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September 9, 2002

Dr. Mary Wolfe  
NTP Board Executive Secretary, NIEHS  
P.O. Box 12233  
MD A3-07  
Research Triangle Park, NC 27709

Dear Dr. Wolfe:

The American Chemistry Council Phthalate Esters Panel (PE Panel) submits these comments on the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction "Draft (7-16-02) NTP-CERHR Report on the Potential Human Reproductive and Developmental Effects of Di-*n*-Butyl Phthalate (DBP)" (Draft DBP Report). 67 Fed. Reg. 53807 (Aug. 19, 2002). The PE Panel includes the major U.S. producers and several processors of phthalate esters. The PE Panel appreciates the opportunity to comment on the Draft DBP Report and urges NTP to likewise solicit comments on all of its draft reports for CERHR chemicals.

For the reasons stated in these comments, the PE Panel believes the data do not support NTP's conclusions in the Draft DBP Report. In addition, NTP should take steps to increase the transparency and clarity of its document.

If you have any questions, please call Marian K. Stanley, Manager of the Phthalate Esters Panel, or email her at [Marian\\_Stanley@americanchemistry.com](mailto:Marian_Stanley@americanchemistry.com).

Sincerely yours,

A handwritten signature in black ink, appearing to read "Marian K. Stanley". The signature is written in a cursive style with a large initial "M".

cc: Dr. Michael Shelby



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## EXECUTIVE SUMMARY

The American Chemistry Council Phthalate Esters Panel (PE Panel) submits these comments on the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction “Draft (7-16-02) NTP-CERHR Report on the Potential Human Reproductive and Developmental Effects of Di-*n*-Butyl Phthalate (DBP)” (Draft DBP Report). The PE Panel includes the major U.S. producers and several processors of phthalate esters. The PE Panel’s comments make the following points:

- The Draft DBP Report falls short of the goal of providing the public “with clear, balanced, [and] scientifically sound information” on DBP. The report focuses on the hypothetical risks posed by DBP without clearly conveying to the reader how very low those risks are. The available data show that *the average exposure to DBP is 30,000 times below a level at which no effects are seen in animals*. Even the highest measured exposure to DBP is hundreds of times below that no observed adverse effect level (NOAEL). Furthermore, there is evidence that primates are much less sensitive to such effects from phthalates than are rodents. Thus, the data indicate that reasonably anticipated exposures to DBP are unlikely to pose a reproductive toxicity risk to humans. By reaching a conclusion of “some concern” for *in utero* developmental effects, the Draft DBP Report gives a contrary impression without presenting an adequate justification and without objectively describing the various assumptions made and acknowledging openly the contrary data.
- NTP should take steps to increase the transparency and balance of the brief.
  - The “level of concern” language is inherently subjective and may lead to confusion and misapprehension on the part of the public. Because the Expert Panel on phthalates used that language, the PE Panel understands NTP’s use of it in the phthalate briefs, but NTP should clearly define the margins of exposure and other considerations used to reach each level of concern determination.
  - NTP needs to provide other information to make the basis for its conclusions regarding DBP transparent, such as information on species differences and more complete information on exposure data, and needs to avoid selectivity in the additional information it provides in the brief.
- NTP’s conclusions regarding DBP are not supported by the data. NTP concludes that there is “some concern” for DBP causing adverse effects on human development, particularly the development of the reproductive system, whereas the Expert Panel expressed “minimal concern.” The NTP conclusion is based on the maximum DBP exposure value for women of reproductive age from a relatively small sample of the population. Such a single data point does not provide a scientifically sound basis for drawing conclusions regarding risk. The 95<sup>th</sup> percentile value from that sample was much lower and supports the Expert Panel’s original conclusion of “minimal risk.” Further, subsequent data indicate that the maximum value used by NTP may have been an anomaly – potentially representing factors such as sampling, analytical or transcription contamination or error.

- NTP's absolute conclusions regarding the threat and potential exposures of DBP are excessively strong and misleading. NTP answers "yes" to the question of whether DBP can affect human development or reproduction, even though it then contradicts itself by stating (correctly) there is only the potential to cause such effects. NTP answers "probably" to the question of whether current exposures to DBP are high enough to cause concern, but this is excessively strong given the available exposure data. NTP should better correlate its conclusions with a balanced, thorough explanation of the supporting data.
- NTP should be cautious when offering its own interpretation of the potential health effects of studied chemicals, especially when that interpretation differs from that of the Expert Panel Report. The Expert Panel presents a large amount of expertise that should be respected by NTP and not lightly set aside. NTP should be fully transparent in explaining the basis for any potential modification to the Expert Panel conclusions and should subject all of its reports, as it has here, to notice and comment.

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## INTRODUCTION

The American Chemistry Council Phthalate Esters Panel (PE Panel), which includes the major U.S. producers and several processors of phthalate esters,<sup>1</sup> submits these comments on the “Draft (7-16-02) NTP-CERHR Report on the Potential Human Reproductive and Developmental Effects of Di-*n*-Butyl Phthalate (DBP)” (Draft DBP Report), issued by the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR).<sup>2</sup> The final report will represent the final step in the CERHR evaluation of DBP begun in 1999, which involved the formation of a panel of 16 experts that evaluated the data for DBP (and six other phthalate esters), culminating in an Expert Panel report issued in October 2000.<sup>3</sup> NTP CERHR solicited comments on that report, which were due December 11, 2000.<sup>4</sup> The Draft DBP Report now released by NTP includes NTP’s Brief on DBP (NTP DBP Brief), a copy of the Expert Panel report on DBP, and copies of comments received on the Expert Panel report.

The PE Panel appreciates the opportunity to comment on the Draft DBP Report. As the first NTP report on a chemical evaluated under the CERHR program, the Draft DBP Report will be a template for other NTP CERHR reports, and it is therefore most appropriate the NTP seek public comment on it.

In addition, the PE Panel believes NTP should seek public comment on each and every report it develops for a CERHR-reviewed chemical. Because the NTP report may consider scientific data published subsequent to the Expert Panel’s deliberations, the NTP report may include new substantive scientific conclusions that should be subject to public review and comment, just as were the conclusions of the Expert Panel.

The NTP DBP Brief presents NTP’s “interpretation of the potential for exposure to DBP to cause adverse reproductive or developmental effects in people.” Draft Report at 2. It is based on the October 2000 report by the CERHR Expert Panel and the public comments received on the Expert Panel Report. NTP also considered “additional scientific information” that has become available since the Expert Panel Report was released. *Id.* According to NTP, the NTP Brief on DBP “is intended to provide readers with clear, balanced, scientifically sound information on the potential for DBP exposures to result in adverse health effects on development and reproduction.” *Id.*

The PE Panel believes that the Draft NTP DBP Brief falls short of the goal of providing the public “with clear, balanced, [and] scientifically sound information” on DBP. The brief focuses on the hypothetical risks posed by DBP without clearly conveying to the reader

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<sup>1</sup> The PE Panel’s members include BASF Corporation, Eastman Chemical Corporation, ExxonMobil Chemical Company, Ferro Corporation, PolyOne Corporation, Sunoco Inc., and Teknor Apex Company.

<sup>2</sup> 67 Fed. Reg. 53807 (Aug. 19, 2002); draft NTP DBP Brief available at <http://cerhr.niehs.nih.gov/news/DraftDBPBrief.pdf>.

<sup>3</sup> *NTP-CERHR Expert Panel Report on Di-n-Butyl Phthalate*. NTP-CERHR-DBP-00, October 2000 (<http://cerhr.niehs.nih.gov/news/dbp-final-inprog.PDF>).

<sup>4</sup> 65 Fed. Reg. 60206 (Oct. 10, 2000).

how very low those risks are. The available data show that *the average exposure to DBP is 30,000 times below a level at which no effects are seen in animals*. Even the highest measured exposure to DBP is hundreds of times below that no adverse effect level (NOAEL). Furthermore, there is evidence that primates are much less sensitive to such effects from phthalates than are rodents. Thus, the data indicate that reasonably anticipated exposures to DBP are unlikely to pose a reproductive toxicity risk to humans. By reaching a conclusion of “some concern” for *in utero* developmental effects, the draft NTP DBP Brief gives a contrary impression without presenting an adequate justification and without objectively describing the various assumptions made and acknowledging openly the contrary data. The PE Panel urges NTP to reexamine the DBP brief as a whole for its balance, objectivity and transparency.

As discussed in Part I of these comments, NTP should take steps to increase the transparency and balance of the brief. The “level of concern” language is inherently subjective and may lead to confusion and misapprehension on the part of the public. Because that language was used by the Expert Panel on phthalates, the PE Panel understands NTP’s use of it in the phthalate briefs, but NTP should clearly define the margins of exposure and other considerations used to reach each level of concern determination. In addition, NTP needs to provide other information to make the basis for the conclusions regarding DBP transparent, such as information on species differences and more complete information on exposure data, and needs to avoid selectivity in the additional information it provides in the brief.

In Part II of these comments, the PE Panel explains that NTP’s conclusions regarding DBP are not supported by the data. NTP concludes that there is “some concern” for DBP causing adverse effects on human development, particularly the development of the reproductive system. This level of concern “is greater than that expressed by the Phthalates Expert Panel and is based on recent exposure estimates that were not available to the expert panel.” Draft Report at 6. The NTP conclusion is based on the maximum DBP exposure value for women of reproductive age from a relatively small sample of the population. Such a single data point does not provide a scientifically sound basis for drawing conclusions regarding risk. The 95<sup>th</sup> percentile value from that sample was much lower and supports the Expert Panel’s original conclusion of “minimal risk.” Further, subsequent data indicate that the maximum value used by NTP is an anomaly – potentially representing factors such as sampling, analytical or transcription contamination or error.

In addition, NTP’s absolute conclusions regarding the threat and potential exposures of DBP are excessively strong and misleading. NTP answers “yes” to the question of whether DBP can affect human development or reproduction, even though it then contradicts itself by stating (correctly) there is only the potential to cause to such effects. NTP answers “probably” to the question of whether current exposures to DBP are high enough to cause concern, but this is excessively strong given the available exposure data. NTP should better correlate its conclusions with a balanced, thorough explanation of the supporting data.

In Part III, the PE Panel makes a related point – NTP should be cautious when offering its own interpretation of the potential health effects of studied chemicals, especially when that interpretation differs from that of the Expert Panel Report. The Expert Panel presents a large amount of expertise that should be respected by NTP and not lightly set aside. NTP

should be fully transparent in explaining the basis for any potential modification to the Expert Panel conclusions and should subject all of its reports, as it has here, to notice and comment.

**I. THE DRAFT REPORT SHOULD BE FULLY TRANSPARENT IN PRESENTING ITS CONCLUSIONS AND DISCUSSING THE SUPPORTING DATA**

The Draft Report is “intended to provide readers with clear, balanced, scientifically sound information on the potential for DBP exposures to result in adverse health effects on development and reproduction.” Draft Report at 2. The conclusions of the Draft Report are based upon the Expert Panel Report, public comments, and additional scientific information available since the Expert Panel meetings.

While the PE Panel commends the efforts of NTP in attempting to achieve these goals, it believes that the Draft Report fails to present a clear, balanced, and scientifically sound presentation of the data on DBP in many important respects. The “level of concern” language is subjective and therefore subject to misunderstanding and mischaracterization. NTP should clearly define the margins of exposure and other considerations used to reach each level of concern determination. In addition, NTP needs to provide other information to make the basis for its conclusions regarding DBP transparent, such as information on species differences and more complete information on exposure data, and needs to avoid selectivity in the additional information it provides in the brief.

**A. The Report Must Make the Content of Its “Level of Concern” Conclusions Transparent**

**1. The Level of Concern Language Obscures Rather Than Clarifies the Relative Risks of the Chemicals**

The purpose of the CERHR, as indicated by its title, is to provide an evaluation of the reproductive *risks* posed by chemicals. In its original charge, the Expert Panel on phthalates was asked to “Rigorously evaluate all relevant data and reach a conclusion regarding the strength of scientific evidence that exposure to a chemical agent(s) may or may not present a risk to human reproduction or development.”<sup>5</sup> Indeed, the word “risk” was used four additional times in the complete charge to the Expert Panel, and the Expert Panel was specifically directed to, “Provide judgments, including qualitative statements of the certainty of the judgments, that an agent presents a potential risk to human reproduction and/or development.”<sup>6</sup>

During the course of the Expert Panel’s deliberations, however, a decision was made to use “level of concern” language rather than provide qualitative statements of “risk.” The PE Panel’s previous comments have objected to this decision, and the PE Panel continues to believe that the level of concern language does not serve the purpose of providing the public with

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<sup>5</sup> Charge to Expert Panel (emphasis added).

<sup>6</sup> *Id.*



“scientifically-based, uniform assessments of the potential for adverse effects on reproduction and development caused by agents to which humans may be exposed.”<sup>7</sup>

The PE Panel believes that the level of concern format is less scientific, less familiar to regulatory agencies, and less clear than statements of potential risk. Such “concern” language invites incorporation of value judgments or policy considerations that are not suitable to the purely scientific assessments that NTP-CERHR should render.

Statements of “concern” are very subjective. For example, in the scale used by the Expert Panel and the Draft DBP Report, the unqualified term “concern” correlates to a lesser margin of exposure than the term “some concern.” However, the PE Panel believes that to many, “some concern” sounds like a greater degree of concern than simple “concern.” Thus, these terms may actually confuse the public about the relative risks posed by various chemicals.

Further, one person’s concern can be another person’s comfort. In general, risk assessment agencies consider a margin of 100 between the animal no observed adverse effect level (NOAEL) and human exposure to provide an adequate margin of safety. For the Expert Panel on phthalates, however, that margin resulted in a finding of “some concern.” In general, the PE Panel believes the level of concern language gives an inflated impression of the likelihood of a human risk or the strength of the evidence that indicates a possible risk.

In addition, the “concern” language is subject to mischaracterization and misuse by those who wish to alarm the public unnecessarily regarding the supposed threat of a chemical, such as DBP, for which there is little scientific basis to make such claims. It is easy to warn that the CERHR expressed concern about the chemical, without explaining the margin of exposure and assumptions about relevance of animal data that underlie the level of concern.

For these reasons, the PE Panel strongly encourages NTP to develop language that more accurately conveys the actual risk posed by chemicals it discusses in future reviews. For purposes of the phthalate esters reports, the NTP reports must more clearly define for the reader the content of the level of concern conclusions.

## 2. The NTP Phthalate Esters Reports Must Clearly Define the Content of the Level of Concern Conclusions

Because the Expert Panel on phthalates used level of concern language for its reports, the PE Panel understands why NTP used that language in the draft NTP DBP brief. However, it is important that NTP more specifically define for the reader the meaning of the concern terms. This is necessary to make the conclusions of the NTP briefs transparent to the reader, and to avoid the subjectivity and confusion discussed in the previous section of these comments.

For each phthalate it reviewed, the Expert Panel on phthalates made an estimate of human exposure to the phthalate and selected an animal NOAEL for the chemical. Review of

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<sup>7</sup> See “Purpose” in the “About CERHR” description at <http://cerhr.niehs.nih.gov/aboutCERHR/index.html>.

the conclusions in the seven Expert Panel phthalate reports shows that, where the margin of exposure (MOE) was greater than 10,000, the Expert Panel generally found “negligible concern.” Where the MOE was in the range of 1000 to 10,000, the Expert Panel expressed “minimal concern.” “Some concern” would correspond to an MOE of 100-1000, and so forth. In addition to these general ranges, the Expert Panel also considered factors such as species differences and age. Information such as this should be presented to the reader so that a conclusion such as “some concern” has content, rather than being a subjective term subject to misinterpretation.

The Expert Panel’s conclusions should be presented in a manner that makes it clear what estimate of exposure it used (for DBP, 2-20 µg/kg/day), what NOAEL it used (for DBP, 50 mg/kg/day for male reproductive tract effects), the resulting margin of exposure (5000 to 25,000), what additional considerations informed the Expert Panel’s conclusions (such as species differences), and the Expert Panel’s conclusions (negligible concern for adult reproductive toxicity and minimal concern for about effects to human development).

If NTP has determined that new information might indicate need for modification of the Expert Panel’s conclusions, it likewise should clearly explain the risk assessment parameters in the brief – what does the new data indicate regarding the NOAEL used by the Expert Panel? What does it indicate regarding the exposure estimate and thus the MOE? In so doing, NTP will provide information that is familiar to risk assessors and that provides a more transparent and less subjective basis for the general public to draw conclusions about the degree of risk posed by the chemical.

#### B. Additional Information Is Needed to Enable the Public to Understand the Risk Posed by the Chemicals

The draft NTP DBP Brief is missing several pieces of information and therefore is lacking in transparency and the ability to convey clear, balanced, and scientifically sound information regarding DBP. NTP has included some information that is helpful in putting the information into perspective – such as comparing the exposure estimate to the weight of a drop of water and grain of table salt. The PE Panel believes the DBP brief should include the additional information to provide readers with a clear perspective.

NTP should make the public aware when species differentiation may modify the level of assessed concern; that is, NTP should make it easily understandable that effects seen in rodents may not be applicable to humans. In particular, NTP should clarify that, for phthalates, there is evidence that primates (of which humans are members) may be less much sensitive to the effects of phthalates than are rodents.<sup>8</sup>

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<sup>8</sup> For example, high doses of DEHP and DINP do not produce testicular effects in primates (Kurata et al., 1997; Hall et al., 1999; Pugh et al., 2000). In addition, rodents are more sensitive than primates to the effects of peroxisome proliferating agents such as phthalates, and the testicular effects of DEHP in rodents show some dependence on the peroxisome proliferation activation receptor (Ward et al., 1998). The Expert Panel found studies on DEHP relevant for considering the mechanism of DBP toxicity (CERHR, 2000, p. 33).

NTP also should clarify that, even if such effects are applicable to humans, there is a large difference between human exposure levels and the levels at which effects are seen in animals. The brief should make clear that the average exposure to DBP (about 1.5 µg/kg/day, based on the CDC monitoring data) is more than 30,000 times below the animal NOAEL. Even the maximum measured exposure (113 µg/kg/day) is 500 times below the NOAEL. Further information to clarify DBP exposures is discussed in Section II.A of these comments.

Further, NTP should avoid selectivity in the additional information it provides in the brief. The PE Panel believes that the draft NTP DBP Brief has selectively incorporated new information, and as a result it is not scientifically balanced in its conclusions. For instance, only one study of exposure published subsequent to the Expert Panel deliberations has been cited (Blount et al., 2000).<sup>9</sup> That study has been followed by two additional studies of a larger population (CDC, 2001) and a specific population of women of childbearing age (Hoppin et al., 2002). As discussed in Section II.A, below, the Panel believes that these additional studies suggest a very different conclusion from that in the draft NTP DBP Brief.

Another example is the selective citation of Shono et al. (2000) as evidence of an antiandrogenic effect from DBP. However, that study in no way represents conclusive mechanistic information that would confirm decreased testosterone synthesis as a mode of action for the developmental effects of DBP (especially since this was a single dose-level study). This lack of a clear mechanism was commented on by Mylchreest and Foster in a letter to the editor in response to a letter by Shono and Suita (Mylchreest and Foster, 2000). If Shono et al. (2000) is discussed in the DBP Brief, the Mylchreest and Foster comments likewise should be discussed.

This lack of a comprehensive discussion of the supporting science conveys an imbalanced view of the data, and will only serve to confuse and mislead the public. Instead, NTP should ensure that it will fairly consider all of the available data in order to present a scientifically sound and precise judgment regarding the chemicals it studies.

## **II. THE DATA DO NOT SUPPORT THE CONCLUSIONS EXPRESSED IN THE DRAFT DBP BRIEF**

As written, the NTP Brief on DBP has overstated many of its conclusions in light of the supporting science. The result is a document that may cause undue alarm among members of the public.

### **A. The Additional Exposure Data Cited by NTP Do Not Provide a Sufficient Basis to Conclude That DBP Presents Some Concern for Adverse Effects**

In its draft DBP Brief, NTP has concluded that “[b]ased upon recent estimated DBP exposures among women of reproductive age, the NTP has some concern for DBP causing

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<sup>9</sup> The brief cites to Kohn et al. (2000) as converting the Blount data into exposure information. David (2000) separately converted the Blount et al. data to phthalate exposures, using a different methodology. The Kohn et al. and David results are very similar, giving confidence in the exposure values derived. The PE Panel believes NTP should cite to David (2000) as well as to Kohn et al. (2000).

adverse effects to human development, particularly development of the reproductive system.” NTP DBP Brief at 6. This level of concern – “some concern” – is greater than that expressed by the Expert Panel, which had concluded that there was “minimal concern” for adverse developmental effects from DBP exposure. The Expert Panel based its conclusion on its estimated general population exposure to DBP of 2-10 µg/kg bw/day (micrograms per kilogram body weight per day).

NTP adjusted the Expert Panel’s conclusion based on the maximum DBP value given by Blount et al. (2000) and Kohn et al. (2000). Blount et al. (2000) measured the amount of the primary DBP metabolites (monobutyl phthalate ester, or MBP) in samples of human urine. Kohn et al. converted the urine metabolite levels to phthalate exposures, using pharmacokinetic information, and concluded that some women of reproductive age (20-40 years old) are exposed to substantially higher DBP levels (over 100 µg/kg bw/day) than other age or sex groups. These higher exposure levels led NTP to adjust the “level of concern” categorization for DBP upward in the NTP Brief.

The PE Panel believes that the maximum value for DBP given by Kohn et al. is not a sufficient basis for adjusting the Expert Panel’s classification of DBP. The sample analyzed by Blount et al. is too small to provide a basis on which a sound, well-balanced scientific judgment may be made about maximum exposures to DBP. Blount et al. reports the results of CDC measurement of phthalate metabolites in the urine of only 289 individuals (which the authors explained was not a representative sample of the general population). Of that 289, only 97 individuals were women between the age of 20 and 40. Thus, only 4 or 5 women would have had levels at or above the 95<sup>th</sup> percentile level. The maximum value – on which NTP has based its increase in level of concern for DBP – represented the value determined for only one woman, and there is always the possibility that that one value represents skewing by any of a variety of factors, such as sampling, analytical or transcription contamination or error.

In general, scientific judgments are seldom, if ever, based on the maximum (or minimum) value provided by a set of data – there is simply too much likelihood that the extreme values in a data set are the result of sampling, analytical or other error. Risk assessments typically are based on the 90<sup>th</sup> or 95<sup>th</sup> percentile. Of note, when the CDC published a larger set of data for phthalates (1029 samples – three times greater than the Blount et al. sample size), it did not provide any data above the 90<sup>th</sup> percentile, and it did not provide any demographic analysis of that data, explaining that the sample size was too small to support such analysis (CDC, 2001).

Kohn et al. estimated that 95th percentile for women aged 20-40 to be 32 µg/kg/day. As the NOAEL for DBP is 50 mg/kg/day (50,000 µg/kg/day), the margin of exposure for such women is over 1500, which supports the Expert Panel’s original conclusion of “minimal concern.” The maximum exposure of 113 µg/kg/day gives a MOE of 500, and apparently this is the basis on which NTP changed the conclusion to “some concern,” but, for the reasons just given, that maximum value is too fragile a basis on which to base such a conclusion.

Additional data published subsequent to Blount et al. and Kohn et al. suggest the maximum value of 113 µg/kg/day may have been an anomaly. As mentioned above, the CDC published the results for monitoring of phthalate metabolites from 1029 persons in 2001 (CDC

2001). The CDC presented the 90<sup>th</sup> percentile rather than the 95<sup>th</sup> percentile and gave no maximum value, and therefore those data are not directly comparable to Blount et al. However, the median value for MBP (22 µg/g creatinine) was less than that from Blount et al. (33 µg/g creatinine). Furthermore, results for 45 women, ages 35-49, were provided by Hoppin et al. (2002). The maximum MBP value for that group was reported as 157 µg/g creatinine, versus the maximum of 2760 µg/g reported by Blount et al. That is, the maximum DBP exposure for women in the Hoppin et al. study was approximately 6 µg/kg/day – a value over 8000 times below the animal NOAEL. The difference between the Blount and Hoppin results potentially could be due to several factors, including the somewhat different age groups, the ethnicity of the sample population, or the sample size. Nevertheless, that the maximum levels were so low in Hoppin compared to Blount indicates that caution should be used in drawing conclusions from the Blount data.

The PE Panel further notes that the basis for concern regarding DBP exposures is potential effects on the fetuses of women exposed to the phthalates. There are no published data to indicate whether pregnant women are among those with higher than average exposure to DBP. At a presentation at the International Society for Exposure Analysis (ISEA) in 2000, Dr. John Brock of the CDC was understood to state that phthalate exposures for pregnant women were actually below the reference population. That data have not been published, but the issue is deserving of further inquiry by NTP.

The CDC intends later this fall to publish additional data on phthalate metabolite monitoring, including the results for analyses from another two years of sampling. CDC has indicated that it will provide demographic breakdowns of this data. The PE Panel urges NTP to wait for the publication of that report prior to issuing the final DBP Brief, since the results will provide a much more definitive picture of DBP exposure. In any event, however, the PE Panel believes that NTP should not base any conclusions on a maximum value, but instead should use a 90<sup>th</sup> or 95<sup>th</sup> percentile exposure. On that basis, the existing data indicate the Expert Panel conclusion of “minimal concern” should remain unchanged.

#### B. The NTP DBP Brief Overstates Its Conclusions

The draft NTP DBP Brief gives answers to the questions it poses which are too absolute given the underlying data. As a result, the NTP Brief is unclear, confusing, and may cause misapprehension and undue alarm among members of the public regarding the degree of risk from DBP exposure.

The NTP Brief conclusively states “yes” to the question of whether DBP can affect human development or reproduction. This firm conclusion is then contradicted by the subsequent sentences. The conclusion is based on studies with laboratory rodents which showed that exposure to DBP can cause adverse effects. NTP states that these reports indicate a *potential* for similar or other adverse effects in human populations, and that these scientific data are sufficient to conclude that DBP *may* adversely affect human reproduction or development if the levels of exposure are sufficiently high. NTP, therefore, has contradicted itself (“potential” and “may” are not the equivalent of an absolute “yes”). Whether DBP may cause adverse effects in humans is not a known fact that supports a “yes” answer.

The PE Panel believes that the answer to a question of whether DBP can affect human development or reproduction should be, at the most, “Maybe.” The answer should clarify for the reader that male reproductive tract development might be affected in the fetus of a pregnant woman *if* data for rodents are relevant to humans (which may not be the case) and *if* humans are 100 to 1000 times more sensitive to DBP than are rodents (although there are no data to support this proposition and some to refute it) and *if* that woman has continuous exposure to DBP at the high end of what has been measured in the human population.

The NTP Brief states “probably” to the question of whether current exposures to DBP are high enough to cause concern. This conclusion is much too strong, given the exposure data as discussed in Section II.A, above. Furthermore, the statement that “data are not available to permit conclusions regarding the possibility of effects in various age groups, occupations, or socioeconomic strata” is very quickly going to be outdated. As indicated above, the CDC intends to publish a report this fall that will provide such data. The PE Panel urges the NTP to wait for and incorporate the results of that report in the final DBP Brief (and other phthalate briefs). At the very least, NTP should inform the reader of the immediacy with which such data will be available.

### **III. NTP SHOULD EXERCISE CAUTION IN OFFERING ITS OWN INTERPRETATION OF DATA APART FROM THAT OF THE CERHR EXPERT PANEL**

The NTP established CERHR to provide valuable expertise on the potential risks to human development and reproduction posed by various chemicals, including DBP. The CERHR has, as a resource, numerous experts from the United States who are knowledgeable in the sciences of reproductive and developmental biology, exposure, medicine, and toxicology. Sixteen of these experts were recruited to participate in the Expert Panel on phthalates. This resource presents expertise that far exceeds the ability of NTP to comprehensively examine relevant data in a scientifically sound manner. Therefore, NTP should exercise great caution in drawing any interpretations or conclusions that differ from the Expert Panel.

Part of this caution should involve diligence in making the basis for any separate conclusion by NTP very transparent to the reader, as discussed above in these comments. In addition, NTP should subject all of its reports to notice and comment prior to issuance of a final report, as it has done here. The PE Panel also urges NTP to specifically solicit comments from the Expert Panel on its draft reports.

### **CONCLUSION**

The PE Panel appreciates this opportunity to comment on the NTP-CERHR Draft DBP Report and NTP DBP Brief. For the reasons described above, the PE Panel believes NTP should take steps to more fully achieve its goal of providing to the public a clear, balanced, and scientifically sound report regarding the risks of DBP exposure. The PE Panel believes the existing data support the Expert Panel’s original conclusion of “minimal concern” for adverse effects on *in utero* development and do not support the NTP’s draft change in that level of concern. The PE Panel urges that NTP be cautious when offering its own interpretation of the

**potential for exposure to chemicals to cause adverse effects, and that the basis for such interpretation be fully transparent to readers.**

## REFERENCES

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