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May 13, 2010

Via Email (coshita@oehha.ca.gov) and FedEx

Joan E. Denton, Ph.D., Director
c/o Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
1001 "I" Street
Sacramento, CA 95814

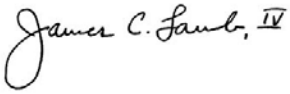
Re: Opposition to Petition for Listing of Bisphenol A Pursuant to Authoritative Bodies Mechanism of Safe Drinking Water and Toxic Enforcement Act of 1986

Dear Dr. Denton:

We were asked by the American Chemistry Council, based upon our knowledge about the potential reproductive and developmental toxicology of bisphenol A (BPA) and based on our experience with the National Toxicology Program and US EPA, to review the available data on BPA's potential developmental toxicity. We write this letter to voice our opposition to the petition by the Natural Resources Defense Council (NRDC) to list BPA as "known to the state to cause reproductive toxicity" under California's Proposition 65 (Prop 65) on the basis of concern for "high" dose developmental toxicity based on the report by NTP CERHR (National Toxicology Program Center for the Evaluation of Risks to Human Reproduction; 2008), under the Authoritative Bodies mechanism. The Authoritative Bodies mechanism of listing, however, does not absolve California from considering the sufficiency of the data in support of the proposed listing. We address in particular the issue of sufficiency of data, which the DART Committee of qualified experts has already voted is not sufficient for BPA to be listed. The statute requires that the determination of sufficiency take into account several factors, including "consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." We believe that maternal (and adult) toxicity has not been

adequately considered in this petition, and that an association in humans between adverse reproductive effects and the toxic agent in question is not plausible. We conclude that BPA should not be listed by the State of California on the basis of "high dose" developmental toxicity.

Sincerely,



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Opposition to Petition for Listing of Bisphenol A Pursuant to Authoritative Bodies Mechanism of Safe Drinking Water and Toxic Enforcement Act of 1986

We were asked by the American Chemistry Council, based upon our knowledge about the potential reproductive and developmental toxicology of bisphenol A (BPA) and based on our experience with the National Toxicology Program and US EPA, to review the available data on BPA's potential developmental toxicity. We write this letter to voice our opposition to the petition by the Natural Resources Defense Council (NRDC) to list BPA as "known to the state to cause reproductive toxicity" under California's Proposition 65 (Prop 65) on the basis of concern for "high" dose developmental toxicity based on the report by NTP CERHR (National Toxicology Program Center for the Evaluation of Risks to Human Reproduction; 2008), under the Authoritative Bodies mechanism. The Authoritative Bodies mechanism of listing, however, does not absolve California from considering the sufficiency of the data in support of the proposed listing. We address in particular the issue of sufficiency of data, which the DART Committee of qualified experts has already voted is not sufficient for BPA to be listed. The statute requires that the determination of sufficiency take into account several factors, including "consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." We believe that maternal (and adult) toxicity has not been adequately considered in this petition, and that an association in humans between adverse reproductive effects and the toxic agent in question is not plausible.

Listing of chemicals for reproductive and developmental toxicity is unique to California under Prop 65. Neither the US EPA nor the NTP CERHR, which are considered authoritative bodies by the State of California, create lists or categories of chemicals based on their types of non-cancer toxicity. The US EPA risk assessment process involves identifying the types of non-cancer toxicity produced by chemicals and derivation of reference doses (IRIS, US EPA, 2010) for the purpose of standard-setting in the context of the potential for human exposure. The process leading to the reference dose is a **hazard** evaluation process. The various risk assessment guidelines, including the developmental toxicity (US EPA, 1991) guidelines discuss the interpretation of data on specific types of toxicity or hazards, but do not propose labeling of chemicals based on their toxicity profile. The **risk** for toxicity of a chemical is based on the relationship between the reference dose and human exposure estimates. Thus, risk considers whether or not there is the potential for exposure at high enough levels to result in toxicity. Under Prop 65, chemicals are labeled for different types of toxicity based on their potential hazard rather than risk.

The NTP CERHR also does not label chemicals as such but rather provides "scientifically sound evaluations of the potential for adverse effects on reproduction or development resulting from human exposures to substances in the environment." It is not the purpose to generate lists of substances that might or might not be classified as reproductive or

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developmental toxicants, as required under California's Prop 65 (Prop 65). The Prop 65 determination cannot be made by simply extracting a sentence from the CERHR report. While the NTP CERHR is relied upon as an authoritative body by California, the underlying and different purposes of the CERHR and the California processes demands that California assess independently the sufficiency of the supporting data under its own standards, rather than relying upon a sentence taken out of context of the CERHR report. It is our understanding that this assessment in California has already been completed last year by the California Developmental and Reproductive Toxicant Identification Committee (DARTIC) whose members decided unanimously that BPA is not a developmental or reproductive toxicant.

The NTP CERHR conclusions about "weight of evidence" for effects of BPA at different dose levels (see Fig. 2b, NTP CERHR, 2008) do not take into account the maternal/adult toxicity at those levels. Specifically, in the case of the CERHR conclusion about "clear" developmental toxicity of BPA at "high" doses, the conclusion does not include the consideration that there was severe maternal/adult toxicity at these same doses, indicating the lack of specific or selective developmental toxicity for BPA, or that the dose levels at which those effects were seen are far in excess of any human exposures. In its overall conclusions, however, NTP-CERHR concluded that it has "*negligible concern* that exposure of pregnant women to BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring." This conclusion does take into account the unlikely potential for human exposures at such high dose levels.

The consideration of maternal toxicity is addressed in the US EPA developmental toxicity risk assessment guidelines (1991). The EPA guidelines discuss the various endpoints of maternal toxicity and state that "at doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level), information on developmental effects may be difficult to interpret and of limited value." The developmental effects reported in the major in vivo developmental toxicity studies on BPA are at high dose levels that cause more than minimal maternal toxicity and are far in excess of the levels at which human exposure may occur.

The NTP CERHR (2008) report was based upon the review and citation of 261 papers on toxicity and exposure to BPA. Many of the studies cited by NTP CERHR were judged as not relevant to the immediate question of the likelihood of BPA to cause developmental toxicity in humans. We have selected the most robust studies cited in that report to determine whether or not BPA can affect development in the absence of significant maternal toxicity. The two major in vivo developmental toxicity animal studies on BPA (Morrissey et al., 1987; Kim et al., 2001) and the four major reproductive toxicity studies (NTP, 1985; Tyl et al., 2002a; Tyl et al., 2002b, Tyl et al., 2008) cited in the CERHR (2008) report are reviewed here. Accompanying tables indicate those endpoints for which effects were seen, but do not detail all endpoints examined in each study. Based on this review, we have concluded that developmental effects were seen only at high dose levels that also caused severe maternal

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toxicity, are part of the pattern of general toxicity attributable to BPA at those doses, and are not specific or selective in terms of reproductive or developmental toxicity.

Developmental Toxicity Studies

Morrissey et al., 1987

In this study, time-mated CD rats were treated by gavage on gestation days (GD) 6-15 with doses of BPA at 0 (corn oil), 160, 320, or 640 mg/kg/day. Time-mated CD-1 mice were treated by gavage on GD 6-15 with doses of BPA at 0 (corn oil), 500, 750, 1000, or 1250 mg/kg/day. Rats were killed on GD20, mice on GD17, and fetuses were examined for external, visceral, and skeletal defects. The endpoints affected in this study are summarized in Table 1.

In the rat study, there were signs of significant maternal toxicity at all dose levels, including reduced maternal weight gain during treatment and gestation, as well as reduced weight gain corrected for gravid uterine weight (GUW). The latter effect, together with the fact that there were no effects on fetal body weight indicates that reduced weight gain during gestation was due to maternal toxicity. No fetal effects of any kind were seen in this study.

In mice, maternal toxicity occurred at all dose levels except controls, rising to death of 18% of animals at the highest dose. Liver weight relative to body weight was also increased at all doses, indicating maternal metabolic effects of BPA. The only fetal effects were an increase in resorptions and reduced body weight in survivors, both of which occurred only at the highest dose level, clearly a dose producing severe maternal toxicity.

Table 1. Endpoints Affected (Morrissey et al., 1987)

Group	Endpoint	Dose (mg/kg/day)				
Rats		0	160	320	640	
Maternal	Weight gain during gestation		↓12%	↓13%	↓14%	
	Weight gain corrected for GUW		↓28%	↓26%	↓34%	
	Weight gain during treatment		↓35%	↓53%	↓54%	
Fetal	None					

Table 1 (Continued). Endpoints Affected (Morrissey et al., 1987)

Group	Endpoint	Dose (mg/kg/day)				
Mice		0	500	750	1000	1250
Maternal	Maternal mortality		↑7%	↑4%	↑6%	↑18%
	Weight gain during gestation					↓32%
	Weight gain during treatment					↓43%
	Relative liver weight		↑9%	↑13%	↑17%	↑26%
Fetal	Resorptions					↑26%
	GUW					↓32%
	Fetal body weight					↓15%

Abbreviations: GUW=gravid uterine weight

Kim et al., 2001

This paper reported the effects of BPA dosing by gavage to Sprague-Dawley rats throughout gestation (GD 1-20) at doses of 0 (corn oil), 100, 300, or 1000 mg/kg. Dams were killed on GD 21, uterine contents examined, and fetuses evaluated for external, visceral and skeletal defects. The endpoints affected in this study are summarized in Table 2.

Maternal weight, weight gain, corrected weight gain and food consumption were all significantly reduced at 300 and 1000 mg/kg/day. Clinical signs were significantly increased at 300 and 1000 mg/kg/day, and included severe GI changes of the stomach, small intestine and large intestine, soft stool, diarrhea, urination and/or perineal soiling, piloerection, reddish tear, reduced locomotion, emaciation, sedation, etc. Pregnancy failure (mated animals that were not pregnant) was significantly increased only at 1000 mg/kg/day.

Fetal effects included a 5-fold increase in early resorptions, 10-fold increase in postimplantation loss, and a corresponding 36% reduction in live litter size. Fetal body weight was reduced in males at 300 and in both males and females at 1000 mg/kg/day. A related finding was a reduction at 1000 mg/kg/day in the number of ossification centers in bones developing around the time of examination.

Anogenital distance (AGD) was measured in this study and was significantly reduced in males at 300 or 1000 mg/kg/day. Females were not affected. When AGD in males was corrected by the cube root of body weight, there were no differences. The authors concluded that BPA was “not a selective reproductive or developmental toxicant in male [or female] fetuses even at a severe maternal toxic dose.”

Thus, fetal effects were seen only at doses in this study that produced severe maternal toxicity.

Table 2. Endpoints Affected (Kim et al., 2001)

Group	Endpoint	Dose (mg/kg/day)			
		0	100	300	1000
Maternal	Weight[A]			↓13%	↓19%
	Weight gain			↓35%	↓52%
	Weight gain corrected for GUW			↓14%	↓15%
	Food consumption[B]			↓24%	↓57%
	Clinical signs[D]			↑	↑
	Pregnancy failure			10%[C]	30%
Fetal	Early resorptions				↑ 5-fold
	Postimplantation loss				↑10-fold
	Litter size				↓36%
	Body weight			↓ 14% (males)	↓20/21% (males/ females)
	Ossification centers				↓8-37%[E]

[A]Weight reduced GD 7 and later at 1000 mg/kg/day, GD 14 and later for 300 mg/kg/day. Percent reductions shown for GD 21.
[B]Significant reduction at GD 4 only.
[C]Not significant; 2/20 females.
[D]See text.
[E]Depending on the bones considered, e.g., 16% reduction in ossification of 1st and 2nd phalanges in forelimbs, 37% reduction in hindlimbs; 8% reduction in ossification of metacarpals or metatarsals; 13% reduction in ossification of sternebrae.

Reproductive Toxicity Studies

Four multi-generation studies have been conducted on BPA, three in mice (Reel et al., 1985; Tyl et al., 2002a; Tyl et al., 2008) and one in rats (Tyl et al., 2002b). Although these studies involved continuous exposure over two or more generations, rather than prenatal-only exposure, they provide support for the conclusion that developmental effects occur only at maternally toxic levels and that BPA is not specific or selective for developmental toxicity.

Reel et al., 1985

This study used the NTP Reproductive and Fertility Assessment by Continuous Breeding protocol which involved 4 tasks and are described below. The endpoints affected in this study are summarized in Table 3.

- Task 1 was the dose-finding phase involving male and female CD-1 mice treated for 14 days with 5 doses of BPA ranging from 0.31-5.0% in feed. BPA at 2.5 or 5.0%

caused severe clinical signs of toxicity and three-fourths of the animals in the 5.0% group died. The data from Task 1 were used to set the dose levels for Task 2.

- Task 2 was the continuous breeding (cohabitation) phase and involved exposing males and females of CD-1 mice for 1 week, then mating pairs for 13 weeks to 0, 0.25, 0.5 or 1.0% BPA, and a during a 3 week separation period for delivery of the last litter. Although not reported specifically, it appears from the tables in the report that F0 body weights were reduced at 0.5% and 1.0% by the end of the cohabitation period. Postpartum maternal weight was significantly reduced in the 1.0% dams. The ability of F0 mating pairs to produce a single litter was not affected, but the cumulative days to produce a litter was increased at 1.0% and the mean number of litters /pair and the number of live pups/litter was reduced at both 0.5% and 1.0%.

- Task 3 involved a cross-over mating of control and high dose (1.0% BPA) males and females. Three combinations of breeding pairs were included: control females x control males, control females x 1.0% males, and 1.0% females x control males. The number of live pups/litter was reduced in the control female x 1.0% male group. In the 1.0% female x control male group, the number of pups and number of live pups was significantly less than in the control x control group or the control female x 1.0% male group. There was an increase in F1 pup mortality before weaning at 1.0% BPA.

  When control and 1.0% F0 animals were killed after Task 3, body weights of females in the 1.0% group were significantly reduced and both males and females showed increased absolute and relative liver and kidney weights and histopathological changes in liver (males: centrilobular hepatocytomegaly, multifocal necrosis and multinucleated giant hepatocytes; females: multifocal necrosis, multinucleated giant hepatocytes) and kidney (both sexes: tubular cell nuclear variability and amplification of normally-occurring tubular and interstitial lesions; females: large microcalculi in the cortical tubules, tubular regeneration and/or dilated tubules containing proteinacious or slightly pigmented tubular casts). In addition, seminal vesicle weight was reduced in males, as was sperm motility.

- Task 4 involved an evaluation of the F1 offspring, as adults. Selected males and females were raised to 74 $\pm$ 10 days of age, then a male and female from different litters but within treatment groups were paired for 7 days. After the 7-day cohabitation period, pairs were separated and females allowed to deliver their litters. F2 pups were counted, sexed and weighed, then discarded. F1 males and females were killed and evaluated three weeks after the 7 day cohabitation period.

  There were no effects on mating, the production of F2 litters, litter size, or pup weight. However, liver and kidney weights were significantly increased at all dose levels, and liver and kidney histopathology was seen in both sexes at all doses,

> except for liver histopathology at 0.25% in females. In addition, seminal vesicle and right epididymal weights were reduced in males at all dose levels. Sperm counts were reduced at all dose levels up to 18% in the 1.0% BPA group, but were not significantly different from controls and did not affect reproductive function.

The complexity of this study design and the limitations in terms of incomplete evaluation of adult toxicity at all dose levels, particularly in the F0 generation, makes interpretation of these data somewhat difficult. However, it is clear that there was severe toxicity in F0 adults at 1.0% BPA (the only dose group evaluated) after the cross-over mating in Task 3, and that F1 animals exhibited significant toxicity at all 3 dose levels. Effects on litter size, number of live pups and survival were seen at 0.5% and 1.0% in the F0 mating pairs (Task 2) and are likely part of the general pattern of BPA toxicity at these exposure levels.

Table 3. Endpoints affected by BPA exposure (Reel et al., 1985)

Group	Endpoint	Dose (%)			
		0	0.25 (437.5 mg/kg/d)	0.5 (875 (mg/kg/d)	1.0 (1750 mg/kg/d)
F0 (Task 2)	Postpartum dam weights				↓ 8-9%
	Cumulative days to litter				↑ 10%
	Mean # Litters/pair			↓ 5%	↓ 9%
	# Live pups/litter			↓ 20%	↓ 48%
BPA-M x C-F (Task 3)	# pups				↓ 25 %
BPA-F x C-M (Task 3)	# live pups				↓ 51%
F0 M (end of Task 3 – only controls and 1.0% evaluated)	Liver weight Liver histopathology Kidney weight Kidney histopathology Seminal vesicle weight (adj) [A] Sperm motility				↑ 29% ↑ ↑ 16% ↑ ↓ 19% ↓ 39%
F0 F (end of Task 3 – only controls and 1.0% evaluated)	Body weight Liver weight (adj) [A] Liver histopathology Kidney weight (adj) Kidney histopathology				↓ 4% ↓ 27% ↑ ↓ 10% ↑
F1 pups	Mortality before weaning				↑ (stat sign)
F1 M (end of Task 4)	Liver weight (adj) [A] Liver histopathology Kidney weight (adj)[A] Kidney histopathology Right epididymal weight Seminal vesicle weight Sperm counts		↑ 7% ↑ ↑ 16% ↑ ↓ 7% ↓ 11%	↑ 7% ↑ ↑ 20% ↑ ↓ 16% ↓ 10% (NS)	↑ 9% ↑ ↑ 20% ↑ ↓ 18% ↓ 28% ↓ 18% (NS)
F1 F (end of Task 4)	Liver weight (adj) [A] Liver histopathology Kidney weight (adj) [A] Kidney histopathology		↑ 6% ↑ 13% ↑	↑ 13% ↑ ↑ 15% ↑	↑ 20% ↑ ↑ 13% ↑
F2	No effects				

Abbreviations: C-M=control males, C-F=control females, F=females, M=males

[A] Adjusted for body weight

Tyl et al., 2002a

This abbreviated one-generation study was conducted in CD-1 mice exposed to 0, 5000 (0.5%) or 10,000 (1.0%) ppm in the diet beginning 2 weeks before mating, 1 week during mating, and throughout gestation. The purpose of this study was to duplicate the basic design components of the Reel et al. (1985) study using a more standard one-generation design and to include a more enhanced evaluation of parental toxicity. Males were necropsied after mating and females and their litters were necropsied after parturition (PND 0).

Toxicity to the F0 males and females was evident at both BPA exposure levels with increases in liver and kidney weights (See Table 4). In addition, F0 maternal animals had reduced body weight, weight gain, food consumption and food efficiency, as well as a slight prolongation of gestation length (10 hours in both exposure groups). At necropsy, F0 females were found to have significant liver and kidney histopathology, and changes in clinical chemistries at both doses. Reductions in pup numbers and live litter size were evident only at the higher dose level.

Data from this study support the conclusion that litter effects occurred only in the presence of severe maternal toxicity. In the Reel et al. (1985) study, there were also litter effects at 0.5%, but the exposure period in that study was much longer (>98 days versus only 5-6 weeks in this study).

Table 4. Endpoints Affected (Tyl et al., 2002a)

Group	Endpoint	Dose (ppm)		
		0	5000 (0.5%) (F 968 PB, 841 G; M 760 PB mg/kg/d)	10,000 (1.0%) (F 1932 PB, 1661 G; M 1518 PB (mg/kg/d)[A]
F0	Absolute & relative liver weight Absolute & relative kidney weight		↑ ↑ (relative weight – F only)	↑ ↑ (absolute weight - F only)
Pregnant F	Weight		↓	↓
	Weight gain		↓	↓
	Food consumption Food Efficiency		↓ ↓	↓ ↓
	Prolonged gestation		↑	↑
F0 F (M not evaluated)	Liver pathology Kidney pathology		Hepatocellular hypertrophy Tubular epithelial degeneration, necrosis, regeneration	Hepatocellular hypertrophy Tubular epithelial degeneration, necrosis, regeneration
	Clinical chemistries		↓ Na, K, Cl	↑ BUN
F1	Total pups/litter			↓
	Live pups/litter			↓

Abbreviations: PB = pre-breed, G = gestation, M = male, F = female

Tyl et al., 2008

This two-generation study in CD-1 mice evaluated the effects of BPA dietary administration at levels of 0, 0.018, 0.18, 1.8, 30, 300, and 3500 ppm (0.003 – 600 mg/kg/day). Animals were exposed for 8 weeks, then mated over a period of 14 days. Pregnant females were individually housed and allowed to deliver. After weaning, pups were selected to raise and mate for production of an F2 generation. Exposure continued for 8 weeks prior to breeding of the F1 animals. F2 pups were examined and necropsied at PND 21. The endpoints affected in this study are summarized in Table 5.

Adult systemic toxicity in the F0 animals included centrilobular hepatocyte hypertrophy at 300 and 3500 ppm, renal nephropathy in males only at 3500 ppm, and reduced body weight, increased kidney and liver weight at 3500 ppm. Gestation length was slightly but significantly delayed (0.3 days) in both the F0 and F1 maternal animals. Effects on reproduction and offspring were seen only at 3500 ppm and included reduced weanling body weight, spleen and testis weight, delayed preputial separation and undescended

testes in weanlings. The effects on reproductive organs did not result in adverse effects on adult reproductive structures or functions, so were considered a developmental delay.

Table 5. Endpoints Affected (Tyl et al., 2008)

Group	Endpoint	Dose – ppm (mg/kg/day)						
		0	0.018 (0.003)	0.18 (0.03)	1.8 (0.3)	30 (5)	300 (50)	3500 (600)
F0	Weight							↓
	Kidney, liver weights							↑
	Centrilobular hepatocyte hypertrophy						↑	↑
	Renal nephropathy – males only							↑
F0, F1	Gestation length							↑ (0.3 days)
F1, F2	Weanling body weight							↓
	Weanling spleen, testis weight							↓
	Preputial separation							Delayed
	Undescended testes - weanling							↑

Conclusions regarding BPA developmental toxicity in mice:

From the four studies conducted in CD-1 mice, it appears that adult toxicity occurred at doses as low as 500 mg/kg/day after prenatal exposure (Morrissey et al., 1985) or 50 mg/kg/day in a two-generation reproduction protocol (Tyl et al., 2008). Developmental toxicity in mice occurred only at doses that also produced severe maternal and adult toxicity (1250 mg/kg/day in the prenatal exposure study, and 600 mg/kg/day in the two-generation study).

Tyl et al., 2002b

A three-generation study was conducted in CD Sprague-Dawley rats administered BPA at dietary concentrations of 0, 0.015, 0.3, 4.5, 75, 750, or 7500 ppm (0.001 – 500 mg/kg/day). In this study, the pre-breeding exposure period was 10 weeks for the F0, F1 and F2 generations. F3 offspring were maintained until adulthood. The endpoints affected in this study are summarized in Table 6.

Adult systemic toxicity included reduced body weight and weight gain, reduced absolute and increased relative weanling and adult organ weights (liver, kidneys, adrenals, spleen, pituitary, and brain) at 750 and 7500 ppm. Females showed slight/mild renal and hepatic pathology at 7500 ppm. Relative ovarian weights were reduced in F0, F1, and F2 females, as were the number of implants, number of pups, and number of live pups/litter on PND 0 and PND 4. On PND 7, 14 and 21, the weight of F1, F2, and F3 pups/litter was reduced. In male offspring, epididymal sperm concentration was reduced in F1s and daily sperm production was reduced in F3s at 7500 ppm.

Table 6. Endpoints Affected (Tyl et al., 2002b)

Group	Endpoint	Dose – ppm (mg/kg/day)						
		0	0.015 (0.001)	0.3 (0.02)	4.5 (0.3)	75 (5)	750 (50)	7500 (500)
F0, F1, F2, F3	Weight, weight gain						↓	↓
	Absolute liver, kidney, adrenal, spleen, pituitary, brain weights						↓	↓
	Relative organ weights						↑	↑ (or unaffected)
F0, F1, F2 F	Slight/mild renal & hepatic pathology							↑
	Relative ovarian weight							↓
F1 M	Epididymal sperm concentration							↓
F3 M	Daily sperm production							↓
F1, F2, F3 offspring	# implants, # pups, live pups/litter PND0 & PND 4							↓
F1, F2, F3 pups	Weight/litter on PND 7, 14, 21							↓
F1, F3 F	Vaginal patency (adj)[A]							↓
F1, F2, F3 M	Preputial separation (adj) [A]						↓ (F1)	↓ (F2, F3)

Abbreviations: M = male, F = female
[A] Adjusted for body weight

Conclusions regarding BPA developmental toxicity in rats:

The rat studies reviewed indicated that maternal/adult toxicity occurred at doses as low as 160 mg/kg/day in the prenatal developmental toxicity study (Morrissey et al., 1987) or 50 mg/kg/day in a three-generation protocol (Tyl et al., 2002b). There were no developmental effects reported in the prenatal developmental toxicity study. In the three-generation study, developmental effects occurred at 500 mg/kg/day, except for delays in preputial separation in the F1 males, which were reduced at 50 mg/kg/day.

Overall Conclusions

The NRDC petition requests the addition of BPA to California's list of Prop 65 chemicals "known to the state to cause reproductive toxicity." The petition is based upon the NTP CERHR report on BPA that was published in 2008. Certain statements have been cited from that report in an attempt to support the petition, though they rely entirely upon effects from excessively high exposures that also caused severe maternal toxicity. The reliance on the CERHR document and on the NTP CERHR as an authoritative body overlooks the requirement to consider the sufficiency of the data. Having reviewed the data underlying the CERHR report, we conclude that BPA should not be listed by the State of California on the basis of "high dose" developmental toxicity. Listing on this basis would raise questions about a number of chemicals that show developmental effects only in the presence of maternal/adult toxicity, and ignores the importance of both general toxicity and the plausibility of such high exposures in humans in drawing conclusions about concern.

We have reviewed the critical studies cited by the NTP CERHR report and have summarized the key findings above. In every case, effects on offspring seen were at dose levels that also produced maternal/adult systemic toxicity greater than what would be considered minimal toxicity. In addition, the levels of exposure at which the maternal/adult toxicity and reproductive and developmental toxicity occurred are far above those exposure levels that might plausibly occur in humans. We believe that the developmental effects reported as a result of BPA exposure are part of the pattern of general toxicity caused by BPA and are not specific or selective for developmental toxicity.

We do not believe the data provide sufficient evidence of developmental toxicity, even at high doses of BPA, due to the degree of maternal/adult toxicity at the same dose levels. Therefore, it is inappropriate to list BPA under Prop 65 as a developmental toxicant in any case, and particularly on the basis of "high dose" effects because the effects seen are part of a general pattern of overall toxicity.

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Authors

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Dr. Carole A. Kimmel is a Senior Managing Scientist in Exponent's Health Sciences Center for Toxicology and Mechanistic Biology. She has 40 years experience in reproductive and developmental toxicology, children's environmental health, and risk assessment, and is an internationally recognized expert in these areas. She led the National Toxicology Program's Reproductive and Developmental Toxicology Program from 1980 to 1984, and was the project officer for the contract with Research Triangle Institute under which the developmental toxicity study on bisphenol A was conducted. From 1984 to 2004, she was a Senior Scientist in the National Center for Environmental Assessment, US EPA, where she worked on advances in risk assessment approaches and development of risk assessment guidelines for non-cancer health effects, particularly reproductive and developmental toxicity and neurotoxicity risk assessment. Her leadership in developing the U.S. EPA *Guidelines for Developmental Toxicity Risk Assessment* is particularly relevant to the issues in this review.

Dr. Kimmel was on the organizing panel that led to the creation of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR), and served as a Board member for several years. She has also served on expert panels for the National Academy of Sciences/National Research Council to evaluate health and safety issues related to environmental contaminants. Dr. Kimmel is Past President of the Teratology Society, the Neurobehavioral Teratology Society, and the Reproductive and Developmental Toxicology Specialty Section of the Society of Toxicology. She has published 175 research manuscripts, reviews and book chapters, and edited several books and proceedings.

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Dr. James C. Lamb is a Principal Scientist and the Director of Exponent's Health Sciences Center for Toxicology and Mechanistic Biology. He has over 30 years experience in toxicology, risk assessment, and scientific and regulatory policy. Dr. Lamb was the Head of the Fertility and Reproduction Group at the National Toxicology Program (NTP), where he led the NTP project on the Fertility Assessment by Continuous Breeding which included the study of bisphenol A.

Dr. Lamb was also on the organizing panel that led to the creation of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR). Dr. Lamb served on several National Academy of Sciences committees on risk assessment, endocrine disruption, and toxicology. He served as President of the American Board of Toxicology, is on the Board of the Academy of Toxicological Sciences and has served in many leadership positions in the Society of Toxicology. He has been an Associate Editor of the

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