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Dr. Michael B. Shelby, Director  
Center for Evaluation of Risks to Human Reproduction  
NIEHS  
P.O. Box 12233, MD EG-32  
Research Triangle Park, NC 27709

February 2, 2006

Re: NTP-CERHR expert panel update on the reproductive and developmental toxicity of di(2-ethylhexyl)phthalate – November 2005

Dear Dr. Shelby:

On behalf of Health Care Without Harm (HCWH), we submit these comments on the NTP-CERHR expert panel update on the reproductive and developmental toxicity of di(2-ethylhexyl)phthalate, issued November 2005.

Health Care Without Harm agrees with the expert panel's conclusions that:

- DEHP is a reproductive and development toxicant in animal studies that are relevant to humans;
- Health care delivery can be a significant source of DEHP exposure;
- Levels of DEHP exposure in sick infants receiving medical care are of serious concern; and
- Because DEHP crosses the placenta, exposures in pregnant women receiving medical treatments are also of concern.

We also emphasize that the expert panel's experiences with the unpublished Mitsubishi and BASF (Schilling) studies confirm the importance of carefully reviewing study design, raw data, data handling, data interpretation, and authors' conclusions if such studies will continue to be used by future CERHR and NTP panels. As the Expert Panel noted, for unjustified reasons the authors of the marmoset study removed from data analysis specific animals that apparently showed adverse impacts of DEHP exposure. Moreover, the study authors failed to examine the histopathology of the testis of each animal as required in their study design. The Expert Panel also concluded that the BASF/Schilling study showed histopathologic impacts of DEHP in the testes of animals in all treatment groups and that no NOAEL was identified in this study. The authors of the original paper provided no justification for ignoring those pathologic changes in the lowest dose treatment group of animals.

Detailed comments follow and are tracked in the PDF document attached. (Our comments are in page order.)

Page iii: In the introductory section to the Panel's conclusions, the report indicates that there was not consensus around reducing the concern level for pregnant women. We agree with some of the panel members, that the level of concern for pregnant women identified in the 2000 expert panel report should NOT be reduced. It is our position that pregnant women's exposure remains a concern, as stated, because:

- 1) MEHP passes the placenta in free form where it may not be detoxified by the fetus, 2) exposure throughout pregnancy is not necessary to cause damage in animal models, and
- 3) current exposure estimates in women of child bearing age do not distinguish peak or episodic exposures from average exposures.

Page 4, Table 5: It does not look like the data are expressed as percentages but rather as micrograms/kg/day. Which is correct? The later reference on page 26 that "more than 90% of the intake is from food" is not consistent with Table 5. Table 5 indicates that less than 90% intake *for infants* is from food.

Page 11, Figure 2: It is not clear what the "x" axis represents on the graph.

Page 26 – The statement that estimates the percentage intake of DEHP from food is not accurate for infants (See comment for page 4, Table 5 above).

Page 27: The report does not indicate what the expert panel thinks about the validity of David's argument and Koch's response. Is there any other research to support David's case? The expert panel report should explicitly note that David has a conflict of interest inasmuch as he has financial ties to the phthalate manufacturing industry.

Page 55: In reference to the Rais Bahrami, et al. study, the panel identifies the utility of the study as minimally significant due to the small sample size and the lack of a comparison group. A major limitation of the study is the lack of measurements of phthalate exposure. The panel report should explicitly note this important limitation of the study.

Page 98, Table 28: In reference to the developmental LOAEL, the panel's conclusion for the LOAEL differs from the author's conclusion, which is apparently quoted in the Table. It is important to note that the Table reflects the authors' conclusion and does not reflect the panel's conclusion, especially so that the subsequent panel discussion of Schilling in Section 4 does not appear to be in contradiction to what is noted here.

Page 143: In reference to the discussion of the Schilling study, the note in the "utility" section states that the study was useful in the evaluation process, showing a LOAEL of 1000 ppm (~100 mg/kg bw/day). This was the lowest dose tested. The panel, however, goes on to say that since this is a conclusion of the Expert Panel and not the authors', it is a cause for concern and limits the confidence that this conclusion can bear. We disagree that the panel's conclusion bears

limited confidence. A review of the original paper clearly shows histological impacts that the authors simply ignored when deriving their conclusion. Adverse impacts of DEHP exposure are discernable at every dose tested.

Page 169: In the section updating the science on reproductive toxicity, the report should make it clear that in the Schilling study ~113 mg/kg/day was the lowest dose tested.

Page 171: In reference to the Schilling study, the “update” states, “Data not considered in the earlier report demonstrated that humans have ~2–3-fold lower levels of intestinal lipases than ferrets and rats.” We are unable to identify a reference for this in the draft report. The summary of Ito et al. (page 41) discusses rodents and marmosets, but *not* humans. The 2001 FDA “Safety Assessment of DEHP Released from Medical Devices” states (page 31):

“Consequently, individuals with high rates of lipase activity and/or low rates of glucuronidation activity could be at higher risk of DEHP-induced adverse effects than the rest of the population. Polymorphisms in genes coding for pancreatic (Hegele et al., 2001) and hepatic (Cohen et al., 1999) lipase in humans are known to exist and these polymorphisms can result in lipase deficiency. Low lipase activity would be expected to exert a protective effect in these individuals with regard to DEHP-mediated effects. Conversely, pancreatic lipase activity is increased by heparin administered to patients on hemodialysis (Montalto et al., 1997) and plasma lipoprotein lipase activity is increased by erythropoietin (Goto et al., 1999), which is also administered to patients on hemodialysis. Increased lipase activity would facilitate the conversion of DEHP to its active metabolite. Smoking is also known to increase lipase activity (Kong et al., 2001) and DEHP itself induces lipase activity in rodents (Mocchiutti and Bernal, 1997). Consequently, some individuals in the DEHP-exposed population can convert DEHP to MEHP more efficiently than others. This variability is evidenced, to some extent, by the variability in the rate at which intestinal mucosal cell preparations obtained from two humans hydrolyzed a number of di-n-alkyl phthalates (Lake et al., 1977). The metabolic rates between these two individuals differed by around 3- to 6-fold. Presumably, the degree of variability would increase with a larger sample size.”

We also note that ref 96 in the Expert Panel report discusses differences in phthalate hydrolysis among non-human primates.

It is also important to keep in mind the absorption and serum levels of DEHP metabolites reported by Koch after he ingested labeled DEHP. Levels were comparable to those in marmosets given far higher doses. This suggests that there may be differences between humans and marmosets with respect to intestinal or pancreatic lipase levels and marmosets should not be assumed to accurately reflect levels in humans without empirical data supporting that conclusion. Moreover, intestinal and pancreatic lipase is inducible and *in vitro* assays will not accurately portray *in vivo* circumstances.

Page 175: In the section identifying additional data needs, we also suggest noting a need for human *in vivo* data. Enzymes are inducible and vary with diet and co-exposure to xenobiotics

capable of enzyme induction. These variables may influence individual susceptibility to DEHP exposure.

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Thank you for considering our comments. We look forward to seeing the CERHR/NTP monograph on DEHP.

Sincerely,

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A handwritten signature in cursive script that reads "Anna Gilmore Hall".

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