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September 28, 2005

VIA EMAIL: shelby@niehs.nih.gov

Dr. Michael D. Shelby
CERHR Director
CERHR
79 T.W. Alexander Drive
Building 4401, Room103
Research Triangle Park, NC 27709

Dear Dr. Shelby:

The American Chemistry Council Phthalate Esters Panel (PE Panel) is submitting the attached comments on the August 2005 *Draft Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate* (Draft Update) to assist the NTP-CERHR Expert Panel in its review of the reproductive and developmental toxicity of di(2-ethylhexyl) phthalate (DEHP) and in response to EPA's request for comments on the Draft Update (70 Fed. Reg. 43870 (Jul. 29, 2005)). The PE Panel includes the major domestic manufacturers of phthalate esters and some users.

The PE Panel appreciates the work in preparing the Draft Update and believes that the Draft Update, in general, provides a good summary of the new information that has become available on DEHP since the first Expert Panel review in 2000. The attached comments and suggestions are intended to improve the Draft Update in terms of the completeness of its review of new information and the robustness of its conclusions.

As explained in the attached comments, the PE Panel believes that the available information for DEHP shows that:

- The data support an oral-exposure NOAEL of 46 mg/kg/day for developmental and reproductive toxicity, which is higher than the NOAEL selected for the previous CERHR assessment;
- Data indicate that a conservative NOEL for intravenous exposure is 60 mg/kg/day;
- Data for three separate populations of neonates, some of which had relatively high exposures due to medical interventions, fail to demonstrate any adverse effects of DEHP exposure on pre-pubescent males;
- Primates exposed to very 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, including humans, are likely much less sensitive to the effects of DEHP;

- Human biomonitoring information demonstrates that DEHP exposures to the general population are within or less than the original 3-30 µg/kg/d estimate identified by the first Expert Panel, and that exposures for neonates exposed during life-sustaining medical intervention are about 1.4 mg/kg/d;

- 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 the above, the PE Panel believes that the overall conclusion is that the concern for risk to human reproduction from DEHP exposure is minimal.

The PE Panel will submit separately several recent studies that are cited in the attached comments that were not reviewed in the Draft Update and which are not easily accessible online.

If you have any questions, or if you need any further information, please call Marian K. Stanley, Senior Director and Manager of the Phthalate Esters Panel, at (703) 741-5623, email her at marian_stanley@americanchemistry.com, or write her at the address below.

Sincerely yours,

Courtney M. Price
Vice-President, CHEMSTAR

Attachments

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

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EXECUTIVE SUMMARY

The American Chemistry Council Phthalate Esters Panel (PE Panel) submits these comments on the August 2005 *Draft Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate* (Draft Update) to assist the NTP-CERHR Expert Panel in its review of the reproductive and developmental toxicity of di(2-ethylhexyl) phthalate (DEHP) and in response to EPA's request for comments on the Draft Update (70 Fed. Reg. 43870 (Jul. 29, 2005)).[1] The PE Panel includes the major domestic manufacturers of phthalate esters and some users.[2]

The PE Panel believes that the Draft Update, in general, provides a good summary of the new information that has become available on DEHP since the first Expert Panel review in 2000. The attached comments and suggestions are intended to improve the Draft Update in terms of the completeness of its review of new information and the robustness of its conclusions. These comments, in addition to several technical suggestions, make the following major points:

- The section in the Draft Update on human exposures to DEHP could be significantly improved by including conversions of urinary metabolite levels to estimates of environmental exposure. The CDC biomonitoring data are the most comprehensive and accurate estimates available of exposures of the U.S. population, including children, to DEHP. The methods and data necessary to perform such a conversion are robust and readily available. In the absence of these conversions, it is not possible to put the CDC data into perspective, and their value to a risk assessment is therefore severely limited. Moreover, without these data the Expert Panel must instead focus on less accurate deterministic exposure estimates, or biomonitoring data from smaller population samples in other countries. Through simple calculations, the CDC biomonitoring data can be used to show that conservative, 95th percentile estimates of DEHP exposure to all U.S. population sub-groups are within the range of 3-30 µg/kg/day DEHP used in the October 2000 Expert Panel Report. Average levels for all subpopulations are less than 3 µg/kg/day. The PE panel strongly urges the Expert Panel to include in the human exposure section exposure estimates based on the CDC biomonitoring data.

- Available data on the absorption, distribution, metabolism, and excretion of DEHP in rodents and primates, some of which are not discussed in the Draft Update, indicate that primates are much less susceptible to reproductive effects from oral exposure to DEHP. In particular, available data indicate that, compared to rodents, primates absorb ingested DEHP less readily, convert less absorbed DEHP to the toxicologically active metabolite MEHP, and, because of higher glucuronidation, experience lower levels of toxicologically active metabolites for a shorter period of time. In addition, because non-human primate data are much more likely to reflect the response of a human primate to a

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[1] The Draft Update is available at http://cerhr.niehs.nih.gov/news/dehp/DEHP-Update-Report-08-08-05.pdf.

[2] The Panel members are: BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, Ferro Corporation and Teknor Apex Inc.

chemical than are rodent data, the Expert Panel could consider use of the primate reproductive NOEL of 2500 mg/kg/day. At the very least, the primate data provide a basis for the Draft Update to acknowledge that the use of rat data for human risk assessment is likely very conservative – that is, health protective.

- The previous CERHR Expert Panel Report did not identify a firm NOEL for developmental toxicity on the developing male reproductive tract. Given the more recent studies reviewed in the Draft Update, a conservative NOEL of 20 mg/kg can be identified based on the NIH-supported study by Li et al. (2000). In that study, neonatal male rats were treated with doses of 20, 100, 200, or 500 mg/kg, and a NOEL of 20 mg/kg was established for effects on the reproductive tract (Sertoli cell vacuolization). Moreover, the multigeneration continuous breeding study conducted by NTP (2004), although not specifically designed as a developmental toxicity study, reports endpoints at the lower doses that are related to developmental effects and indicate that the NOAEL is 46 mg/kg/day.

- Medical device exposures to DEHP, particularly exposures to critically ill infants undergoing intensive therapeutic interventions, were a primary concern of the first Expert Panel. As noted in the Draft Update, since the first Expert Panel review new data have become available that support a NOEL of 60 mg/kg/day for intravenous exposures to DEHP. In particular, in a recent study by Cammack et al. (2003), no histological or organ weight effects of any kind were observed in Sprague-Dawley treated intravenously with 60 mg/kg/day for 21 days. Moreover, there was no germinal cell depletion or Sertoli cell alteration observed in any dose group at any time and no effects on sperm count, sperm morphology, or sperm motility were observed at 90 days of age in any of the groups.

- The Draft Update reviewed the multigeneration continuous breeding study in rats conducted by the NTP (2004) and noted that while the study authors chose a NOEL of 7500 ppm, the Expert Panel suggested a NOEL of 1000 ppm might be more appropriate. The PE Panel concurs with this assessment, and believes that a NOAEL of 1000 ppm (46 mg/kg) is appropriate, based on the incidence and severity of the response at the lower dose levels, and is supported by data from other multigeneration studies with DEHP.

- The Draft Update includes descriptions of human studies by Latini et al. (2003) and Swan et al. (2005). Consideration of these studies should be tempered by information regarding the methodologies employed by these studies that casts doubt on their results.

- The Draft Update asserts that young rats are more sensitive to the reproductive toxicity of orally administered DEHP than adult rats. However, available data show that the apparent increased sensitivity of young rats to DEHP is due to toxicokinetic, not toxicodynamic, differences as the absorption of MEHP in rats is age-dependent, with younger rats absorbing MEHP more readily than older rats.

- Given that: 1) 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; 2) there is clear

evidence that primates are less sensitive than rodents to the reproductive and developmental effects of DEHP; and 3) there are no data to suggest that adverse effects occur in neonates with relatively high exposures, the PE Panel believes that the overall conclusion is that the concern for risk to human reproduction from DEHP exposure is minimal

I. COMMENTS ON SECTION 1: USE AND HUMAN EXPOSURE

A. CDC Biomonitoring Data For the U.S. General Population Should be Converted into Exposure Estimates to Put Those Data into Perspective

The Draft Update reviews the majority of existing literature on human biomonitoring studies and provides a review of studies estimating environmental concentrations of phthalate esters in potential sources such as dust and food, among others. The Draft Update also reviews studies that evaluated exposures from the use of medical devices containing DEHP-plasticized PVC. Although some of the non-medical biomonitoring studies include estimates of exposure (e.g., Koch et al., 2003a; 2004; 2005), others (e.g. CDC 2003; 2005) report only urinary metabolite measurements, and provide no corresponding estimates of exposure. Similarly, the Draft Update reports estimated exposure levels for medical applications based on measured releases of DEHP from medical devices, but, for several of the medical biomonitoring studies, the Draft Update does not use the urinary metabolite data to estimate exposures. Without converting these measurements to exposures, it is not possible to compare the exposures represented by the urinary metabolite data to effect levels in animal studies.

Therefore, the PE Panel strongly recommends that the Expert Panel convert the available biomonitoring data into estimates of exposure and include those results in the Draft Update. The information necessary to convert biomonitoring data to exposure estimates is readily available. Anderson et al. (2001; not reviewed in the Draft Update), provides molar excretion information for humans for the major phthalate esters, including DEHP. This information was used by David (2000; not reviewed) and Koch et al. (2003a; 2004) to calculate human exposure levels to phthalates. In addition, Kohn et al. (2000; not reviewed) have used a completely different approach to convert urinary metabolite data to exposures. Both David (2000) and Kohn et al. (2000) used their method to derive exposures from initial data reported by researchers at the Centers for Disease Control and Prevention (CDC) (Blount et al. (2000). The exposure levels calculated by each method were very similar, providing confidence that each estimation method is accurate.

The David method calculates the exposure using the simple formula:[3]

$$\text{Daily Intake (mg/kg/day)} = \frac{\text{Urine Concentration (mg/g creatine) x Creatinine Excretion (g/kg/day)}}{\left[\frac{\text{MW Diester (g/mol)}}{\text{MW Monoester (g/mol)}}\right] \times \left[\frac{\text{Monoester in Urine (mol)}}{\text{Diester Ingested (mol)}}\right]}$$

[3] Note: This formula was misprinted in the publication of David (2000), but is correct as given above.

in which the molar excretion ratio (monoester in urine (mol)/diester ingest (mol)) represents experimental data such as that of Anderson et al. (2001). Koch et al. (2003b) determined the molar excretion ratios for secondary DEHP metabolites reported by the CDC (2005) in the urine of the general population.

By applying estimates of daily creatinine excretion for different age groups to this formula, and using current CDC urinary metabolite biomonitoring data for the U.S. population (CDC 2003; 2005), calculated DEHP exposures at the 95th percentile, using any of the metabolites measured, are all within the range of 3-30 µg/kg/day DEHP used in the October 2000 Expert Panel Report. Geometric mean levels for all groups are below 3 ug/kg/day. These estimates are presented in Tables 1 and 2 below.

Table 1. DEHP Exposures[a] Based on Data Published by CDC in 2003.

Subpopulation	**Geometric mean (µg/kg/day)**	**95th percentile (µg/kg/day)**	**Sample Size**
Overall	0.62	4.34	2541
Adults 20+ years	0.61	3.51	1461
Children 6-11 years[b]	0.57	4.62	328
Adolescents 12-19 years[b]	0.28	1.33	752
Males	0.58	4.33	1215
Females	0.67	3.27	1326
Mexican Americans	0.63	3.15	814
Non-Hispanic Blacks	0.62	3.69	603
Non-Hispanic Whites	0.62	4.01	912

a = data presented as µg/kg/day DEHP exposure based on standard creatinine excretion values and the concentration of MEHP in urine per g creatinine. Creatinine excretion of 20 mg/kg/day used. Molar excretion value of 14% from Anderson et al. (2001) used to calculated exposure.

b = creatinine excretion of 11 mg/kg/day used for this age subpopulation.

Table 2. DEHP Exposures[a] Based on Data Published by CDC in 2005.

Subpopulation	Geometric mean (µg/kg/day)			95th percentile (µg/kg/day)			Sample Size
	MEHP	MEOHP	MEHHP	MEHP	MEOHP	MEHHP	
Overall	0.73	1.86	2.08	3.37	14.55	14.46	2782
Adults 20+ years	0.79	1.87	2.07	6.67	14.59	15.32	1647
Children 6-11 years[b]	0.55	2.29	2.66	4.62	12.64	13.00	393
Adolescents 12-19 years[b]	0.39	1.15	1.35	1.33	6.11	7.05	742
Males	0.70	1.95	2.14	6.25	14.81	15.10	1371
Females	0.91	2.15	2.45	7.03	17.42	16.78	1411
Mexican Americans	0.81	1.91	2.25	4.91	11.54	11.96	677
Non-Hispanic Blacks	0.93	2.29	2.51	7.98	17.53	18.36	703
Non-Hispanic Whites	0.76	2.07	2.31	6.57	19.38	17.45	1216

a = data presented as µg/kg/day DEHP exposure based on standard creatinine excretion values and the concentration of MEHP, MEOHP, or MEHHP in urine per g creatinine. Creatinine excretion of 20 mg/kg/day used. Molar excretion value of 14% from Anderson et al. (2001) used to calculated exposure from MEHP excretion; molar excretion value of 24.7 and 14.9% from Koch et al. used to calculated exposure from MEOHP and MEHHP excretion, respectively.

b = creatinine excretion of 11 mg/kg/day used for this age subpopulation.

The CDC biomonitoring studies represent DEHP metabolite data collected from more than 5300 individuals (2541 for the 2003 CDC report and 2782 for the 2005 report) in the general U.S. population, including children. The CDC studies were carefully designed so that the sampled population would be representative of the U.S. population, and they provide the most accurate estimates available of exposures of the U.S. population to DEHP, representing the aggregate of all exposures to DEHP. Moreover, the exposures derived from the CDC data are less than those estimated by previous deterministic methods, providing confidence that there are no unidentified sources of DEHP that contribute significantly to exposures of the general population.

Without these calculated DEHP exposure levels for the general U.S. population, the Draft Update focuses on either less accurate deterministic estimates of exposure (e.g., Clark et al., 2003) or biomonitoring data from other countries. For example, much of the exposure information discussed in the Draft Update is from Koch et al. (2003a: 2004: 2005), which estimated DEHP exposures in isolated populations in Germany. While it may be appropriate to include such data for completeness, or for comparison to data for the U.S. population, it is incorrect to focus on these studies given that: 1) the deterministic exposure estimates presented in the Draft Update from Clark et al. (2003) were based only on likely sources of exposure for the U.S. population (as noted in the Draft Update); and 2) high-quality exposure estimates can be readily calculated for the U.S. population from the robust CDC biomonitoring data. Therefore, the monograph would be greatly improved, and would allow a more robust risk assessment, if it included and focused on exposure levels derived from biomonitoring data, as outlined above.

In addition to representing a non-U.S. population, the PE Panel notes that the exposures calculated by Koch et al. (2003a) may overestimate actual exposures. Koch et al. (2003a) evaluated DEHP levels in 86 members of the German population. Using the formula of David (2000) to calculate exposures, they reported significantly higher exposures than indicated by the CDC data. However, it appears that was due to their use of data from Schmid and Schlatter (1985) on excretion of metabolites, rather than data from Anderson et al. (2001). Schmid and Schlatter collected data from only 2 individuals with some inter-individual variability. The molar excretion fraction for MEHP from their data is 2.4%, far lower than the 14% calculated by Anderson et al. (2001) using groups of 8 individuals for each dose level. Both Kohn et al. and David (2000) calculated exposures from the urinary excretion data set of Blount et al. (2000). The exposure level calculated by Kohn et al. (2003a) did not incorporate a molar excretion fraction, and the exposure level is nearly identical to the value calculated by David using the 14% molar excretion fraction from Anderson et al. (2001). This would imply that 14% is an accurate value for MEHP rather than 2.4%. Furthermore, the percentage of excreted MEHP from Schmid and Schlatter differs from that noted by Dirven et al. (1993), who measured the urinary metabolite profiles of workers exposed to DEHP, and others who measured excretion from non-human primates. Koch et al. themselves subsequently measured a molar conversion factor for MEHP that is approximately a factor of 3 higher than that reported by Schmid and Schlatter (Koch et al., 2004). Using the Anderson et al. molar excretion fraction, the calculated median exposure for DEHP from the Koch et al. data would be 1.8 µg/kg/day rather than 10.5 µg/kg/day as calculated by the authors. Thus, the PE Panel believes the Draft Update should include an analysis of U.S. general population exposure based on the CDC biomonitoring data and recommends that the discussion of estimated DEHP exposure levels from non-U.S. populations be limited, and not used as a basis for the risk assessment.

As well as reviewing exposure to the general population, the Draft Update reviews previous FDA (2001; 2004) estimates of medical-device exposures to neonates that have undergone life-sustaining medical intervention (Table 9 in Draft Update) and 2 studies that measured levels of DEHP metabolites in the urine of neonates from neonatal intensive care units (NICUs) (Calafat et al., 2004; Green et al., 2005). While the Draft Update includes a discussion of the differences in metabolite levels between high and low exposure groups in the NICU studies, it does not put the metabolite levels into perspective by converting the metabolite levels to exposures. Such calculations show that exposures from medical devices are not likely to be higher than those predicted previously by the FDA. Calafat et al. (2004) reported a geometric

mean of 2003 ng/mL MEHHP in the urine of critically ill neonates. This was the metabolite in highest concentration. Based on a molar excretion ratio of 14.9% (Koch et al., 2003b) and assuming an intravenous fluid flow of 80 ml/kg/d for critically ill neonates (Bell and Acarregui, 2005) an exposure of 1.4 mg/kg/d is likely. The PE Panel recommends that these calculations be performed and the results included in the Draft Update to put the results of the NICU studies in proper perspective.

In conclusion, the section in the Draft Update on human exposures to DEHP could be significantly improved by including conversions of urinary metabolite levels to estimates of environmental exposure. The CDC biomonitoring data are the most comprehensive and accurate estimates available of exposures of the U.S. population, including children, to DEHP. The methods and data necessary to perform such a conversion are robust and readily available. In the absence of these conversions, it is not possible to put the CDC data into perspective, and their value to a risk assessment is therefore severely limited. Moreover, without these data the Expert Panel must instead focus on less accurate deterministic exposure estimates, or biomonitoring data from smaller population samples in other countries. As described above, through simple calculations, the CDC biomonitoring data can be used to show that conservative, 95th percentile estimates of DEHP exposure to all U.S. population sub-groups are within the range of 3-30 µg/kg/day DEHP used in the October 2000 Expert Panel Report. Average levels for all subpopulations are less than 3 µg/kg/day. The PE panel strongly urges the Expert Panel to include in the human exposure section exposure estimates based on the CDC biomonitoring data.

B. **Additional Comments on Human Exposure**

There are a few studies that are either missing from the Draft Update, or are presented in other sections of the Draft Update that should also be addressed in the section on human exposure.

1. The biomonitoring information for MEHP in human amniotic fluid reported in Silva et al. (2004) are critical to review relative to *in utero* exposure. Silva et al. reported that MEHP was present in amniotic fluid in much lower concentrations than in urine or serum. While these data cannot be used to estimate absolute maternal exposures, they can be used to compare, relatively, maternal exposures to fetal exposure. Such information, in conjunction with pharmacokinetic data from similar species such as the marmoset, would help provide a better understanding of DEHP pharmacokinetics.

2. In its review of Koch et al. (2005), the Draft Update states that the authors reported "that serum [MEHP] levels were present [in humans] at the same orders of magnitude as in animal studies, despite the fact that the human dose was 50–1000 times lower than in animal studies. The authors noted that if it is assumed that MEHP in blood is a surrogate for toxic potential, then DEHP would be 15–100 times more toxic in humans than in marmosets or rats."[4] This statement is without real supporting data and is inflammatory. All the animal evidence and pharmacokinetic evidence (see Section II below) indicate that while absorption of DEHP may be very efficient at low dose levels, it is not applicable to higher dose levels at which effects in laboratory animals are observed.

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[4] Draft Update at 8.

3. While the studies by Duty et al. (2003a; 2003b; 2004; 2005) were reviewed by the Expert Panel in the section on reproductive toxicity, they should also be addressed in the section on human exposure because they contain phthalate metabolite biomonitoring data.

In discussing exposures from medical devices, it is important to recognize that, in most cases, such exposures are acute or subacute. In contrast, animal effect levels are from subchronic or chronic studies.

II. COMMENTS ON SECTION 2.1: TOXICOKINETICS

Pharmacokinetic and metabolic information indicate that primates, which are a better model for investigating human reproductive toxicity than rats (Sharpe, 2000) are likely to be much less sensitive to DEHP than rats based on pharmacokinetic information alone. The presumption, based on phylogenetic similarity, is that primate data are more likely to reflect the response of a human primate to a chemical than are rodent data, and that, therefore, primates are a better model than rats for investigating the risk of human reproductive toxicity. In contrast to rodents, the recent study in marmosets treated with DEHP from weaning through sexual maturity found no effects on reproductive development even at very high doses of 2500 mg/kg/day (Tomonari et al., 2004; MCSI, 2003). The lower sensitivity of primates to reproductive effects of DEHP is, at least in part, the result of significant differences between rodents and primates in the absorption, distribution, metabolism, and excretion (ADME) of DEHP. These differences are described below.

Following oral administration to rats, DEHP itself is poorly absorbed but is efficiently transformed in the gut by nonspecific pancreatic lipase and mucosal esterase to its rapidly absorbed monoester, MEHP (White et al., 1980; Albro et al., 1982; Albro and Thomas, 1983; Albro and Lavenhar, 1989; Ito et al., 2005), the toxicologically relevant metabolite of DEHP (Sjoeberg et al., 1986a, 1986b; Teirlynck et al., 1988; Richburg and Boekelheide, 1996; Li et al., 2000; Dalgaard et al., 2001). As a result of this efficient metabolism and absorption, at least 50% – 60% of orally administered DEHP is absorbed by rats across a broad range of doses (i.e., 50 – 2000 mg/kg/day) as measured by the amount of DEHP and its metabolites appearing in the urine (Lhuguenot at al., 1985; Rhodes et al., 1986; Astill, 1989; Kurata et al., 2005) (The poster presenting data corresponding to the Kurata et al. (2005) abstract is attached to these comments as Attachment B). In rats, the absorbed MEHP is oxidized to other secondary metabolites. These metabolites are present in the blood and eventually excreted in the urine primarily in their free form, although limited (< 35%) glucuronide conjugation may occur (CERHR, 2000; Kurata et al., 2005). This is in contrast to humans and other primates where MEHP and other secondary metabolites are present in serum and urine primarily (> 70%) as glucuronide conjugates (CERHR, 2000; Silva et al., 2003; Kato et al., 2004; Kurata et al., 2005). This is an important interspecies difference because glucuronidation (a) increases the water solubility of metabolites and enhances their urinary excretion, and (b) reduces the biological activity of toxicologically active metabolites. The remainder of the administered dose is excreted largely in the feces, primarily as DEHP with lesser amounts of MEHP and other DEHP metabolites (Astill, 1989; Laignelet and Lhuguenot, 2000a and 2000b; Kurata et al., 2005).

The relatively stable absorption efficiency across the range of toxicologically relevant doses may help explain why the peak blood level for MEHP in the rat increases with dose from ~ 3 mg/l at 30 mg/kg oral DEHP to ~ 70 mg/L at 2000 mg/kg (See Table 3). However, there may be a limit to gastrointestinal absorption efficiency as evidenced by the observation that rats given ^{14}C-DEHP at 2800 mg/kg have peak MEHP blood levels of ~ 30 mg/L and excrete only 19% of the orally administered dose in the urine, the remainder being excreted in the feces (Teirlynck and Belpaire, 1985). The decrease in gastrointestinal absorption efficiency is likely due to the saturation of lipase activity at high doses, as evidenced by the increase in the percent of the administered dose that appears in feces as DEHP as the dose increased from 200 mg/kg (12%) to 1000 mg/kg (23%)(Laignelet and Lhuguenot, 2000a and 2000b).

Table 3: Maximum Blood MEHP Levels (mg/L) in Different Species

	Kessler et al., 2004	Kurata, 2005	Rhodes et al., 1986	MCSI, 2003	Rhodes et al., 1986	Laignelet and Lhuguenot, 2000 a-d	Kessler et al., 2004	Laignelet and Lhuguenot, 2000 a-d	Kessler et al., 2004	Pollack et al., 1985	Pollack et al., 1985	MCSI, 2003	Teirlynck and Belpaire, 1985
	Oral DEHP Dose (mg/kg)												
Species	30	100	100	100	200	200	500	1000	1000	2000	2000	2500	2800
Mouse						23.4		59.8					
Rat	2.8	8.7[a]				10.1	58	40.7	108	60	70		31.6[a]
Marmoset	2.2	1.3[a]	6.7[b]	2.8[a]	12[b]		18					10.7[a]	

[a] Assumes Blood [MEHP] = Plasma [MEHP]/2

[b] Assumes [MEHP] = 40% Cmax Radioactivity (Kurata et al., 2005)

The important role of pharmacokinetics in the toxicity of DEHP is also evidenced by limited data in mice. Mice are considered to be more sensitive to the developmental and reproductive effects of DEHP than rats (Price et al., 1988; Tyl et al., 1988; Lamb et al., 1987; Schilling et al., 2001; CERHR, 2000). Comparative pharmacokinetic data between pregnant and non-pregnant rats and mice from Laignelet and Lhuguenot (2000a-d) provide evidence that the increased sensitivity of mice can, at least in part, be explained by pharmacokinetic differences. These data demonstrate that peak MEHP blood levels are significantly higher in mice than rats administered comparable dose levels. The peak MEHP blood level in pregnant mice receiving a single dose of 200 mg/kg DEHP was 84 nmol/g compared with 36.4 nmol/g in rats. At 1000 mg/kg DEHP, the peak MEHP blood level in pregnant mice was 215 nmol/g compared with 146 nmol/g in rats. The data also indicate that rats excrete more of the administered DEHP dose in the feces after 3 days than do mice as the dose increases from 200 mg/kg/day (rats = 12%; mice

= 7%) to 1000 mg/kg/day (rats = 23%; mice = 18%). These observations are consistent with the finding that lipase activity in the mouse is higher than that of the rat (Ito et al., 2005). Thus, mice are an even less suitable model of human reproductive sensitivity to DEHP than are rats.

In contrast, the absorption of orally administered DEHP by primates is significantly less efficient than in rodents and results in lower blood levels of MEHP. Available data indicate that marmosets and cynomolgus monkeys gavaged with 100 mg/kg/day ^{14}C-DEHP excrete 15% to 30% of the administered dose via urine, the remainder being excreted largely in the feces, primarily as DEHP (Rhodes et al., 1986; Astill, 1989; Kurata et al., 2005). When the administered dose is increased to 500 to 2500 mg/kg/day, the fraction of the administered dose excreted in the urine falls to 4% to 15%. This decrease in absorption efficiency may explain why the peak blood level for free MEHP in the marmoset increases from ~ 2 mg/L at an oral dose of 30 mg/kg DEHP to a level that does not exceed 20 mg/L, even at a dose of 2500 mg/kg DEHP (See Table 3).

In addition, when exposed to similar levels of DEHP, primates experience much lower levels of the toxicologically relevant metabolite, MEHP, for a shorter period of time than do rodents. This is supported by Rhodes et al. (1986) who reported that marmosets dosed with dietary DEHP at 2000 mg/kg/day achieved a maximum absorbed dose that was 10 to 25-fold lower than that of equally dosed rats. Similar results were obtained in studies in cynomologus monkeys (Astill, 1989). Both findings are supported by results of a recent study (Kurata et al., 2005) in which juvenile rats and marmosets were gavaged with 100 mg/kg DEHP. Plasma radioactivity measurements taken up to 24 hr post-dosing indicated that rats absorbed 20 to 100-fold more DEHP than marmosets. While this radiolabel study could not differentiate between DEHP and its metabolites, results of another recent study (Kessler et al., 2004) bear on this issue. In Kessler et al., pregnant and nonpregnant rats and marmosets were given oral doses of 30 or 500 mg/kg/day DEHP. In rats, the normalized AUCs for MEHP were 100-fold higher than the normalized AUCs for DEHP; in marmosets, however, this difference was only about 10-fold. There was also a significant interspecies difference in plasma MEHP levels. Peak blood levels of MEHP in rats were 1 to 3-fold higher than those in marmosets, while AUC measurements demonstrated that MEHP levels in rats were 3 to 10-fold higher than those of marmosets, indicating that MEHP is eliminated from plasma more quickly in marmosets, a conclusion supported by Kurata et al. (2005). In sum, primates absorb a lower percentage of orally administered DEHP as MEHP and, because of higher glucuronidation, experience lower levels of toxicologically active metabolites for a shorter period of time than do rats.

The higher plasma levels of MEHP in rodents versus primates are also consistent with the results of a recent study by Ito et al. (2005; not reviewed in Draft Update), which evaluated the metabolism of DEHP in mice, rats and marmosets. Of the metabolic pathways evaluated, the most dramatic species differences were noted in lipase activity, which catalyzes the hydrolysis of DEHP to MEHP. The authors reported that lipase activity in the liver, small intestine and kidneys were highest in the mouse and lowest in the marmoset, with lipase activity in the liver and small intestine of the rat being more than 10-fold higher than that in marmosets. These species differences in lipase activity were consistent with kinetic data that showed the Vmax / Km ratio for lipase was almost 200-fold greater in rats than the marmoset. These data are consistent with the percent of the administered oral dose that appears in the feces of these species as DEHP and MEHP one day post-exposure: mice = 6.6% and 8.6%, respectively; rats =

11% and 6.3%, respectively (200 mg/kg oral DEHP each; Laignelet and Lhuguenot, 2000a-d); rats = 13% and 2.6%, respectively; marmosets = 47% and 2.8%, respectively (100 mg/kg oral DEHP each; Kurata et al., 2005). Therefore, these data support the conclusion that equivalent exposures to DEHP will result in much higher concentrations of the toxicologically relevant metabolite, MEHP, in rodents than in marmosets.

Recently Koch et al. (2005) reported that a human male volunteer given an oral dose of 0.65 mg/kg DEHP exhibited a peak free MEHP blood level of 2.5 mg/L, a level comparable to those reported in marmosets exposed at 50-fold (Kessler et al., 2004) or 150 fold (Kurata et al., 2005) higher levels of DEHP. The authors concluded that DEHP, at doses well below toxicologically relevant doses in rodents or marmosets, is almost completely absorbed by humans and excreted in the urine because (a) not all the known monoester metabolites were included in this study, and (b) labeled DEHP metabolites were still detectable in the urine two days post-exposure. In contrast, at 24 h post-exposure to a much higher oral dose of DEHP (100 mg/kg), marmosets excreted only 13% of the administered dose in the urine and 50% in the feces, the latter consisting of 95% DEHP (Kurata et al., 2005). This suggests that at high oral doses, absorption of DEHP by primates is significantly depressed. These observations indicate that low dose exposures in humans cannot be extrapolated to high dose exposures in humans or animals where the absorption (bioavailability) of DEHP is significantly depressed

In addition, studies on the distribution of radiolabeled DEHP and metabolites following oral administration to rats and marmosets have been reported (Tanaka et al. 1975; Ono et al. 2004; Kurata et al. 2005). The data indicate that high levels of radioactivity are found in plasma, gastrointestinal tract, liver and kidney, while lower levels of radiolabel are found in the testes. In a study of juvenile rats and marmosets exposed to 100 mg/kg ^{14}C-DEHP (Kurata et al. 2005), a preferential accumulation of radiolabel in the testes was not observed in either species, although the amount of radiolabel in the rats' testes was about 20-fold higher than that of the marmosets'. This difference is consistent with the difference in gastrointestinal absorption noted between the two species (Rhodes et al., 1986; Astill, 1989; Kurata et al., 2005). Radiolabel localized in the testes was lost from the tissue with a kinetic pattern comparable to the elimination of radiolabel from the test animal.

In conclusion, the ADME data discussed above indicate that toxicokinetic differences noted between rodents and primates are likely to play a significant role in the reproductive toxicity of oral exposures to DEHP. These toxicokinetic differences indicate that primates are much less susceptible than rodents to the reproductive effects of DEHP. In addition, because non-human primate data are much more likely to reflect the response of a human primate to a chemical than are rodent data, the Expert Panel could consider use of the primate reproductive NOEL of 2500 mg/kg/day. At the very least, the primate data provide a basis for the Draft Update to acknowledge that the use of rat data for human risk assessment is likely very conservative – that is, health protective.

III. COMMENTS ON SECTION 3: DEVELOPMENTAL TOXICITY DATA

A. The Data Reviewed in the Draft Update Support an Oral Developmental NOEL of 46 mg/kg/day.

The previous CERHR Expert Panel Report did not identify a firm NOEL for developmental toxicity on the developing male reproductive tract.[5] Given the more recent studies reviewed in the Draft Update, none provide a sufficient dose-response range to indicate a NOEL. However, a conservative NOEL of 20 mg/kg can be identified based on the NIH-supported study by Li et al. (2000). In that study, neonatal male rats were treated with doses of 20, 100, 200, or 500 mg/kg, and a NOEL of 20 mg/kg was established for effects on the reproductive tract (Sertoli cell vacuolization). Moreover, the multigeneration continuous breeding study conducted by NTP (2004), which is currently addressed only in the section on reproductive toxicity, supports a higher developmental NOAEL. Although the NTP study was not specifically designed as a developmental toxicity study, the endpoints at the lower doses are related to developmental effects and indicate that the NOAEL is 46 mg/kg/day (see Section IV.A of these comments).

B. The Data Reviewed in the Draft Update Support a Conservative Intravenous Developmental NOEL of 60 mg/kg/day.

Medical device exposures to DEHP, particularly exposures to critically ill infants undergoing intensive therapeutic interventions, were a primary concern of the first Expert Panel. As noted in the Draft Update, since the first Expert Panel review, in addition to new exposure information, new data have become available on the toxicity of intravenous exposures to DEHP. In particular, in a recent study by Cammack et al. (2003), DEHP was administered to 3 to 5-day-old male Sprague-Dawley rats by daily intravenous injections of 60, 300, or 600 mg/kg/day or by daily oral gavage of 300 or 600 mg/kg/day for 21 days. Histopathological evaluation and organ weight measurements were performed on some animals after 21 days of dosing (primary group) and at a later date on the recovery group animals that were held without further treatment until sexual maturity at approximately 90 days of age. No effects of any type were observed in animals treated intravenously with 60 mg/kg/day. Testicular changes, consisting of a partial depletion of the germinal epithelium and/or decrease in diameter of seminiferous tubules, were present in all animals of the 300 and 600 mg/kg/day groups after the 21-day dosing period. Testes weight decreased and liver weight increased in these animals. Testes changes were dose-related and generally more severe among animals dosed orally versus intravenously. In the recovery animals, a residual DEHP-induced decrease in seminiferous tubule diameter was present in the testis of several animals dosed orally at 300 and 600 mg/kg/day, but not in animals dosed intravenously. There was no germinal cell depletion or Sertoli cell alteration observed in any dose group at any time. Notably, no effects on sperm count, sperm morphology, or sperm motility were observed at 90 days of age in any of the groups.

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[5] The Expert Panel stated "The Panel is not confident that the lowest dose has been established at which developmental toxicity (the development of the male reproductive system) occurs." Expert Panel Report at 88.

Thus, the NOEL for intravenous administration of DEHP in Cammack et al. was 60 mg/kg/day. This was the NOEL used by the FDA to develop its intravenous tolerable intake for DEHP (FDA, 2001). This should be considered a conservative NOEL because the effects observed at the lowest observed effect level of 300 mg/kg/day were relatively mild and nearly all reversible, indicating that the "true" NOEL is probably closer to 300 mg/kg/day than to 60 mg/kg/day. As with the rodent oral toxicity studies discussed above, the marmoset data indicating that primates are likely much less sensitive to DEHP than rodents provide additional confidence that the 60 mg/kg/day intravenous exposure NOEL is conservative, and protective of human health.

C. The Draft Update's Discussion of Human Developmental Toxicity Data in Latini et al. (2003) and Swan et al. (2005) Should be Tempered With a Discussion of Additional Information Which Brings These Studies' Conclusions into Question.

Section 3.1 of the Draft Update, concerning human developmental toxicity data, includes descriptions of studies by Latini et al. (2003) and Swan et al. (2005). Consideration of these studies should be tempered by the information that follows. In addition, there are some additional studies that can be included in this section.

As indicated in the Draft Update, Latini et al. (2003) measured DEHP and MEHP in cord blood of 84 newborns, and found that MEHP-positive newborns showed a significantly lower gestational age than MEHP-negative newborns. A review of the data suggests that this association may reflect greater use of medical procedures with shorter pregnancies. DEHP has a urinary excretion half-life of about 6 hours (Peck and Albro, 1982). Latini et al. reported mean concentrations of DEHP and MEHP of 1.19 and 0.52 μg/ml respectively. Because DEHP is converted to MEHP in plasma with a half-time of 30 minutes (Peck and Albro, 1982), the only situation in which one would expect the DEHP concentration to exceed the MEHP concentration is if the sample collection had been immediately after the dose administration. Looking at the data in Table 1 of the paper, for 10 of the pregnancies there was no DEHP or MEHP detected. All newborns in this group were full term and there were no small-for-gestational-age infants. The absence of DEHP or MEHP may reflect that in this group there were no medical procedures, or they took place long before sample collection. There were 9 pregnancies for which DEHP but not MEHP were detected. Again, all were full term and there were no small for gestational age children. So, for these two groups, the blood data suggest that medical procedures were minimal and limited to those administered near the time of birth. There were 56 pregnancies for which both DEHP and MEHP were detected. Of these, 8 were preterm, 3 of the pre-terms were < 1500 g, and 2 were small for gestational age. This suggests that some of these pregnancies may have been more problematic, so that more medical procedures may have been employed, over a longer period of time. Finally, there were 9 pregnancies in which only MEHP was detected, of which 6 were full term and 3 were preterm. In this case, all 3 of the pre-terms were > 1500 g although 2 were considered to be small for gestational age. The presence of only MEHP suggests that medical procedures were employed but not at the time of delivery. Perhaps as the preterms in this group were not as small as those in the DEHP+/MEHP+ group, less needed to be done at the time of delivery. In any event, because of the short half-life of DEHP in the body, the cord blood DEHP and MEHP levels would reflect exposure within a day or two of the time of delivery, and therefore cannot explain the nature of the pregnancies.

The Draft Update states that the Swan et al. (2005) study is "very useful for the evaluation process" (p. 36). The PE Panel disagrees. Attachment A is a critique of the Swan study indicating that there are serious questions about the methodologies used for the study and therefore the usefulness of the results. In any event, as indicated in the Draft Update, Swan et al. found no correlation between anogenital distance and MEHP urinary levels.

Additional relevant studies include several that have evaluated reproductive and developmental effects in dialysis patients, a class of persons receiving higher-than-average exposure to DEHP over extended periods of time. Studies of pregnant women exposed to DEHP during dialysis do not indicate an increase in malformed offspring (Reister et al., 1999; Chan et al., 1998; Toma et al., 1999; Blowey and Warady, 1998).

Another recent study the PE Panel recommends including in the Draft Update is that of Main et al. (2005). Breast milk samples were obtained during the first three post-natal months from the mothers of 130 boys and analyzed for phthalate esters metabolites. Sixty-two of the boys exhibited cryptorchidism, and 68 did not. The study found no association between phthalate monoester levels and cryptorchidism. In addition, there was no significant correlation between MEHP and serum samples of gonadotropins, sex-hormone binding globulin (SHBG), testosterone and inhibin B.

D. **Additional Comments on Developmental Toxicity**

1. Page 69. The discussion of abstract from Foster et al. (2002; reference 105) contains a conclusion that is different from that stated by the authors in the meeting at which these data were presented. Attachment C is a copy of the poster presentation distributed at the meeting by the authors. Unlike the conclusion attributed to this study in the Draft Update, the poster presentation clearly indicates that additivity or synergy was NOT observed in experiments where rats were dosed with DBP and DEHP. To date, the PE Panel is unaware of any data to support the concept of additivity for these structurally unrelated phthalate esters.

2. The Draft Update occasionally cites abstracts of unpublished work which, in some instances, was subsequently published and also reviewed in the Draft Update. For example:

- Borch et al. (2002: reference 103) was subsequently published and reviewed in the Draft Update (Borch et al., 2003; reference 83);
- Phokha et al. (2002; reference 104) and Numtip et al. (2003; reference 111) were subsequently published in Kessler et al. (2004; reference 67);
- Wilson et al. (2004a; reference 109) was published in Wilson et al. (2004b; reference 86).

The inclusion of these references to abstracts may cause the reader to think that that these studies represent late-breaking information not yet published. To avoid such confusion, the PE panel recommends that the Draft Update refer only to the published studies.

IV. SECTION 4: REPRODUCTIVE TOXICITY

A. The Data Reviewed in The Draft Update Support a Reproductive NOEL of 46 mg/kg/day.

The Draft Update reviewed the multigeneration continuous breeding study in rats conducted by the NTP (2004; reference 145) and noted that while the study authors chose a NOEL of 7500 ppm, the Expert Panel suggested a NOEL of 1000 ppm might be more appropriate. The PE Panel concurs with this assessment. The PE Panel does not, however, agree with the comment that biologically relevant treatment-related findings were observed at lower dose levels in this study. The authors reported observations of "small" prostates, epididymides, or testes in 1-2 animals (4 for prostate) for the 1,000 and 300 ppm groups (about 46 and 14 mg/kg/day, respectively). However, the weights of these organs were normal. Since the effects were only reported in non-mating males, data were not available to indicate that the "small" organs had any effect on reproductive success. In addition, historical data from contract laboratories indicate that there is a 2-3% incidence of testicular atrophy at necropsy in control populations of sexually mature Sprague-Dawley rats from Charles River Laboratories. In the absence of reduced organ weight (individual or group mean) or evidence of lowered reproductive success, the "small" organs reported at 1000 and 300 ppm should not be considered toxicologically significant. The PE Panel believes that a NOAEL of 1000 ppm (46 mg/kg) is appropriate, based on the incidence and severity of the response at the lower dose levels, and is supported by data from other multigeneration studies with DEHP (Schilling et al., 2001; Tanaka, 2002; 2005).

B. Perspective on the Significance of Dietary Vitamins C and E

The Draft Update reviewed Ablake et al. (2004; reference 136) and its data showing reduced testicular effects of DEHP in male mice whose diet was supplemented with vitamins C and E, but did not review a similar study by Ishihara et al. (2000) in which rats treated with a combination of vitamins C and E also had reduced testicular toxicity. These studies together suggest an oxidative stress mechanism for testicular effects.

The impact of these studies for assessing risk to primates should be put into perspective relative to the ability of rats to manufacture vitamin C, an ability lacking in primates. Ishihara et al. (2000) demonstrated that rats given vitamins C and E in drinking water (about 450-500 mg/kg/day vitamin C) exhibited reduced testicular effects, relative to animals not receiving vitamins, from exposure to 20,000 ppm (1,000 – 1,500 mg/kg/day) DEHP in the diet. The absolute testes weights of DEHP/vitamin treated animals were significantly lower than controls (although testes-to-body weight ratios were comparable to controls), but significantly higher than DEHP-exposed rats that did not receive vitamins C and E. In addition, testicular pathology of DEHP/vitamin rats was improved relative to DEHP rats, though not entirely normal (spermatogenesis was present, but not at control levels; severe aspermatogenesis was not observed in DEHP/vitamin animals). Thus, the combination of vitamins C and E afforded some protection to the rats against the reproductive toxicity of high doses of DEHP. However, any potential protective effect of vitamin C cannot be distinguished from that of vitamin E because the two were provided together. Verma and Nair (2001) showed that mice pretreated with vitamin E showed little or no signs of testicular toxicity following treatment with aflatoxin. On

the other hand, Cave and Foster (1990) reported that very high levels of vitamin C (2 mM) were required for any protective effect against *m*-dinitrobenzene or *m*-nitrosonitrobenzene toxicity on Sertoli cells *in vitro*. Hence, it is possible that vitamin C had little impact on testicular toxicity, and that vitamin E played the larger role in the protective effect observed by Ishihara et al. in rats.

Because rats, unlike primates, produce about 150 mg/kg/day of their own vitamin C (Chatterjee, 1973), the rats in the Ishihara et al. study were effectively exposed to a total vitamin C dose of 600 – 650 mg/kg/day (plus 225 mg/kg vitamin E) and still exhibited smaller testes and reduced spermatogenesis after exposure to 1,000 mg/kg/day DEHP. The PE Panel believes it is important to note this because one might question the possible impact of DEHP exposure on human health given that the recommended daily allowance for vitamin C is 75 mg/person/day for women and 90 mg/person/day for men (NRC, 2003). Considerations relating to dietary administration of Vitamins C and E in mitigating the effects of DEHP are discussed in more detail in the Panel's April 2005 comments to CERHR.[6]

C. The Apparent Increased Sensitivity of Young Rats to DEHP Is Due to Toxicokinetic, Not Toxicodynamic, Differences

The Draft Update asserts that young rats are more sensitive to the reproductive toxicity of orally administered DEHP than adult rats.[7] However, the apparent increased sensitivity of young rats to DEHP is due to toxicokinetic, not toxicodynamic, differences as the absorption of MEHP in rats is age-dependent, with younger rats absorbing MEHP more readily than older rats. When rats of increasing age (25, 40, and 60 days old) were gavaged with 1000 mg/kg/day DEHP for 14 days, the mean area under the plasma concentration-time curve (AUC) of MEHP in the youngest group was twice as high as those in the two older groups (Sjoeberg et al., 1986b). Similarly, when 25 and 60 day-old rats were gavaged with 100 mg/kg ^{14}C-DEHP, twice as much radioactivity was found in the urine of the 25 day-old rats than in the 60 day-old rats (Sjoeberg et al., 1986b).

The enhanced absorption of MEHP in younger rats explains their seemingly greater susceptibility to the testicular effects of orally administered DEHP. As further evidence, when rats (25 and 40 days of age) were administered the highest tolerable dose of DEHP intravenously (six infusions of 500 mg/kg/day every other day), the age-dependent testicular effects seen after oral administration disappeared (Sjoeberg et al., 1986b). These results indicate that purported enhanced (toxicodynamic) testicular sensitivity of 25-day old rats to intravenous DEHP is, in fact, not higher than that of 40-day old animals. The absence of toxicodynamic differences between young and adult animals is also supported by the fact that the NOAEL for testicular toxicity reported in the Draft Update for young rats (3-5 mg/kg-d) is essentially identical to the NOAEL for adult rats (3.7 mg/kg/day; CERHR, 2000).

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[6] American Chemistry Council Phthalate Esters Panel. 2005. Comments: Recent Information on Exposure to and Toxicology of Di(2-ethylhexyl) Phthalate (DEHP). April 21, 2005. Available at: http://cerhr.niehs.nih.gov/news/dehp/pubcomm1/ACCCERHRDEHPcomments4-20-05.pdf.

[7] Draft Update at p. 91: "Studies on the male reproductive effects of DEHP in rodents often employ young animals because these animals are more sensitive to the testicular effects of phthalates."

D. Additional Comments on Reproductive Toxicity

1. Pages 92-93. The Draft Update characterizes the study by Kang et al. (2002) as "not useful for the evaluation process." While this study may be of questionable value for evaluation of post-pubertal reproductive toxicity, the PE Panel believes that Kang et al. has important implications for the evaluation of DEHP effects on the developing male reproductive tract. Phthalate esters are known to inhibit Gap Junctional Intercellular Communication in the carcinogenic process (Klaunig et al., 2003), and this decrease in intercellular communication can result in dysgenesis of gonocytes (Yu et al., 2005) similar to the dysgenesis observed following in utero treatment with DBP and DEHP (Mylchreest et al., 2002; Fisher et al., 2003; Barlow et al., 2003). Furthermore, Kleymenova et al. (2005) recently demonstrated that exposure to DBP alters the cytoskeleton in Sertoli cells, and interferes with communication with gonocytes. The impaired communication between Sertoli cells and gonocytes might lead to the inability of dividing gonocytes to properly segregate. The PE Panel believes that the data from Kang et al. are useful in understanding some of the key events in the potential mode of action for developmental effects on the male reproductive tract and should not be wholly dismissed the in the Draft Update as "not useful."

2. Page 87. The Draft Update discusses a study by Cobellis et al. (2003) and concludes it has limited utility for the evaluation process. The PE Panel agrees the study has limited value. Cobellis et al. (2003) measured DEHP and MEHP in plasma and interperitoneal fluid of 55 women with endometriosis and 24 controls. They found that the endometriotic women showed significantly higher levels of plasma DEHP than the controls. As noted above (Section 3), DEHP is converted to MEHP in plasma with a half-time of 30 minutes (Peck and Albro, 1982). Because MEHP levels were not elevated in the endometriotic women, it appears the high DEHP levels either reflected recent medical intervention (not unlikely for patients undergoing treatment) or analytical error.

3. An additional human study that could be included in the developmental toxicity section is Hack et al. (2002), which investigated various parameters in young adults who had been very-low-birth-weight infants (and thus probably had relatively high DEHP exposure due to intensive medical interventions). The authors found no difference in the rates of sexual intercourse, pregnancy, or live births between normal birth-weight men and men who had very-low-birth-weight. This suggests that probable high exposures to DEHP as neonates had no adverse effect on male reproductive function in these men. There was a significant difference in these parameters between very-low-birth-weight and normal-weight women, which could be due to a variety of factors.

4. The PE Panel also notes that, although existing human data is limited, the weight of available human data suggests that human exposures to DEHP do not cause adverse reproductive effects.

V. SECTION 5: SUMMARIES, CONCLUSIONS AND CRITICAL DATA NEEDS

In the original NTP-CERHR evaluation of DEHP, questions were raised about the exposure of pre-adolescent males and pregnant women to DEHP. In addition, using estimates of exposure to neonates receiving life-sustaining medical intervention, concern was raised about the

effects from such high exposures. The new data reviewed in the Draft Update appear to respond to those uncertainties by:

- Providing human biomonitoring information for the general public (CDC, 2003; 2005), fetuses (Silva et al., 2004), and neonates exposed during life-sustaining medical intervention (Calafat et al., 2004; Green et al., 2005), which demonstrate (after simple conversions) that exposures to the general population are within or below the 3-30 µg/kg/day estimate identified previously, and that exposures for neonates receiving intensive medical interventions are about 1.4 mg/kg/day;

- Providing data for three separate populations of neonates, some of which had relatively high exposures due to medical interventions, that failed to demonstrate any adverse effects of DEHP exposure on the pre-pubescent male (Rais-Bahrami et al., 2004; Swan et al., 2005; Main et al., 2005);

- Providing data which show that primates exposed to very high doses of DEHP from pre-puberty through puberty exhibited none of the testicular effects (i.e., Sertoli cell vacuolization, aspermatogenesis, testicular atrophy) found in rodents exposed to lower doses, suggesting that primates, including humans, are likely much less sensitive to the effects of DEHP;

- Providing data which support an oral-exposure NOAEL of 46 mg/kg/day for developmental and reproductive toxicity, which is higher than the NOAEL selected for the previous CERHR assessment; and

- Providing data which indicate that a conservative NOEL for intravenous exposure is 60 mg/kg/day.

The Draft Update assesses the reproductive and developmental toxicology of DEHP based primarily on data from studies of rats. The PE Panel believes that primates are a better model than rats for investigating human reproductive toxicity and that the Draft Update would benefit from either adopting a reproductive NOEL based on primate data, or at least acknowledging that a NOEL based on rat data is conservative in the face of data indicating that primates are likely much less sensitive to DEHP than rats.

Given that: 1) 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; 2) there is clear evidence that primates are less sensitive than rodents to the reproductive and developmental effects of DEHP; and 3) there are no data to suggest that adverse effects occur in neonates with relatively high exposures, the PE Panel believes that the overall conclusion is that the concern for risk to human reproduction from DEHP exposure is minimal.

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ATTACHMENTS

A. Technical Critique of Swan et al. (2005) by M. Gerald Ott, Ph.D and Dirk Pallapies, MD, MSc, BASF Corporation.

B. Poster presentation entitled “Metabolism of Di(2-ethylhexyl) Phthalate (DEHP) in Juvenile and Fetal Marmoset and Rat” distributed at the 2005 Society of Toxicology annual meeting by Kurata et al.

C. Poster presentation entitled “Antiandrogenic Effects of a Phthalate Combination on *In Utero* Male Reproductive Development in the Sprague-Dawley Rat: Additivity of Response?” distributed at the 2002 Society of Toxicology annual meeting by Foster et al.

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