April 10, 2013

Via e-mail to: P65Public.Comments@oehha.ca.gov

Ms. Monet Vela
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-23B
Sacramento, CA 95812-4010

Re: Comments on Notice of Proposed Rulemaking – BPA MADL

Dear Ms. Vela:

On behalf of the Polycarbonate/BPA Global Group of the American Chemistry Council[1] (ACC), I am submitting these comments in response to OEHHA's Notice of Proposed Rulemaking regarding the proposed Maximum Allowable Dose Level (MADL) for bisphenol A (BPA). The Polycarbonate/BPA Global Group consists of the leading global manufacturers of BPA and polycarbonate plastic, which for many years have supported and conducted scientific research to understand whether BPA has the potential to cause health or environmental effects and to support scientifically sound public policy.

These comments address the proposed MADL, but should not be construed in any way to signify agreement with the proposed listing of BPA as known to cause reproductive toxicity via the authoritative bodies mechanism under Proposition 65. We have separately submitted comments in response to the Notice of Intent to List BPA and have recently filed a complaint for declaratory and injunctive relief against such listing in Superior Court.

[1] The American Chemistry Council represents the leading companies engaged in the business of chemistry. Council members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. The Council is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $435 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector.

Please do not hesitate to contact me if I can be of further assistance to clarify any comments or if additional information is needed. If it would be helpful, we would also be willing to meet with OEHHA staff to discuss our comments. I can be reached at (202) 249-6624 or by e-mail at steve_hentges@americanchemistry.com.

Respectfully submitted,

Steven G. Hentges, Ph.D.
Polycarbonate/BPA Global Group

Attachment

COMMENTS OF THE POLYCARBONATE/BPA GLOBAL GROUP ON OEHHA'S PROPOSED MADL FOR BPA

April 10, 2013

Summary

The Initial Statement of Reasons to establish a maximum allowable dose level (MADL) for BPA relies on a limited number of high-dose studies identified in a National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (NTP) report on BPA. In particular, OEHHA proposes to base the MADL on developmental toxicity data from two multi-generation studies on rats and mice. Reliance on high-dose studies to establish a MADL and, in particular, on the two multi-generation studies is consistent with the proposed listing of BPA as causing reproductive toxicity. Other studies, in particular numerous low-dose studies reviewed in the NTP report, are not appropriate for this purpose because they are not the basis for the proposed listing of BPA.

However, the results from the high-dose studies do not support OEHHA's proposed MADL. OEHHA has incorrectly assigned the no observed effect level (NOEL) from these studies as 5 mg/kg-day. For both of the key multi-generation studies, the correct NOEL for developmental effects is 50 mg/kg-day. Furthermore, benchmark dose (BMD) methodology is both authorized by the Proposition 65 regulations and provides a superior method for determining a no effect level. For the endpoints identified by OEHHA as the most sensitive developmental effects, BMD values range from 163-572 mg/kg-day.

Taken as a whole, the scientific evidence indicates that the MADL for BPA should be at least a factor of 10 higher than the level proposed by OEHHA. Based on the actual NOEL values taken directly from the two multi-generation studies (50 mg/kg-day) and the lowest BMD value (163 mg/kg-day), a scientifically appropriate MADL ranges from 2,900 to 9,454 micrograms per day. A MADL value that is higher than the one proposed by OEHHA is further supported by the significant differences in the pharmacokinetics of BPA in rodents and primates. These pharmacokinetic differences indicate that a given dose of BPA is less likely to cause developmental effects in primates than in rodents. OEHHA's calculations do not reflect this well-recognized and important species difference.

1. The MADL Must Be Based on the NOEL for Reproductive Effects From High-Dose Studies Identified by NTP

a. OEHHA's Proposed Listing of BPA is Based Solely on High-Dose Studies

As described in the Notice of Intent to List BPA, and reiterated in the Initial Statement of Reasons to establish a MADL, the proposed listing of BPA as causing reproductive toxicity is

based on developmental toxicity data from certain studies described in an NTP report on BPA.[1] Specifically, the NTP report identified eight studies that reported data on developmental effects at "high" doses.[2] The data from these eight studies are cited by OEHHA as the basis for the proposed listing of BPA as causing reproductive toxicity, and as the basis for the proposed MADL.

Although the NTP report reviewed other reproductive and developmental toxicity studies on BPA, in particular studies that examined "low" doses, only the eight high-dose studies relied on by OEHHA are potentially appropriate for derivation of a MADL. The selection of studies for determination of a "no observable effect level" (NOEL), from which the MADL is calculated, is specified by California Code of Regulations Title 27, Section 25803(a)(1):

> "Only studies producing the reproductive effect which provides the basis for the determination that a chemical is known to the state to cause reproductive toxicity shall be utilized for the determination of the NOEL."

In contrast, the low-dose studies reviewed by NTP examined different endpoints or effects than those reported in the high-dose studies. Because the low-dose studies did not provide the basis for the proposed listing, they may not be used for determining the NOEL, which is used in calculating the MADL. In addition, Section 25803(a) provides:

> "The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause reproductive toxicity."

The low-dose studies are not sufficient to support listing BPA under Proposition 65, and were not cited by OEHHA as the basis for listing, and, thus, are also not suitable for establishing a NOEL or MADL.

b. The NOEL Used to Calculate the MADL Must Be Based on Reproductive Effects

As specified by California Code of Regulations Title 27, Sections 25801 and 25803, the NOEL for Proposition 65 purposes must refer to reproductive effects, which, as defined by Proposition 65, also includes developmental effects:

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[1] National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2008). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08-5994.

[2] The developmental effects reported in these studies are fetal death, decreased litter size, or decreased number of live pups per litter in rats and mice, reduced growth in rats and mice, and delayed puberty in male mice, male rats and female rats.

> "For purposes of this article, "NOEL" shall mean that no observable effect level, which is the maximum level of exposure at which a chemical has no observable reproductive effect." (Section 25801(c), emphasis added by underline)

> "The NOEL shall be the highest exposure level which results in no observable reproductive effect …" (Section 25803(a)(2), emphasis added by underline)

It is not unusual for studies to determine separate NOELs for reproductive and developmental effects as well as other effects that might be observed, in particular systemic toxicity that does not affect reproduction or development. In such cases, the appropriate NOEL under Proposition 65 is the one that applies to reproductive or developmental effects, as specified in the excerpts from California's regulations above.

2. The Correct NOEL for Developmental Effects From Scientific Studies Is No Lower Than 50 Mg/Kg-Day and Results in a Significantly Higher MADL

The Initial Statement of Reasons relies on two multi-generation studies (Tyl *et al.*, 2002b[3] and Tyl *et al*., 2008[4]) to establish a NOEL for calculating the proposed MADL. These two studies provide comprehensive sets of data covering reproductive and developmental endpoints in both rats and mice. In both studies, the NOEL for developmental effects is no lower than 50 mg/kg-day, not 5 mg/kg-day as reported by OEHHA.

a. The Developmental Effects NOEL From Tyl *et al*. (2008) Is No Lower Than 50 Mg/Kg-Day

The Tyl *et al.* (2008) study is a 2-generation study in mice that examined a wide range of doses from approximately 0.003 to 600 mg/kg-day. As stated by the authors of this study, the NOEL for developmental toxicity is 50 mg/kg-day:

> "The systemic no observable effect level (NOEL) was 30 ppm BPA (~5 mg/kg/day); the reproductive/developmental NOEL was 300 ppm (~50 mg/kg/day). Therefore, BPA is not considered a selective reproductive or developmental toxicant in mice."[4]

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[3] Tyl, R.W., Myers, C.B., Marr, M.C., Thomas, B.F., Keimowitz, A.R., Brine, D.R., Veselica, M.M., Fail, P.A., Chang, T.Y., Seely, J.C., Joiner, R.L., Butala, J.H., Dimond, S.S., Cagen, S.Z., Shiotsuka, R.N., Stropp, G.D., and Waechter, J.M. 2002. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicological Sciences. 68(1):121-146.

[4] Tyl, R. W., Myers, C. B., Marr, M. C., Sloan, C. S., Castillo, N. P., Veselica, M. M., Seely, J. C., Dimond, S. S., Van Miller, J. P., Shiotsuka, R. N., Beyer, D., Hentges, S. G., and Waechter, J. M. 2008. Two-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD-1® (Swiss) mice. Toxicological Sciences. 104(2):362-384.

The reported NOEL for adult *systemic* toxicity (not developmental toxicity) is 5 mg/kg-day. These values were confirmed in OEHHA's Notice of Intent to List BPA, which reported a lowest observed adverse effect level (LOAEL) of 600 mg/kg-day for developmental toxicity (and systemic maternal toxicity) based on the Tyl et al. (2008) study. Because the next lower dose in this study was 50 mg/kg-day, that is the NOEL for developmental toxicity reported in the study.[5]

Based on the 50 mg/kg-day NOEL from the Tyl *et al.* (2008) study and the formula used by OEHHA, the calculated MADL is 2,900 micrograms/day.

b. The Developmental Effects NOEL for Tyl *et al.* (2002b) Is No Lower Than 50 Mg/Kg-Day

The Tyl *et al.* (2002b) study is a 3-generation study in rats that examined a wide range of doses from approximately 0.001 to 500 mg/kg-day. As stated by the authors of this study, the NOAEL for developmental toxicity is 50 mg/kg-day:

> "Adult systemic no observed adverse effect level (NOAEL) = 75 ppm (5 mg/kg/day); reproductive and postnatal NOAELs = 750 ppm (50 mg/kg/day). There were no treatment-related effects in the low-dose region (0.001–5 mg/kg/day) on any parameters and no evidence of nonmonotonic dose-response curves across generations for either sex. BPA should not be considered a selective reproductive toxicant, based on the results of this study."[3]

The reported NOAEL for adult *systemic* toxicity (not developmental toxicity) is 5 mg/kg-day. The reported NOAEL for developmental toxicity is 50 mg/kg-day.

In contrast, OEHHA's Notice of Intent to List BPA reports a LOAEL of 50 mg/kg-day for developmental toxicity, specifically increases in the age of sexual maturation for both males and females, which implies a NOAEL of 5 mg/kg-day for developmental toxicity. OEHHA's position, however, is not supported by the study results.

In particular, the Notice of Intent to List relies upon reported increases in the age of vaginal opening and age of preputial separation in the F1 generation with a LOAEL of 50 mg/kg/day. However, as discussed in detail by Tyl *et al.* (2002b), delays in sexual maturation are most likely caused by reduced body weight. When age of acquisition of puberty was analyzed with body weight as a co-variant, there were no consistent differences attributable to

[5] Moreover, we question whether the offspring effects observed at the 600 mg/kg-day dose are developmental effects as defined by Proposition 65. Under Proposition 65, developmental effects must be due to prenatal exposure. However, the Tyl *et al.* (2008) study involved both prenatal and *postnatal* exposure. As described in the Notice of Intent to List BPA, the developmental effects reported at 600 mg/kg-day were decreased pup body weight at PND 7, 14 and 21 and delayed preputial separation. Systemic toxicity in the form of reduced body weight is consistent with postnatal exposure to a high dose of BPA, and the slight delay in preputial separation was attributed by Tyl *et al.* (2008) to reduced body weight. Regardless of whether the reported effects qualify as developmental effects under Proposition 65, the NOEL for Tyl *et al.* (2008) can be no lower than 50 mg/kg day.

treatment below the highest dose of 500 mg/kg-day. As reported in Tyl *et al.* (2002b), there was no effect on age of vaginal opening in any generation at 50 mg/kg-day. For males, a slight delay in age of preputial separation was reported in the F1 generation only. Because this effect was not replicated across the three generations examined in this study, the study authors determined that the no effect level was 50 mg/kg-day.[6]

Based on a 50 mg/kg-day NOEL from the Tyl *et al.* (2002b) study and the formula used by OEHHA, the calculated MADL is 2,900 micrograms/day.

c. A NOEL of 50 Mg/Kg-Day Based on the Tyl *et al*. (2002b and 2008) Studies Has Been Confirmed by Regulatory Agencies Worldwide

The Tyl *et al*. (2002b and 2008) studies have been independently reviewed by multiple regulatory agencies worldwide as part of their assessments of BPA. In each of those assessments, it was determined that the NOEL for developmental effects is 50 mg/kg-day. These agencies include the U.S. Food and Drug Administration,[7,8] the European Food Safety Authority,[9] the European Union,[10] and the Japanese National Institute of Advanced Industrial Science and Technology.[11,12]

In sum, the two comprehensive multi-generation studies by Tyl *et al*. (2002b and 2008) cited in the Initial Statement of Reasons as the basis for the MADL have NOELs for developmental effects no lower than 50 mg/kg-day and do not support OEHHA's use of a NOEL of 5 mg/kg-day.

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[6] Moreover, as with the two-generation study in mice discussed above (Tyl *et al*., 2008), we question whether the effects on body weight and age of acquisition of puberty are developmental effects as defined by Proposition 65. These effects are more likely the result of postnatal exposure, with reduced body weight being a systemic effect from high postnatal doses of BPA, and effects on age of puberty being the result of reduced body weight. Regardless of whether the reported effects qualify as developmental effects under Proposition 65, the NOEL for Tyl *et al.* (2002b) can be no lower than 50 mg/kg day.

[7] FDA memorandum Shackelford/Twaroski, 06/24/2007: Review of Two-Generation Reproductive Toxicity Evaluation of Bisphenol A Administered in the Feed to CD-1® Swiss Mice; RTI study number (Study number 65C-09301.000.003/0209301.000.003)

[8] FDA memorandum Gu/Twaroski, 07/18/2007: Review of study entitled "Three-Generation Reproductive Toxicity Evaluation of Bisphenol A in the Feed of CD® (Sprague-Dawley) Rats." RTI study number 65C-07036-000.

[9] See http://www.efsa.europa.eu/en/topics/topic/bisphenol.htm.

[10] European Union Risk Assessment Report – 4,4'-isopropylidenediphenol (Bisphenol-A). Available at http://echa.europa.eu/documents/10162/c6a8dcfc-1823-4d31-8a24-2c1168f0d217.

[11] Bisphenol A Risk Assessment Document. English version available at http://unit.aist.go.jp/riss/crm/mainmenu/e_1-10.html.

[12] Updated Hazard Assessment of Bisphenol A. English version available at http://www.aist-riss.jp/main/modules/product/index.php?content_id=73&ml_lang=en.

3. Benchmark Dose Methodology Is Appropriate to Establish a NOEL for BPA and Results in a Significantly Higher MADL

a. Benchmark Dose Methodology Is Authorized Under Proposition 65

According to California Code of Regulations Title 27, Section 25803(a)(2), the NOEL may be taken directly from scientific studies or calculated with generally accepted scientific methodology:

> "The NOEL shall be the highest exposure level which results in no observable reproductive effect expressed in milligrams of chemical per kilogram of bodyweight per day. This may be the no observed effect level in a scientific study or, alternatively, may be calculated by means of a generally accepted scientific methodology such as the benchmark dose methodology."

The benchmark dose (BMD) methodology is well-suited for calculating a NOEL for reproductive effects and, therefore, should be utilized in such matters because it better informs decision-making.[13,14] This point has been noted by the U.S. Environmental Protection Agency, which has been involved with the development and application of BMD methodology for many years:

> "The benchmark dose (BMD) approach … incorporates and conveys more information than the No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect level (LOAEL) process traditionally used for noncancer health effects."[13]

b. Benchmark Dose Methodology Provides a Scientifically Appropriate and More Accurate Estimate of the NOEL Based on the Tyl *et al.* (2002b and 2008) Studies

The Tyl *et al.* (2002b and 2008) studies are based on comprehensive and rigorous experimental designs, with each study including a dose range spanning nearly six orders of magnitude. Limiting the developmental effects NOEL assignment to only dose-specified values fails to take advantage of the superior BMD methodology for establishing a more accurate estimate of the no effect level. The NOEL values taken directly from the Tyl *et al.* (2002b and 2008) studies are somewhat uncertain due to issues around pre-selected and fixed dose spacing and the fact that monotonic changes in reproductive and developmental parameters do not begin until well after the 50 mg/kg-day dose level. Because of the dose-spacing and the high-dose (*e.g.*, 500-600 mg/kg-day) biological response to BPA, there exists significant uncertainty in

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[13] Benchmark Dose Technical Guidance. Risk Assessment Forum. EPA/100/R-12/001. June 2012.

[14] European Food Safety Authority. Scientific Opinion. Use of the benchmark dose approach in risk assessment. Guidance of the Scientific Committee. The EFSA Journal. 1150:1-72.

simply selecting a NOEL based only on the nominal dose levels. The true point of departure probably lies between the no effect and the adverse effect dose levels recorded in the studies. As explained by EFSA "[t]he BMD approach is of particular value for [such] situations where the identification of a NOAEL is uncertain . . . .".[14]

c. Benchmark Dose Values Are Included in the NTP Report

Recognizing the value of BMD methodology, the NTP expert panel calculated BMD values for key studies, including the Tyl *et al*. (2002b and 2008) studies. These values are summarized in the table below for the developmental endpoints with the lowest LOAELs identified in the Notice of Intent to List.

	Dose (mg/kg-day)			
Endpoint	**BMD_{10}**	**$BMDL_{10}$**	**BMD_{1SD}**	**$BMDL_{1SD}$**
Tyl *et al*. (2002b)				
F1 Age of vaginal opening	394	343	206	176
F1 Age of preputial separation	466	411	188	163
Tyl *et al*. (2008)				
Pup body weight, PND 7	560	313	582	407
Pup body weight, PND 14	585	382	617	506
Pup body weight, PND 21	548	267	580	370
Age of preputial separation, F1 parental males	754	576	551	414
Age of preputial separation, F1 retained males	727	572	491	364

As shown in the table above, the NTP report provided two BMD estimates:

1. BMD based on a 10% response rate (BMD_{10}/$BMDL_{10}$)
2. BMD 1-Standard Deviation based on the point of departure that differs from the controls (BMD_{1SD}/$BMDL_{1SD}$).

The "L" in both estimates stands for the lower confidence interval for the BMD estimate and typically extends the BMD estimate below the no effect level.

Typically, the BMD is set at a specified benchmark response rate and is employed for quantal data. If the $BMDL_{10}$ estimates are selected, the points of departure for the developmental endpoints are in the range of 267-572 mg/kg-day. Because the developmental endpoints occur over a range of days, a continuous approach provided by the $BMDL_{1SD}$

estimates is appropriate. Because the highest BPA dose just begins to enter the monotonic range, and the maximal response upon which a benchmark response rate depends has not been achieved, the $BMDL_{1SD}$ may be superior in that it is based on the control and no-effect responses. If the $BMDL_{1SD}$ estimates are selected, the points of departure for the developmental endpoints are in the range of 163-506 mg/kg-day. Finally, as an added measure of conservatism, all of the BMD/BMDL estimates are corroborated by 4 to 5 dose levels below the estimated points of departure where no changes in reproductive or developmental parameters were observed.

Based on the lowest BMD value of 163 mg/kg-day and the formula used by NTP, the calculated MADL is 9,454 micrograms/day.

4. Pharmacokinetic Differences Between Rodents and Primates Provide Further Support for a Higher MADL

a. Consideration of Pharmacokinetic and Metabolic Information Is Authorized Under Proposition 65 and Justified in the Case of BPA

According to California Code of Regulations Title 27, Section 25803(a)(7), the assessment for determination of a NOEL may consider additional relevant data:

> "When available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment."

Of particular relevance for BPA are the extensive pharmacokinetic data generated by a comprehensive set of studies recently conducted by the U.S. Food and Drug Administration (FDA). These data are relevant for consideration because they highlight distinct differences between rodents and primates. The developmental toxicity data that are used to determine a NOEL are entirely derived from studies on rodents (*i.e.*, rats and mice), but the MADL is intended to provide a threshold level for human exposure. Physiological differences between rodents and humans should be considered because they could support adjusting the MADL up or down from the level calculated from a NOEL derived from rodent toxicity data.

b. BPA Is Metabolized More Efficiently and Cleared Faster by Primates as Compared to Rodents, Which Supports a Higher NOEL

Detailed pharmacokinetic studies in Sprague-Dawley rats[15] and rhesus monkeys[16] have been conducted during pregnancy, which is the relevant exposure time period for developmental

[15] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., Brown, R. P., and Fisher, J. W. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. Toxicology and Applied Pharmacology. 255(3):261-270.

toxicity under Proposition 65. A key finding from these studies is that BPA is more rapidly cleared from monkeys compared to rats due to the presence of enterohepatic recirculation in rodents. In rodents, most BPA is eliminated from the liver via bile to the gastrointestinal tract, where it is reabsorbed for repeated passes through the body before eventual elimination from the body. In contrast, monkeys rapidly eliminate BPA through urine, which precludes the possibility of prolonged internal exposure because BPA passes through the body only once with no possibility of reabsorption. As a result, the clearance of BPA takes longer in rodents than in primates. It is well known that humans also eliminate BPA entirely through urine, with no possibility of enterohepatic recirculation.[17]

The findings in pregnant animals are very similar to the findings in a parallel set of studies on non-pregnant adult rats[18] and monkeys.[19] In both sets of studies, BPA was more rapidly cleared in monkeys compared to rats. As has been noted by the FDA authors, the pharmacokinetic profile of BPA in monkeys is very similar to what has been observed in controlled human studies.[19]

Overall, these results indicate that the high doses of BPA that caused effects in rodent toxicity studies are less likely to cause effects in primates, including humans. Consequently, a MADL derived from rodent toxicity studies is likely to be overly conservative for humans. This observation provides further support to increase the MADL as discussed in the sections above.

c. BPA Is Metabolized More Efficiently in Neonatal Primates Than in Neonatal Rodents

As discussed above, the developmental effects reported at high doses in the Tyl *et al.* (2002b and 2008) studies are likely to be the result of postnatal exposure to BPA and should not be considered as developmental effects under Proposition 65. However, to the extent these effects are considered, pharmacokinetic data on mice, rats and monkeys indicate significant inter-species differences in the ability of neonates to metabolize BPA.[20]

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[16] Patterson, T. A., Twaddle, N. C., Roegge, C. S., Callicott, R. J., Fisher, J. W., and Doerge, D. R. 2013. Concurrent determination of bisphenol A pharmacokinetics in maternal and fetal rhesus monkeys. Toxicology and Applied Pharmacology. 267(1):41-48.

[17] Völkel, W., Colnot, T., Csanady, G.A., Filser, J.G., and Dekant, W. 2002. Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. Chemical Research in Toxicology. 15(10):1281-1287.

[18] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology. 247(2):158-165.

[19] Doerge, D. R., Twaddle, N. C., Woodling, K. A., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicology and Applied Pharmacology. 248(1):1-11.

[20] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2011. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicology Letters. 207(3):298-305.

In both rodents and primates, BPA is converted via Phase II metabolism to biologically inactive glucuronide and sulfate conjugates. However, whereas the Phase II metabolic system in monkeys is fully developed at birth, it is not yet fully developed in neonatal rodents. The result is that a given dose of BPA will result in a higher internal level of unconjugated BPA in rodents compared to monkeys. This is significant because unconjugated BPA is the biologically active form, which suggests that neonatal rodents are likely to be more susceptible to potential health effects from exposure to BPA than neonatal primates:

> "These results suggest that if BPA doses causing adverse effects in rodent models were attributable to discrete neonatal development windows, such effects should be less likely for comparable neonatal primate exposures on the basis of internal dosimetry."[20]

This significant difference between rodents and primates has also led FDA researchers to suggest that extrapolation from toxicity studies in rats to humans requires dose adjustment:

> "A comparison of the dosimetry of BPA across immature rats and monkeys suggests that dose adjustments would be necessary to extrapolate toxicity studies from neonatal rats to infant humans."[21]

Although the difference is not as large, the same trend is apparent for adult rats and monkeys. These results also indicate that a MADL derived from rodent toxicity studies, in particular studies that include postnatal dosing, is likely to be overly conservative for humans. This observation provides further support to increase the MADL as discussed in the sections above.

CONCLUSIONS

For the reasons discussed in these comments, the MADL of 290 micrograms/day proposed by OEHHA should be revised upward by a factor of at least 10. Such an increase is supported by several lines of scientific evidence:

- The no effect level assigned by OEHHA to the Tyl *et al*. (2002b and 2008) studies is incorrect. For both studies the correct NOEL for developmental effects is 50 mg/kg-day.
- Benchmark dose methodology provides a superior method for deriving no effect levels for BPA based on the Tyl *et al*. (2002b and 2008) studies. For the most sensitive developmental effects identified by OEHHA from those studies, the lowest BMD value is 163 mg/kg-day.

[21] Yang, X., Doerge, D. R., and Fisher, J. W. 2013. Prediction and evaluation of route dependent dosimetry of BPA in rats at different life stages using a physiologically based pharmacokinetic model. Toxicology and Applied Pharmacology. In Press.

- Pharmacokinetic data on rodents and monkeys indicates significant inter-species differences. Due to more efficient metabolism and clearance of BPA in monkeys, a MADL derived from rodent toxicity studies is likely to be overly conservative for humans.

Taken together, the scientific evidence indicates that the MADL for BPA should be at least a factor of 10 higher than the level proposed by OEHHA, and in the range of 2,900 to 9,454 mg/kg-day.