

**Comments of The
American Chemistry Council Phthalate Esters Panel
On the Draft NTP Brief on the Potential Human Reproductive and Developmental
Effects of Di(2-ethylhexyl) Phthalate (DEHP)**

July 5, 2006

Table of Contents

Introduction.....	1
1. For The Sake of Clarity, Balance and Scientific Soundness, the Draft Brief Should at Least Discuss the Implications of the Marmoset Data to the Risk Assessment.	2
2. There Is No Evidence Provided to Suggest that the Proportion of People Exposed to DEHP Reported in the 1999-2000 NHANES Study Underestimates Actual Exposures.....	5
3. The Response to the Question “Can DEHP Affect Human Development or Reproduction?” Should be Changed from “Probably” to “Possibly.”	5
4. The Response to the Question “Are Current Exposures to DEHP High Enough to Cause Concern?” Should be Changed from “Yes” to “Possibly,” with an explanation that any potential concern is restricted primarily to situations where infants may be exposed through certain medical treatments.	8
5. Technical Comment.....	9
Conclusion	9

Introduction

The American Chemistry Council Phthalate Esters Panel (PE Panel)¹ submits these comments on the May 2006 Draft NTP Brief on the Potential Human Reproductive and Developmental Effects of Di(2-ethylhexyl) Phthalate (DEHP) (“Draft Brief”).² The PE Panel appreciates the opportunity to submit these comments, and requests that NTP CERHR take them into consideration as it finalizes the NTP Brief on DEHP. These comments make the following general points:

¹ The PE Panel includes the major domestic manufacturers of phthalate esters and a user. The PE Panel members are: BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, Ferro Corporation and Teknor Apex Inc.

² The DEHP Brief is available at:
<http://cerhr.niehs.nih.gov/chemicals/dehp/DEHP%20Brief%20Draft1.pdf>

- The Draft Brief states that it “is intended to provide clear, balanced, scientifically sound information,” yet it acknowledges little if any of the PE Panel’s previous comments, and in particular provides no discussion of the implications of marmoset data showing that primates are much less sensitive to DEHP than rodents. Even if not relying on the marmoset data to establish its levels of concern, the Draft Brief should, for the sake of clarity, balance, and scientific soundness, discuss the implications of the marmoset data to the risk assessment.
- There is no evidence provided to suggest that the proportion of people exposed to DEHP reported in the 1999-2000 NHANES study underestimates actual exposures.
- The response to the question “Can DEHP Affect Human Development or Reproduction?” should be changed from “Probably” to “Possibly.”
- The response to the question “Are current exposures to DEHP high enough to cause concern?” should be changed from “Yes” to “Possibly,” with an explanation that any potential concern is restricted primarily to situations where infants may be exposed through certain medical treatments.
- The PE Panel believes the overall conclusion is that the concern for risk to human reproduction from DEHP exposure is “minimal.”

Each of these points is explained in greater detail below.

1. For The Sake of Clarity, Balance and Scientific Soundness, the Draft Brief Should at Least Discuss the Implications of the Marmoset Data to the Risk Assessment.

Over the past 15 months, the PE Panel has submitted several sets of comments to assist NTP-CERHR in its updated review of DEHP reproductive and developmental toxicity. In April 2005, the PE Panel submitted comments addressing much of the new information that had become available on DEHP since the first Expert Panel review in 2000.³ As explained in those comments, the new information on DEHP indicates that concern for adverse effects of DEHP exposure on human reproduction is much lower than that expressed by the first Expert Panel. Central to these comments was information from a new study on marmosets which showed that primates exposed to extremely high doses of DEHP from pre-puberty through puberty exhibited none of the testicular effects found in rodents exposed to lower doses – suggesting that primates are much less sensitive than rodents to the effects of DEHP.⁴

In September 2005, the PE Panel submitted comments on the August 2005 *Draft Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate*

³ ACC, Recent Information on Exposure to and Toxicology of Di(2-ethylhexyl) Phthalate (DEHP) (April 21, 2005), available at: <http://cerhr.niehs.nih.gov/chemicals/dehp/pubcomm/ACCCERHRDEHPcomments4-20-05.pdf>.

⁴ Mitsubishi Chemical Safety Institute. 2003. Sixty-five week repeated oral dose toxicity study of di(2-ethylhexyl) phthalate (DEHP) in juvenile common marmosets. Study No. B000496. (“Mitsubishi Study”).

(“Draft Update”).⁵ In those comments, the PE Panel again highlighted the importance of the new marmoset data which indicate that primates are much less sensitive than rodents to DEHP. In addition, those comments pointed out that data for three separate populations of human neonates, some of which had experienced relatively high exposures due to medical interventions, have failed to demonstrate any adverse effects of DEHP exposure on pre-pubescent males. The comments on the Draft Update also emphasized that the most recent CDC human biomonitoring information shows that DEHP exposures to the general population are basically the same as those identified by the first Expert Panel, that exposures for neonates exposed during life-sustaining medical intervention are about 1.4 mg/kg/day, and that Margins of exposure for the U.S. general population are greater than 1000 at the 95th percentile exposure and greater than 10,000 at the mean. Based on this and other information, the PE Panel expressed its opinion – which it still holds – that the overall conclusion is that the concern for risk to human reproduction from DEHP exposure is “minimal.”

In February 2006, following a public meeting in October 2005, the PE Panel submitted comments on the November 2005 *Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate* (“Final Update”).⁶ In its comments on the Final Update, the PE Panel reiterated and expanded on its previous scientific comments, and addressed some of the Expert Panel’s concerns with regard to the usefulness of the primate data for characterizing reproductive toxicity of DEHP to humans. In particular, those comments provided to NTP-CERHR the opinions of two experts in primate reproduction (Drs. Schlatt and Tardif) which indicated that the marmoset, despite some unique aspects of its biology, is a valuable model for male human reproductive toxicity – especially for the evaluation of developmental and toxicological aspects of the testis and spermatogenesis. The expert opinion of Dr. Schlatt also indicated that the principal primate study, the Mitsubishi marmoset study, while presenting some concerns about the health of the animals, nonetheless provides “strong evidence that DEHP had no major effect on testicular development even after very long and intense DEHP exposure.”⁷ Moreover, those comments expressed the PE Panel’s belief that several flaws in the Expert Panel’s review process, and in particular in the conduct of the public meeting, compromised the ability of the Expert Panel to render an objective and thoughtful opinion as to the reproductive toxicity of DEHP. The PE Panel requested that NTP-CERHR keep these points in mind as it weighed the Expert Panel’s conclusions while drafting its DEHP Brief, and again expressed its belief that the overall concern for risk to human reproduction from DEHP exposure is “minimal.”

Finally, in April 2006, the PE Panel submitted supplemental comments on the Final Update to address the Expert Panel’s incorrect assessment of the NOAEL from a two-generation

⁵ ACC, Comments of The American Chemistry Council Phthalate Esters Panel On the Draft NTP-CERHR Expert Panel Update On The Reproductive And Developmental Toxicity Of Di(2-Ethylhexyl) Phthalate (September 28, 2005), available at: <http://cerhr.niehs.nih.gov/chemicals/dehp/pubcomm/ACC%20PE%20Panel%20CERHR%20Comments%209-28-05.pdf>

⁶ ACC, Comments of The American Chemistry Council Phthalate Esters Panel On the Final NTP-CERHR Expert Panel Update On The Reproductive And Developmental Toxicity Of Di(2-Ethylhexyl) Phthalate (February 3, 2005), available at: <http://cerhr.niehs.nih.gov/chemicals/dehp/pubcomm/ACC%20PE%20Panel%20CERHR%20DEHP%20Final%20Update%20Comments%202-3-06.pdf>

⁷ See, Opinion of Dr. Schlatt, Attachment 1 to ACC comments on Final Update, at p. 4.

rat reproductive study.⁸ The supplemental comments also reiterated the importance of evaluating reported effects in light of historical control data, specifically with regard to the results of NTP (2004), the study upon which the Expert Panel based its developmental NOAEL of 3-5 mg/kg/day. Without such a comparison and validation, the PE Panel questioned the validity of the Expert Panel basing its developmental NOAEL for DEHP on the findings of this study.

As stated in the Introduction to the Draft Brief, “The NTP Brief is intended to provide clear, balanced, scientifically sound information” about the potential for exposure to DEHP to cause adverse reproductive or developmental effects in people.⁹ In submitting the comments described above, the PE Panel has presented NTP-CERHR with a substantial amount of scientific information to help the NTP Brief achieve this objective, with the hope that its comments also would help guide the NTP-CERHR to the more scientifically supported and reasonable conclusion that the potential risks posed by DEHP are lower than those expressed by the Expert Panel in its original review of DEHP, and low enough that the overall concern for risk to human reproduction is “minimal.” In light of these efforts, the PE Panel is disappointed that the Draft Brief appears to take little notice of the majority of its comments and dismiss the most significant information with only cursory explanation.

The PE Panel believes that to fully meet its goal of providing a “clear, balanced, scientifically sound” evaluation of DEHP reproductive toxicity, NTP CERHR should present and discuss the implications of the marmoset data to the risk assessment. Viewed in combination with the other scientific information provided by the PE Panel in its previous comments, the implications of the marmoset findings are, in the PE Panel’s opinion, that the levels of concern presented in the Draft Brief are generally overstated, and in fact are “minimal.”

As stated in its comments on the Final Update, the PE Panel believes that, while there are some concerns with the health of the animals in the Mitsubishi study, and some differences between marmosets and humans, on balance, the marmoset is actually a better model for evaluating effects on the male human reproductive system than rodents. By basing its conclusions purely on rodent data that have their own set of limitations for human risk assessment and completely disregarding the marmoset data, NTP CERHR is essentially holding the marmoset data to a higher scientific standard than rodent data. A more balanced approach would present both the rat and marmoset data, recognize the advantages and limitations of each, and present conclusions about risk and concern based on each. For example, if the DEHP Brief identifies the reasons that marmoset data are of “uncertain utility” it should also clearly recognize the differences between rodents and humans, and the reasons why primates, including humans, are likely less sensitive to effects of DEHP than rodents. This information should be presented clearly in the DEHP Brief so that the reader understands the health protective nature of the analysis, and also understands that the true risk could be much lower than the risk estimated based on rodent data. The PE Panel believes a “clear, balanced, scientifically sound” analysis of the data would make all of these points.

⁸ Letter from Marian K. Stanley, ACC to Dr. Michael D. Shelby, CERHR, re: Supplemental Comments on the NTP-CERHR Expert Panel Final Update.

⁹ Draft Brief Introduction.

2. There Is No Evidence Provided to Suggest that the Proportion of People Exposed to DEHP Reported in the 1999-2000 NHANES Study Underestimates Actual Exposures.

The Draft Brief answers the question “Are People Exposed to DEHP?” with “Yes.” As part its explanation for answering “Yes,” the Draft Brief notes that the use of the metabolite MEHP to determine human exposure in the 1999-2000 NHANES study may underestimate the portion of people exposed to DEHP “because two other urinary metabolites of DEHP not screened for in the 1999–2000 study were subsequently reported to occur in higher concentrations in human urine (Silva et al., 2004).¹⁰” While it is clear that some people are exposed to DEHP to varying degrees, it is unclear how the Draft Brief’s conclusion that the NHANES data may underestimate the portion of people exposed is supported by the data it cites. Neither Silva et al., nor the Expert Panel’s Final Update conclude that higher concentrations of these two other metabolites are indicative of more widespread exposure and there is no suggestion that the two additional metabolites would be present in the absence of MEHP. Also, the CDC’s Third National Report on Human Exposure to Environmental Chemicals does not report the percentage of samples containing DEHP metabolites. Accordingly, there is no evidence provided to suggest that the proportion of people exposed to DEHP reported in the 1999-2000 NHANES study underestimates actual exposures.

3. The Response to the Question “Can DEHP Affect Human Development or Reproduction?” Should be Changed from “Probably” to “Possibly.”

The Draft Brief answers this question with “Probably.” Based on its previous comments, as summarized above, the PE Panel believes strongly that the science supports a change of this answer to “Possibly.” Indeed, “Possibly” would better correspond with the weight of the evidence conclusion represented in Figure 2a, which indicates that there is “insufficient evidence for a conclusion” as to whether DEHP causes adverse developmental or reproductive toxicity effects in humans. This conclusion is supported by other information in the Draft Brief, which declares “there is no direct evidence that exposure of people to DEHP adversely affects reproduction or development,” and then acknowledges that the only evidence that DEHP has developmental and reproductive toxicity effects comes from rodent studies.¹¹ The PE Panel appreciates the recognition in the Draft Brief that human studies have failed to identify developmental and reproductive toxicity effects, even in populations experiencing relatively high exposures to DEHP and/or during sensitive stages of development.¹² However, although the Draft Brief states that the usefulness of this finding is limited by the lack of concomitant exposure measurements, other investigations of humans receiving comparable high exposures from medical interventions support the conclusion that human exposures, in extreme situations, can approach the NOAEL observed in rodent studies.¹³ Despite these relatively high exposures,

¹⁰ Silva, M. J., Barr, D. B., Reidy, J. A., Malek, N. A., Hodge, C. C., Caudill, S. P., Brock, J. W., Needham, L. L. and Calafat, A. M. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999-2000. *Environ Health Perspect* 2004; 112: 331-8.

¹¹ Draft Brief at p. 1.

¹² Draft Brief at p. 2.

¹³ See, e.g., Calafat, AM, et al. 2004. Exposure to di-(2-ethylhexyl) phthalate among premature neonates in a neonatal intensive care unit. *Pediatrics* 113: 429-434; and Green, R. et al., 2005. Use

DEHP has not been observed to cause developmental and reproductive toxicity effects in humans. This information is corroborative of the data showing that primates are less sensitive than rodents to DEHP effects, and should not be disregarded in the Draft Brief.

Because the Draft Brief bases its answer to the question “Can DEHP Affect Human Development or Reproduction?” on rodent data, whether humans are as sensitive as rodents to the developmental and reproductive toxicity effects of DEHP is a critical inquiry. To help address this issue, the PE Panel provided a new study on juvenile marmosets to the Expert Panel. The study showed that oral DEHP doses as high as 2500 mg/kg/day had no adverse effects on the male reproductive tract. This NOAEL is at least 100-fold higher than the dose causing male reproductive tract effects in orally-exposed juvenile rats. The Draft Brief, however, dismisses the import of this dramatic species difference with the following brief statement:

Because of differences between marmosets and humans in intestinal lipase activity, absorption and excretion of DEHP, and testosterone levels during development of the male reproductive tract, there is uncertainty as to the utility of the marmoset as a model for studying the possible effects of DEHP on development of the human male reproductive tract. In addition, this marmoset study encountered problems with the health and growth of the study animals and did not investigate the most sensitive stage in the development of the male reproductive tract, i.e., the perinatal period.¹⁴

As explained below, this brief dismissal of the marmoset data is unfounded.

There is no evidence provided that any such metabolic differences between marmosets and humans exist. The Final Update is in fact mute on this topic, other than listing such information as an additional data need (i.e., “In vitro and in vivo metabolic data including information across ages and species on lipase, cytochrome P450, glucuronyl transferase, and dehydrogenase enzyme kinetics. There is a critical lack of human in vitro data”).¹⁵ As pointed out more than once in the PE Panel’s previous comments, available ADME data among species indicate that intestinal lipase activity is greater in the rat than the marmoset or human¹⁶ and that glucuronidation of DEHP metabolites is greater in the human and marmoset than the rat.¹⁷ Rather than bringing the utility of the marmoset model into question, this information provides a partial explanation for why marmosets and other primates may be less sensitive to exposure to DEHP. The Draft Brief also fails to note that a portion of the testicular toxicity caused by DEHP in rodents is mediated via PPAR alpha receptor activation,¹⁸ a mechanism generally recognized

of di(2-ethylhexyl) phthalate containing medical products and urinary levels of mono(2-ethylhexyl) phthalate in neonatal intensive care units. *Environ Health Perspect* 113:1222-1225.

¹⁴ Draft Brief at p. 3.

¹⁵ Final Update at p.175.

¹⁶ *Id.* at 41-42.

¹⁷ *Id.* at 46.

¹⁸ *See*, Ward J, Peters J, Perella C, Gonzalez F. 1998. Receptor and non-receptor mediated organ specific toxicity of di(2-ethylhexyl) phthalate (DEHP) in peroxisome proliferators- activated receptor α -null mice. *Toxicology* 126:237-246.

as irrelevant to humans. Thus, to be complete, the DEHP Brief should at least note that, based on both toxicokinetic (ADME) and toxicodynamic differences among species, developmental and reproductive toxicity effects are less likely to occur in primates than rats – the latter being the model used by NTP to assess potential toxicity in humans.

The observation in the Draft Brief that new world monkeys such as the marmoset have slightly higher blood testosterone levels during development than humans or old world monkeys should not be used by NTP to dismiss the marmoset as an animal model for DEHP toxicity as the biological significance of this difference, like potential species differences in the kinetics of testosterone-receptor binding as well as post-receptor binding events, is unknown. In support of the utility of marmoset model despite this difference, a short-term oral exposure of pre-pubertal cynomolgus monkeys (an old world, non-human primate with blood testosterone levels comparable to that of humans) to 500 mg/kg/day DEHP – an exposure acknowledged in the first DEHP Expert Panel Report to produce testicular lesions in pre-pubertal rats¹⁹ – did not elicit testicular lesions in the cynomolgus monkeys.

The Draft Brief goes on to question the marmoset model because it “did not investigate the most sensitive stage in the development of the male reproductive tract, i.e., the perinatal period.”²⁰ It is true that perinatal studies in marmosets have not been conducted. However, this should not be used to dismiss the marmoset data. In rodents, the perinatal period appears no more sensitive to DEHP developmental and reproductive toxicity effects than the pre-pubertal and pubertal periods. Indeed, it was data in pubertal rodents that first led to further inquiry regarding potential adverse effects in young children.²¹ This initial observation is complemented by those of other investigators which demonstrate that developmental and reproductive toxicity effect NOAELs and LOAELs in pre-pubertal (1 - 10 mg/kg/day)²² and pubertal (3.7 - 38 mg/kg/day²³) rodents are comparable to those identified in perinatal rodent studies (14 - 141 mg/kg/day²⁴; 5 - 14 mg/kg/day²⁵). Thus, if pre-pubertal/pubertal rodent data serve as the basis for concerns about the susceptibility of young children to DEHP developmental and reproductive toxicity effects, the data in pre-pubertal marmosets are germane to the discussion.

Finally, the Draft Brief discounts the marmoset data because the Mitsubishi study “encountered problems with the health and growth of the study animals.” As explained in the

¹⁹ NTP CERHR, NTP CERHR Expert Panel Report on Di(2-ethylhexyl)phthalate (October, 2000) (“First Expert Panel Report”) at p. 95. Available at: <http://cerhr.niehs.nih.gov/chemicals/dehp/DEHP-final.pdf>.

²⁰ Draft Brief at p. 4.

²¹ See, First Expert Panel Report.

²² Akingbemi, B. T. et al. 2001. Modulation of rat Leydig cell steroidogenic function by di(2-ethylhexyl)phthalate. *Biol Reprod*; 65: 1252-9; Akingbemi, B.T. et al. (2004). Phthalate induced Leydig cell hyperplasia is associated with multiple endocrine disturbances. *PNAS*; 101: 775-80.

²³ Poon, R. et al. 1997. Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. *Food Chem Toxicol* 1997; 35: 225-239.

²⁴ Lamb, J. C. I., Chapin, R. E., Teague, J., Lawton, A. D. and Reel, J. R. 1987. Reproductive effects of four phthalic acid esters in the mouse. *Toxicol Appl Pharmacol*; 88: 255-269.

²⁵ NTP, 2004. Diethylhexylphthalate: Multigenerational reproductive assessment by continuous breeding when administered to Sprague-Dawley rats in the diet. Research Triangle Park NC.

expert opinion of Dr. Schlatt included with the PE Panel's comments on the Final Update, despite these problems, Mitsubishi still provides strong evidence that DEHP had no major effect on testicular development even after long-term DEHP exposure at very high concentrations that would have profound adverse effects on rodent testes. This information should at least be mentioned in the Draft Brief.

For the above reasons, and those stated in its previous comments, the PE Panel believes NTP CERHR should change the answer to the question "Can DEHP Affect Human Development or Reproduction?" from "Possibly."

4. The Response to the Question "Are Current Exposures to DEHP High Enough to Cause Concern?" Should be Changed from "Yes" to "Possibly," with an explanation that any potential concern is restricted primarily to situations where infants may be exposed through certain medical treatments.

The PE Panel believes strongly NTP CERHR should change the answer to the question "Are current exposures to DEHP high enough to cause concern?" from "Yes" to "Possibly," with an explanation that any potential concern is restricted primarily to situations where infants may be exposed through certain medical treatments. As discussed in the PE Panel's previous comments and reiterated above, there is no clear evidence that DEHP causes developmental and reproductive toxicity effects in humans. Available toxicokinetic and toxicodynamic data, albeit limited, indicate that humans and marmosets actually respond to DEHP in a comparable manner that is different from that seen in rodents. These data suggest that DEHP is, in fact, a less potent reproductive toxin in humans than in rodents. Because DEHP has not been shown to cause effects in humans, and available toxicokinetic and toxicodynamic data indicate humans are less sensitive to DEHP than the rodents upon which NTP CERHR bases its concern, the answer to the above question should be at most "Possibly."

In addition, the Draft Brief itself finds minimal concern for adverse effects on adults, and only finds increased levels of concern for infants and children - in particular infants exposed through certain medical procedures. The increased concern expressed for non-medically exposed male infants and children is based on assumed exposures "at the high end" of the 1-30 $\mu\text{g}/\text{kg}/\text{day}$ range estimated by the first Expert Panel.²⁶ However, Calafat and McKee (2006)²⁷ estimated that mean non-medical DEHP exposure to children 12 to 18 months old was only about 2.8 $\mu\text{g}/\text{kg}/\text{day}$, much less than the 30 $\mu\text{g}/\text{kg}/\text{day}$ assumed in the Draft Brief. Moreover, Calafat and McKee (2006) also reported that general population exposures to DEHP estimated using two additional oxidative metabolites (MEHHP and MEOHP), while higher than those estimated using MEHP, are still well within the 1-30 $\mu\text{g}/\text{kg}/\text{day}$ estimated by the first Expert Panel.²⁸ Given that: 1) no adverse effects of DEHP exposure have been documented in humans,

²⁶ Draft brief at p. 3, Note 3 to Figure 3.

²⁷ Calafat, A.M. and McKee, R.H. (2006) Integrating Biomonitoring Exposure Data into the Risk Assessment Process: Phthalates (Diethyl Phthalate and Di[2-Ethylhexyl] Phthalate) as a Case Study, Environ Health Perspect (online June 12, 2006), available at: <http://ehp.niehs.nih.gov/members/2006/9059/9059.pdf>. See the Attachment to these comments.

²⁸ Calafat and McKee demonstrated that the MEHP-based 95th percentile estimate of DEHP exposure for adults was 7.1 $\mu\text{g}/\text{kg}/\text{day}$, while the MEHHP and MEOHP-based 95th percentile estimates were 16.8 and 15.6 $\mu\text{g}/\text{kg}/\text{day}$, respectively.

even in infants exposed through medical procedures at levels high enough to cause effects in rats; and 2) the Draft Brief, based on exposure levels that are likely overstated, finds minimal concern for adverse effects on the largest segment of the population, adults, the answer to the above question should be “Possibly.” Even an answer of “Possibly” should be qualified to explain that any concern pertains primarily to a relatively small subset of the population under very specific circumstances and that studies of those populations thus far have not demonstrated any clear evidence of reproductive harm.

For the above reasons, the PE Panel suggests the response to the question “Are current exposures to DEHP high enough to cause concern?” be changed from “Yes” to “Possibly,” with an explanation that any potential concern is restricted primarily to a limited number of situations where infants may be exposed through certain medical treatments.

5. Technical Comment

The Draft Brief refers to “animal studies” and “effects in laboratory animals” throughout. Given the different responses of primates and rodents, and the Draft Brief’s reliance on rodent data, it would be more accurate to refer to “rodent studies” and “effects in laboratory rodents.”

Conclusion

For the reasons stated in the above comments, and those stated in its previous comments, the PE Panel believes the overall conclusion is that the concern for risk to human reproduction from DEHP exposure is “minimal” and that the Draft Brief should state this. In addition, the PE Panel believes that a document intended to “provide clear, balanced, scientifically sound information,” on the reproductive toxicity of DEHP should discuss the implications to the risk assessment of marmoset data showing that primates are likely much less sensitive to effects of DEHP than rodents; those implications being that the levels of concern based on rodent data indicated in the Draft Brief may be overstated, and at the least are very conservative. As for other specific findings in the Draft Brief, the PE Panel believes: 1) There is no evidence provided to suggest that the proportion of people exposed to DEHP reported in the 1999-2000 NHANES study underestimates actual exposures; 2) the response to the question “Can DEHP Affect Human Development or Reproduction?” should be changed from “Probably” to “Possibly”; and 3) the response to the question “Are current exposures to DEHP high enough to cause concern?” should be changed from “Yes” to “Possibly,” with an explanation that any potential concern is restricted primarily to situations where infants may be exposed through certain medical treatments.

The PE Panel hopes NTP CERHR will take these comments into consideration as it finalizes the DEHP Brief.