in experimental animals most of which do not demonstrate an adverse effect on sexual function and fertility, or on development. Furthermore, these effects are not always observed in the absence of other toxic effects (weight loss, increases in liver and kidney size) suggesting that the evidence is not sufficiently convincing to place the substance in Category 1. For a classification of Category 1B this requires that it should be known that BPA produces adverse effects on sexual function and fertility in humans which the evidence to date does not support. Alternatively, a strong presumption that interference with reproduction in humans based upon clear evidence from animal experiments may also determine a Category 1B classification. There is no clear data from animal experiments that BPA by the oral route (the route of exposure in humans) is responsible for reproductive toxicity with the majority of the oral or dietary doses showing no toxicity or, at very high doses, showing toxicity to reproductive tissues, liver and kidney and inducing weight loss indicative of systemic toxicity. This together with the lack of data on acute toxicity suggest that secondary non-specific reproductive toxicity may be the cause of at least some of the observed toxicities. A classification of Category 1A is not appropriate

Date	Country	Organisation	Type of Organisation	Comment
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				number
10.10.2013	Sweden	ChemSec	International NGO	24
Comment received				
<p>BPA is a largely studied chemical and its health effects have been officially recognized through its 29th ATP entry (Directive 2004/73) It is also classified as specific target organ toxicity Cat. 3.</p> <p>We would like to remind that the proposed classification entry of BPA follows also the initial findings of the UK CA submission in 2002 to classify it as Repr. Cat. 1B. ChemSec supports the findings justifying a classification as at least Repr. Cat. 1B on adverse developmental effects indentified in the 2011 ANSES report. The findings conclude that animal studies show effects that could be confirmed on male sperm production, induction of ovarian cysts, endometriosis and advanced puberty in females. The ANSES 2011 study also confirms adverse behaviour effects, effects on lipogenesis and breast development but also cardiovascular diseases. There is a strong body of evidence available allowing stakeholders to presume -without doubt- that the substance has the capacity interfere with reproduction in humans.</p> <p>A large amount of studies show that is acts as an endocrine disruptor on fertility at low doses. About 800 peer-reviewed studies make the case that BPA is toxic at low human exposure levels.</p> <p>As with other hormones, effects are often not observed until later in the lifecycle (making the causal link to BPA exposure difficult). However in this regard, we would wish to remind that the purpose of the CLP Regulation is to ensure a high level of protection of human health and the environment (Article 1 of CLP Regulation). The assessment of the weight of evidence and the application of the classification criteria set within the CLP Regulation need to bear in mind its underlying purpose.</p> <p>A further but important issue relates to underlying test protocols used and the non-monotonic dose-response curves for BPA. It has been found since 1997 (Colerangle and Roy) that BPA is more potent at low dose effects and that the window of exposure also matters (confirmed by numerous studies such as Vandenberg et al. 2012). Several studies make the case that irreversible developmental effects are caused depending on time windows of exposure during foetal, neonatal or juvenile periods of exposed organisms (Richter et al. 2007; Palanza et al. 2008; and Soriano et al 2012). Studies indicate that BPA does affect females: alteration of ovarian cyclicity / induction of early cessation of oestrus cycles, impairs reproduction, alters mammary gland development (Rudel et al. 2011b) and induces gland neoplasia, interferes with sexual differentiation of brain, alteration of behaviour (Soto and Sonnenschein 2010). Studies also indicate BPA can interfere with spermatogenesis (vom Saal et al. 1998; Okada et al. 2008a). Based on results from resent in vivo and in vitro studies the past assumption that BPA would be a weak oestrogen could be reversed: BPA can act through non-classical membrane-bound oestrogen receptor (Nadal et al 2000,2004 and Alonso-Magdalena et al 2005), or can bind with high affinity to estrogen related receptor (ERR-γ) (Okada et al. 2008b) or various receptors: GPR30 (Thomas and Dong 2006) and AhR (Kruger et al. 2008).</p> <p>The EEA has found in its second version "Late lessons for early warnings" that the case of BPA is very revealing on where independent research deviates strongly from industry-sponsored studies (please refer to tables 10.1 and 10.2 with summaries of mammalian studies on BPA with effect level at or below 50μ/kg bw d (oral)) and the list of references pages 230-239). It appears that 2 studies -sponsored by the society of the Plastic Industry Inc- (Tyl et al</p>				

2002 and Ryan 2010) have not identified major concerns of BPA, and have been used as the main studies for regulatory purposes because these have been done according to GLP testing protocols.

The issue of potential conflict of interests needs to be carefully considered by ECHA when ranking the various studies undertaken on BPA and put forward by various stakeholders under this public consultation.

Justification for classification as reproductive toxicant Cat 1 A:

According to the CLP Regulation, substances are to be classified in Category 1A if it is "largely based on evidence from humans". What matters for the Category 1 classification is on whether there is "a strong presumption that the substance has the capacity to interfere with reproduction in humans".

Based on the evidence available and the further attached submissions, ChemSec deems these criteria to be fulfilled.

A recent review of literature research on human health effects of BPA has been conducted by Johanna R. Rochester from The Endocrine Disruption Exchange (TEDX) [Rochester JR, Bisphenol A and Human Health: A review of the literature., *Reproductive Toxicology* (2013), <http://dx.doi.org/10.1016/j.reprotox.2013.08.008>].

A comprehensive literature search found 91 epidemiological studies linking BPA to human health effects in humans; of which 53 published were within the last year. The review outlines this body of literature, showing clear associations between BPA exposure and adverse prenatal, childhood, and adult health outcomes, including reproductive and developmental effects, metabolic disease, and other health effects. These studies encompass both prenatal and postnatal exposures, and include several study designs and population types.

The growing human epidemiologic studies correlating environmental BPA exposure to adverse effects in humans, along with laboratory studies in many species including primates, provides increasing support that environmental BPA exposure can be harmful to humans, especially in regards to behavioural and other effects in children.

In respect to the literature review (attached) ChemSec would wish to highlight:

- 22 studies in humans focusing on BPA and children's health outcomes that were published between 2002 and April 2011;
- 53 epidemiologic cross-sectional, prospective cohort, case report, case-control and randomised clinical trial studies have been examined;
- a further reference to 16 earlier studies is included in this literature review.

Most of the studies are also references in the HCL report submitted by France.

The shortlisted studies were analysed for quality based on the National Toxicology Program Office of Health Assessment and Translation (OHAT) approach and for rigorous assessment on strength of evidence. The review includes a sub total of 34 recent human studies (2010-2012), of which 94% indicate strong evidence on capacity to interfere with reproduction in humans .

The overview tables per category of effects on human health are provided in a separate document.

The conclusions of these findings are summed up as follows:

Fertility:

- the report indicated that there is some evidence that BPA may contribute to infertility in humans

Male Sexual function:

- the report concludes that there is a strong link between BPA exposure and male sexual function which would be strengthened by replication of findings on workers in another cohort

Reduced Sperm Quality:

- there are high quality studies showing consistent results in different populations indicating clear relation of adult BPA exposure to (decreased) sperm quality in men.

Sex Hormone Concentrations:

- the studies relating sex hormone concentration and BPA exposure are strong and fairly consistent effects across many types of populations and age groups confirming that BPA has antirational effects on circulation level of sex hormones.

Miscarriage:

There is some evidence of a relationship between recurrent miscarriage and BPA exposure in women, which may be due to an increase in chromosomal abnormalities of the oocovytes due to meiotic disruption, shown in mice.

Premature Deliveries:

There is a significant association between elevated total BPA and premature delivery.

Childhood Behaviour / Neurodevelopment

The report concludes that there is strong evidence that BPA is associated with neurobehavioral problems in children. (However it is unclear if BPA alone is responsible for the behavioural effects)

Childhood Asthma / Wheeze

The report suggests that there may be prenatal and postnatal windows of susceptibility, which may change the magnitude/direction of the health effect. Prenatal BPA exposure has been confirmed to induce asthma in mouse pups, additional longitudinal studies with different populations would be needed to verify the link.

Metabolic Disease:

The report concludes that there is strong evidence in human studies that Type-2 Diabetes is associated with BPA.

Further there is strong evidence that adult exposure to BPA is associated with cardiovascular diseases, in many populations.

Overall conclusion:

Strong evidence available today and recent human studies corroborating the animal findings confirm a strong presumption that BPA has the capacity to interfere with reproduction in humans, suggesting a HCL entry as Repr. Cat 1A.

There is strong evidence that BPA has the capacity to alter human reproduction, i.e. reduced ovarian response and IVF success, reduced fertilization success and embryo quality, implantation failure, miscarriage, premature delivery, reduced mal sexual function, reduced sperm quality, altered sex hormone concentrations, PCOS, altered hormone concentrations, blunted immune function, type-2 diabetes, cardiovascular disease, altered

liver function, obesity, albuminuria, oxidative stress and inflammation, and altered epigenetic markers and gene expression.

Exposure to BPA at certain exposure windows can also cause increased spontaneous abortions / male genital abnormalities / abnormal gestation time / reduced birth weight and childhood obesity. There is particularly strong evidence of BPA effects on altered behaviour and disrupted neurodevelopment in children. There is also a strong presumption that BPA is linked with infertility.

The report submitted by France also confirms that all studies in humans assessed point out to "a correlation between higher BPA levels and different sexual parameters (quality of sperm, sex hormones, and sexual function and quality) and then strengthen the plausibility of causality." [see page 109 in the HCL report]

The epidemiological studies performed by Meeker et al. 2010, Mendiola et al. (2010) and Galloway et al. (2010) , Li et al (2010) have been addressed. Further it states that little boys among whom one or both parent(s) had an occupational exposure to BPA exhibit shorter AGD when compared to control boys, with irrevocable results. A dose-response relationship has also been established between increased BPA exposure levels during pregnancy and shortened AGD in male offspring. Effects are also recognised on the issue of IVF (Bloom et al. 2011). The report concludes that "the effects seen in men are consistent with the one observed in animals like effects on the sexual hormones and on male sexual function including sperm parameters" [See page 113 in the HCL report].

A classification to Repr. Cat 1A will lead to immediate positive effects for human health effects and environmental protection because of immediate regulatory response in terms of labelling and further restrictions for certain uses of BPA containing products. We like to remind that the effects identified by BPA are irreversible.

The full review paper is attached for your consideration.

(ECHA note: The following attachments were provided:

"Background information on new literature research of BPA by TEDX"

"Bisphenol A and Human Health: A review of the literature, Accepted Manuscript"

"Table 1. Studies on Bisphenol A (BPA) and Health Effects. From Rochester JR, Bisphenol A and Human Health: A review of the literature, Reproductive Toxicology (2013 in press)."

[Attachments 10-12]

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2013	United Kingdom	Exponent	International NGO	25

Comment received

This document reviews the epidemiologic literature in the ANSES CLH report on Bisphenol A and is a response to the invitation from ECHA for public comments. It is divided into two sections, parallel to the ANSES report, on 1: the female reproductive system and 2: the male reproductive tract. The concern about the poor quality of many studies expressed in the report on page 10 is shared. Most importantly, nearly all the studies rely upon a spot serum or urine sample with which to determine exposure. Given the short half-life of BPA, a single sample is not representative for general exposure, a concern also raised by a joint committee of FAO/WHO (2010) and by Teeguarden et al (1). Further with few exceptions, none of the samples was collected during the etiologic relevant period for disease. The population-based studies did not collect any information from the subjects to distinguish

any dietary or other behaviors and to confirm the observed BPA concentrations. Most of the studies employ a cross sectional design which can only demonstrate a mathematical correlation of the observed data and not temporal association or causal connection. After a thorough review of the epidemiology studies included in the ANSES report, we conclude that the inconsistent results, in combination with the poor quality, do not provide additional evidence for BPA toxicity. The inconsistency, null findings, doubtful results and contradictory findings in the 20 epidemiology studies are best compatible with a situation where there is no biologically plausible relationship that can be established. Consequently, the presence of any robust adverse health effects caused by BPA can be excluded.

(ECHA note: The following attachment was provided:

"Review of the epidemiology studies described in the ANSES 2013 report on harmonized classification and labeling of Bisphenol A"

[Attachment 13])

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2013	Germany		MemberState	26

Comment received

In the present CLH proposal on BPA predominantly „low-dose effects“ are proposed as leading effects for an upgrade of classification for reproductive toxicity from Repr. 2H361 to Repr. 1BH360F.

The hypothesis of low dose effects in terms of adverse effects relevant for human health, however, is far from being consented by the scientific community and it is still a matter of scientific debate.

The observation of „low-dose effects“ of any substance including BPA is currently considered insufficient (and not appropriate) to serve for the scientific justification of regulatory measures such as classification and labeling of chemical substances.

With regard to low-dose effects, it is to note that the dose-relationship of the observed effects gives in general the strongest evidence on the causal proof that the effect of concern is related to the substance administered. Despite the absence of monotonic dose-related effects, as seen in many study using very low doses, the observed effects at singular doses (independent of the dose level) are explained as evidence of non-monotonic effects caused by BPA without any plausible mode of action for the non-monotonic action. The DS interpretation of monocausality of low-dose, non-monotonic effects that often showed diverse directions of their responses and contradictory effects is seen as rather uncertain and from a scientific aspect considering the strength of evidence as non-justified. In addition consistency on each of the observed 'low-dose' effects across studies is rather limited.

The CLH report appears to weigh the evidence from studies that are in compliance with OECD test guidelines less than the indications from low dose studies using artificial applications. In order to support Cat 1 B the criteria require that clear evidence on the adverse effect should be given. Instead, some evidence and inconsistencies across effects and discrepancies between studies confirms the present classification Cat 2.

Preference should be given to oral and dermal studies following the OECD testing regimen, in particular studies testing multiple doses should be considered as key studies. Those studies using invasive administration routes (e.g. subcutaneous injection or implantation of pumps) were not in compliance with standard requirements of OECD test guidelines. The relevance of these studies using other administration routes than the oral, dermal or inhalation route for classification purposes is questioned. Evidence from such studies can only be used as giving supportive evidence, if they are (as regards the observed effects) coherent to the outcome of those studies with relevant routes. To assess the dose-

dependency of effects, their outcome should be assessed taking into account the uncertainties as regards the dermal absorption rate and differences in metabolism due to different sites of administration (dermal vs. subcutis).

With regard to effects on the female reproductive system, it has been stated that the guideline (key) studies contradict the findings of other studies. However, a critical appraisal as regards the robustness of low dose studies using artificial dosing and their contribution to the overall evidence was not conducted. The limited evidence for fertility effects as seen in the multigeneration study (Tyl et al., 2002, 2008, Ema et al., 2001, NTP, 1985a) that are key for the decision on Cat 2 or Cat 1B taking into account the effects seen in the other studies with oral administration (Mendoza-Rodriguez et al., 2011, Ryan et al., 2010, Rubin et al., 2001, Hunt et al., 2003) is limited. E.g. the effects on the oestrus cycle were rather inconsistent across studies and the observation of meiotic abnormalities at low doses in the Hunt study was not confirmed by any other (multigeneration) study. Similar shortcomings may also apply to the section on effects on the male reproductive tract. E.g., assumed key effects on sperm production (reduction) as obtained from the studies of Chitra et al., 2003 or Herath et al., 2004 were not seen in the multigeneration studies (Tyl et al., 2002, 2008) and are of questionable significance.

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Switzerland	Dow Europe GmbH	Company-Manufacturer	27
Comment received				
See public attachments.				
<p><i>(ECHA note: The following attachments were provided:</i> <i>"Annex A - BPA REACH Consortium CLH male and female endpoints 10-10-2013"</i> <i>"Annex B - BPA REACH Consortium CLH information on Tyl 10-10-2013"</i> <i>"Annex C - BPA REACH Consortium CLH summary NCTR-2013 10-10-2013"</i> <i>"Annex D - BPA REACH Consortium CLH overview relevant studies for BPA classification 10-10-2013"</i> <i>"Annex E - BPA REACH Consortium CLH review epidemiology studies described in the CLH proposal 10-10-2013"</i> <i>"BPA REACH Consortium comment on CLH proposal on BPA prepared by ANSES 10-10-2013_final"</i> <i>[Attachments 1-6])</i></p>				

Date	Country	Organisation	Type of Organisation	Comment number
04.10.2013	Norway		MemberState	28
Comment received				
<p>The last time the classification of BPA for human health was discussed and decided, in TC C&L in 2002, the proposal from UK was to classify the BPA as Repr. Cat 2; R60. Nevertheless some members stressed the fact that classifying the BPA as Repr. Cat. 2 was a borderline it was agreed to rather classify as Repr. Cat. 3. Since 2002, several new studies with more mechanistic data, supporting a Repr. 1B classification, have been published</p> <p>We support the proposal to classify BPA for reproductive toxicity with Repr. 1B - H360F based on the weight of evidence of numerous animal studies where it appears that BPA impacts the male reproductive system with effects on the seminiferous tubules, the reproductive hormones levels and the quantity and quality of sperm. In female animals an</p>				

increased occurrence of ovarian cysts or disturbance of estrous cycle are observed in all studies. Decrease in the number of pregnancies and implantations was systematically reported and pre-implantation loss seems to be responsible of the effect of BPA on fecundity in rodents. These observations corroborate risks identified in humans through epidemiological studies. There are methodological limitations in the epidemiological studies. Human data should therefore be considered as additional/supportive evidence in the weight of evidence for classification with Repr 1B, but not sufficient for a classification with Repr. 1A.

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Belgium		MemberState	29
Comment received				
<p>We welcome the FRENCH proposal on the BPA classification. Please find our comments in attachment.</p> <p><i>(ECHA note: The following attachment was provided: "Proposal for harmonised classification and labelling : Bisphenol A" [Attachment 8])</i></p>				

Date	Country	Organisation	Type of Organisation	Comment number
11.10.2013	Sweden		MemberState	30
Comment received				
<p>The Swedish CA agrees that there is sufficient evidence from studies in animals for concluding that bisphenol A (Cas No 80-05-07) produces adverse effects on the male and female reproductive system that warrants classification in Repr. 1B; H360F. Based on the weight of evidence of numerous animal studies it is concluded that bisphenol A affects the male reproductive system in rats and mice after in utero exposure (in absence on major maternal toxicity). Effects were also seen after neonatal or peri-pubertal exposure as well as after exposure of adult animals. The observed effects on the reproductive system varied with the age of the animal at the time of exposure and included effects on fertility, effects on the seminiferous tubuli, effects on reproductive organ weights as well as effects on sperm production, sperm quality and level of the reproductive hormones. Bisphenol A also produces adverse effects on the female reproductive system. A large number of recent studies is available and several kinds of effects which may impair the fertility were observed. We agree with the notion presented in the report that this leads to consider the weight of evidence instead of basing the conclusion on few key studies limited to very specific models. Effects were observed following exposure during the prenatal, postnatal and adult stage, including increased occurrence of ovarian cysts and disturbance of the estrous cycle, which were observed in all of the animal studies presented in the report, and decrease in the number of pregnancies and implantations. All these findings support that a classification in Repr. 1B (H360F) is warranted. In addition, epidemiological studies also indicate that bisphenol A could be adverse for human reproduction and therefore the SE CA would welcome a discussion within RAC whether the data from these studies are robust enough to support a Repr. 1A (H360F) classification.</p>				

ATTACHMENTS RECEIVED

1. Annex A - BPA REACH Consortium CLH male and female endpoints 10-10-2013

submitted by:

Dow Europe GmbH (on 11/10/2013)

Momentive Specialty Chemicals B.V. (on 10/10/2013)

Bayer MaterialScience AG (on 10/10/2013)

ReachCentrum BPA Consortium (on 10/10/2013)

[Please refer to comments 19, 20, 21, 27]

2. Annex B - BPA REACH Consortium CLH information on Tyl 10-10-2013

submitted by:

Dow Europe GmbH (on 11/10/2013)

Momentive Specialty Chemicals B.V. (on 10/10/2013)

Bayer MaterialScience AG (on 10/10/2013)

ReachCentrum BPA Consortium (on 10/10/2013)

[Please refer to comments 19, 20, 21, 27]

3. Annex C - BPA REACH Consortium CLH summary NCTR-2013 10-10-2013

submitted by:

Dow Europe GmbH (on 11/10/2013)

Momentive Specialty Chemicals B.V. (on 10/10/2013)

Bayer MaterialScience AG (on 10/10/2013)

ReachCentrum BPA Consortium (on 10/10/2013)

[Please refer to comments 19, 20, 21, 27]

4. Annex D - BPA REACH Consortium CLH overview relevant studies for BPA classification 10-10-2013

submitted by:

Dow Europe GmbH (on 11/10/2013)

Momentive Specialty Chemicals B.V. (on 10/10/2013)

Bayer MaterialScience AG (on 10/10/2013)

ReachCentrum BPA Consortium (on 10/10/2013)

[Please refer to comments 19, 20, 21, 27]

5. Annex E - BPA REACH Consortium CLH review epidemiology studies described in the CLH proposal 10-10-2013

submitted by:

Dow Europe GmbH (on 11/10/2013)

Momentive Specialty Chemicals B.V. (on 10/10/2013)

Bayer MaterialScience AG (on 10/10/2013)

ReachCentrum BPA Consortium (on 10/10/2013)

[Please refer to comments 19, 20, 21, 27]

6. BPA REACH Consortium comment on CLH proposal on BPA prepared by ANSES 10-10-2013_final

submitted by:

Dow Europe GmbH (on 11/10/2013)

Momentive Specialty Chemicals B.V. (on 10/10/2013)

Bayer MaterialScience AG (on 10/10/2013)

ReachCentrum BPA Consortium (on 10/10/2013)

[Please refer to comments 19, 20, 21, 27]

7. Bisphenol classification (submitted by Italy on 11/10/2013. *Contents of attachment copied under Comment number 16*)

- 8. Proposal for harmonised classification and labelling : Bisphenol A** (submitted by Belgium on 11/10/2013) *[Please refer to comment 29]*
- 9. Comments on the proposal for harmonized classification and labeling of Bisphenol A.** (submitted by the Netherlands on 11/10/2013) *[Please refer to comments 1,15]*
- 10. Background information on new literature research of BPA by TEDX** (submitted by ChemSec on 10/10/2013) *[Please refer to comment 24]*
- 11. Bisphenol A and Human Health: A review of the literature, Accepted Manuscript** (submitted by ChemSec on 10/10/2013) *[Please refer to comment 24]*
- 12. Table 1. Studies on Bisphenol A (BPA) and Health Effects. From Rochester JR, Bisphenol A and Human Health: A review of the literature, Reproductive Toxicology (2013 in press)** (submitted by ChemSec on 10/10/2013) *[Please refer to comment 24]*
- 13. Review of the epidemiology studies described in the ANSES 2013 report on harmonized classification and labeling of Bisphenol A** (submitted by Exponent on 10/10/2013) *[Please refer to comments 9, 25]*

CONFIDENTIAL ATTACHMENT

- 14. Bisphenol A and Human Health: A review of the literature** (submitted by the European Environmental Bureau (EEB) on 11/10/2013) *[Please refer to comment 14]*