ExxonMobil Biomedical Sciences, Inc.
1545 US Highway 22 East
Annandale, NJ 08801-3059
908 335 3298 Tel
908 335 1199 Fax
jennifer.e.foreman@exxonmobil.com

July 28, 2017

Dr. George Borlase (via US Mail and via email: GBorlase@cpsc.gov)
Associate Executive Director
Office of Hazard Identification and Reduction
U.S. Consumer Product Safety Commission (CPSC)
4330 East West Highway
Bethesda, MD 20814

I am writing in furtherance of prior comments regarding the data to support the Commission's rulemaking on phthalates and phthalate alternatives. In the comments submitted to the docket, most recently in reference to the "Estimated Phthalate Exposure and Risk to Pregnant Women and Women of Reproductive Age as Assessed Using the 2013/2014 NHANES Biomonitoring Data", detailed discussion has been provided on why it is not appropriate to represent data as individual risk values.[1] A biostatistical method, intraclass correlation coefficients (ICC), can be used to evaluate data reproducibility. Application of this method to phthalate biomonitoring values underscores previous comments to CPSC that the spot sample results of NHANES biomonitoring data and the hazard quotients and indices (HQ and HI) derived from those results cannot be used to reliably estimate individual risk. Several publications have developed values for phthalates (see attached summary tables). Two of the publications (Adibi et al., 2008 and Braun et al. 2012) were relied upon by the CHAP for its report.

The ICC values are a statistical measure of the reliability of a single spot sample to be reflective of a typical sample for that individual (i.e., can sample 1 reliably predict what the value for sample 2 will be). An ICC < 0.4 indicates poor reproducibility, 0.40-0.59 – Fair, ICC 0.6 – 0.74 – good, and 0.75 to 1.00 is excellent reproducibility[2]. ICC values for DEHP metabolites range from 0.08 to 0.36 across studies and the two reported ICC values for MCOP (a DINP metabolite) are 0.15 and 0.03. These values indicate spot samples have poor reproducibility and any individual risk value derived from these values would have poor reproducibility. That is, a single HQ or HI derived from a spot sample cannot be considered representative of the general risk for that individual, nor can that individual's HI be considered representative for the sample population. The ICC values for phthalates reinforce that individual risk values from spot samples are not reliable, and the appropriate exposure metric for evaluating risk from biomonitoring data based on single spot samples for phthalates are sample population percentiles no greater than the 95th percentile.

Please let me know if you have any questions or would like further materials regarding this matter.

Sincerely,

Jennifer E. Foreman, Ph.D., DABT
Toxicology Associate

[1] In summary, CDC studies outside of NHANES demonstrate that phthalate levels in an individual vary greatly over the day, so that a given spot sample may represent a short-term peak. However, the effects of concern from phthalates are not acute, but require a longer period of exposure. See Appendix A of ExxonMobil Chemical Company comments on "Estimated Phthalate Exposure and Risk to Pregnant Women and Women of Reproductive Age as Assessed Using 2013/2014 NHANES Biomonitoring Data" for further details.

[2] Rosner B. 2000. Fundamentals of Biostatistics. 5th edn. Duxbury, Pacific Grove, CA

Cc (w/attachments):

Docket No. CPSC-2014-0033
Patricia Adkins, CPSC (PAdkins@cpsc.gov)
Dr. Alice Thaler, CPSC (AThaler@cpsc.gov)
Dr. Michael Babich, CPSC (MBabich@cpsc.gov)
David DiMatteo, CPSC (DDiMatteo@cpsc.gov)
Chris Wallace, ExxonMobil Chemical Company

ATTACHMENT 1

Variability and predictors of urinary concentrations of phthalate metabolites during early childhood.
Watkins DJ, Eliot M, Sathyanarayana S, Calafat AM, Yolton K, Lanphear BP, Braun JM.
Environ Sci Technol. 2014;48(15):8881-90. doi: 10.1021/es501744v. Epub 2014 Jul 9.
PMID: 24977926

Phthalate metabolite(s)	Annual ICC 1-5 years of age (all)	Short term ICC 1-3 years of age (all)
∑DEHP metabolites	0.11	0.20
MCOP (DINP metabolite)	0.15	0.03
MnBP	0.40	N/A
MiBP	0.36	N/A
MBzP	0.25	0.39

Variability of urinary phthalate metabolite and bisphenol A concentrations before and during pregnancy.
Braun JM, Smith KW, Williams PL, Calafat AM, Berry K, Ehrlich S, Hauser R.
Environ Health Perspect. 2012 May;120(5):739-45. doi: 10.1289/ehp.1104139. Epub 2012 Jan 19. Erratum in: Environ Health Perspect. 2013 Apr;121(4):A114-5.
PMID: 22262702

Phthalate metabolite(s)	ICC before pregnancy	ICC during pregnancy
∑DEHP metabolites	0.11	0.08
MBP	0.40	0.45
MiBP	0.36	0.38
MBzP	0.35	0.25

Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples.
Adibi JJ, Whyatt RM, Williams PL, Calafat AM, Camann D, Herrick R, Nelson H, Bhat HK, Perera FP, Silva MJ, Hauser R.
Environ Health Perspect. 2008 Apr;116(4):467-73. doi: 10.1289/ehp.10749.
PMID: 18414628

Parent	Phthalate metabolite(s)	ICC late pregnancy
DEHP	MEHP	0.35
	MEOHP	0.34
	MEHHP	0.36
	MECPP	0.33
DnBP/DiBP	MnBP	0.62
	MiBP	0.54
	MCPP	0.44
BBzP	MBzP	0.66

APPENDIX A

For the Cumulative Risk Assessment Methodology of the CHAP, the 95th Percentile Provides a Conservative Estimate of Chronic Exposures for all Individuals in the Population

In order to conduct a risk assessment, cumulative or otherwise, toxicology and exposure must be integrated to determine risk. An important consideration of this integration is the time scale of toxicity and the time scale of the exposure. The nature of the toxicity in the CHAP document is developmental effects that occur after repeated exposure. The relevant exposure period for potentially adverse developmental effects is an extended period of time (repeat dose exposure), but the exposure data are from samples taken at a single point in time (acute exposure). It is not the highest exposure during this period of time that dictates the toxicity, but the maintenance of exposure above a specified level. For example, in Figure A-1 below, the black line represents the person's average exposure over a seven day period, and the red line represents the dose of the compound to which a person can be exposed before being at risk for an adverse health effect. So even though the person exceeds that given level at several points during the 7 day period, their average value is below the toxicity value and this person is not at risk (*i.e.*, HI<1).

Figure A-1: Acute exposure should not be compaired to a chronic hazard for risk estimation

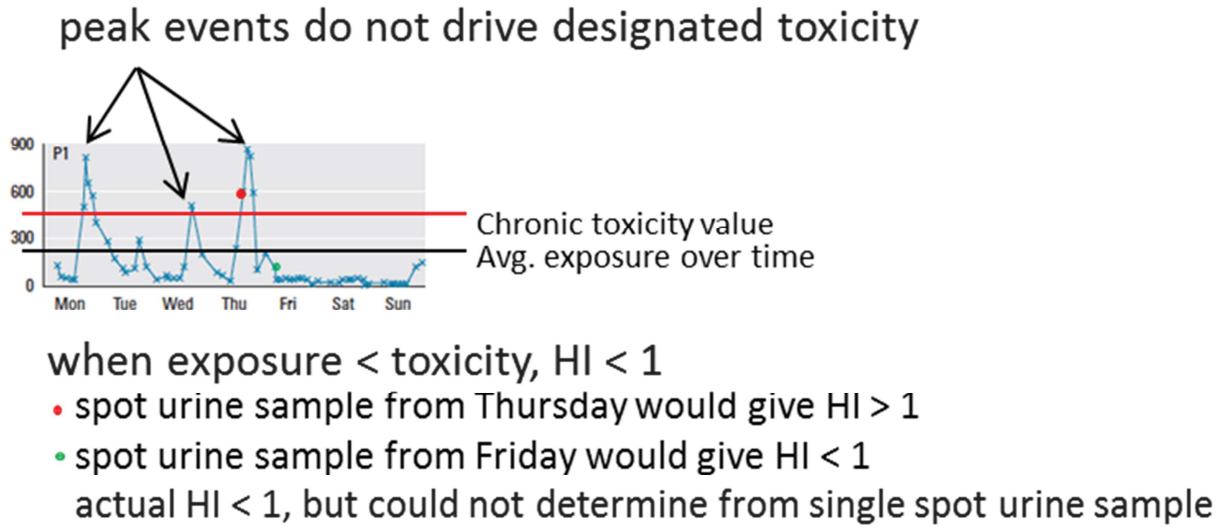


Figure A-1: Phthalates are metabolized quickly and exposure levels over the course of a day or a week vary greatly depending upon when a measurement is taken versus when the last exposure occurred. The figure shows an example of an individual's exposure levels to a phthalate over a one week period, based on multiple spot urine samples. As can be seen in the figure, the average exposure over that period can be lower, or higher, than any single measurement. When toxicity is based on repeated exposures, as is the case for the reproductive effects for phthalates in rodents, it is appropriate to compare the toxicity value to the average exposure value over time. When that average exposure value is less than the toxicity value a person is deemed not at risk (HI < 1).

Figure A-2 below demonstrates how phthalate metabolite concentrations vary over time for each individual, as determined in a study by CDC scientists (separate from the NHANES). There are eight graphs showing phthalate metabolite concentrations over time for eight individuals (P1 to P8). Each point on each graph (small blue dot) plots the results from a single spot urine sample. These spot samples were taken at several times each day over a week (Preau et al., 2010).[1]

Figure A-2: Spot urine concentrations of MEHHP from CDC study

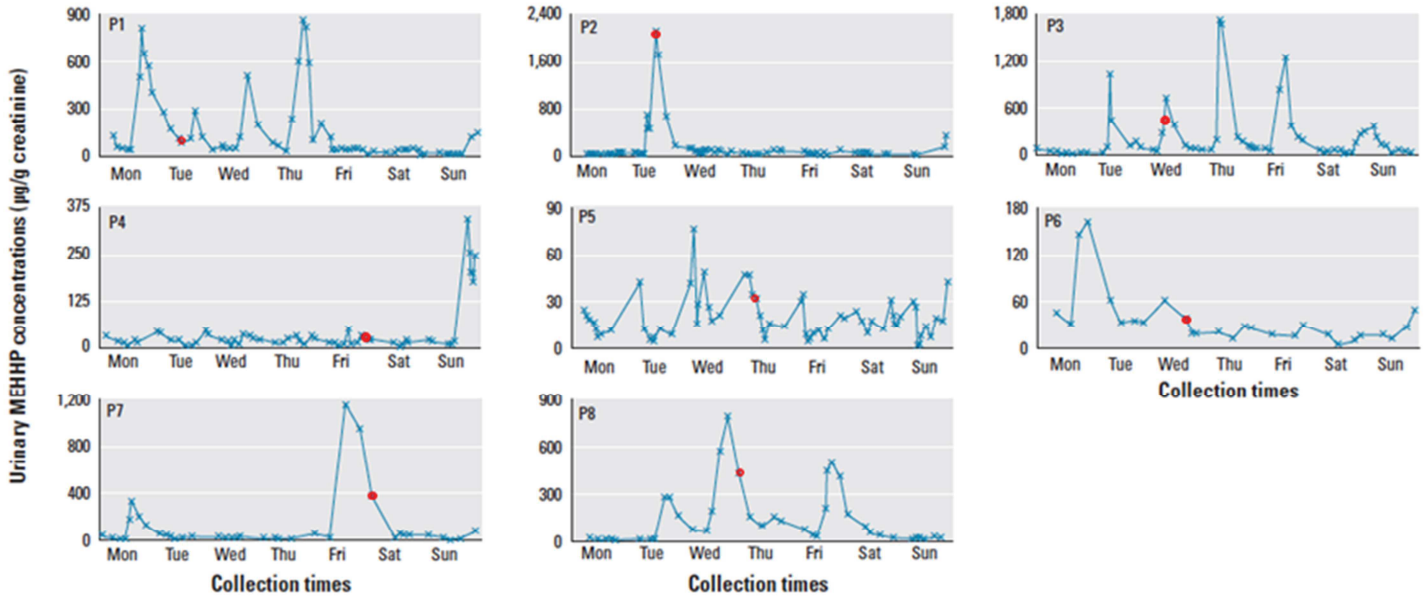


Figure 2. Creatinine-corrected concentrations of MEHHP (µg/g creatinine) for all study participants (P1–P8) during 1 week.

Source: Preau et al., 2010. The red dots have been added to the original figure and represent hypothetical single spot urine samples.

The exposure values used in the CHAP CRA were from single spot urine samples, and would relate back to a single point. This is hypothetically illustrated with the red dot placed in the Figure A-2 graphic for each individual. For any given individual person in the NHANES survey, their spot sample may have been captured at the peak or valley of their exposure, or any place in between. For example, subject P2 would have their average exposure level over-estimated by the illustrated spot urine sample, whereas subject P1 would have their average level under-estimated.

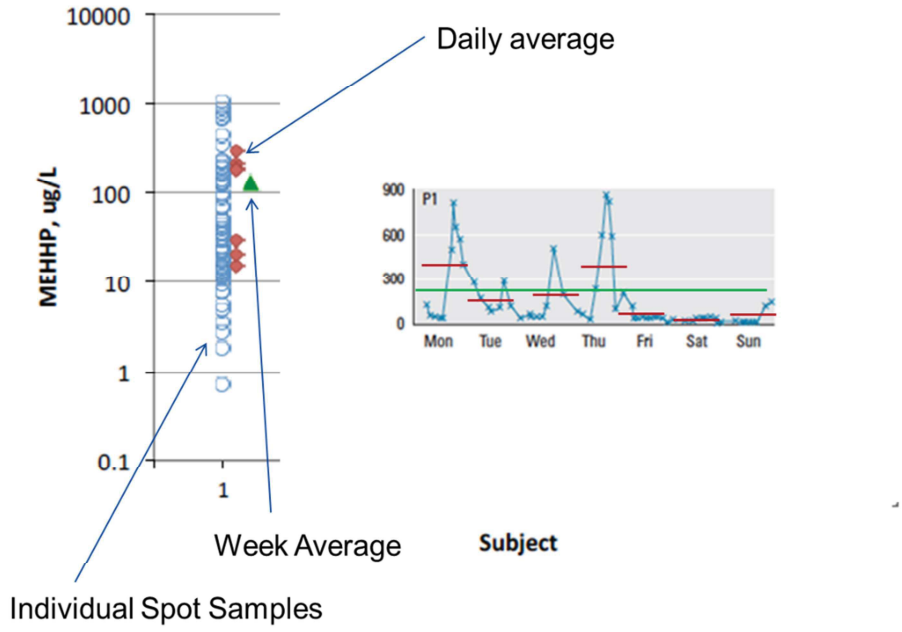
---

[1] Preau, J. L., Wong, L. Y., Silva, M. J., Needham, L. L., & Calafat, A. M. (2010). Variability over 1 week in the urinary concentrations of metabolites of diethyl phthalate and di (2-ethylhexyl) phthalate among eight adults: an observational study. Environmental Health Perspectives, 118(2), 1748-1754, http://www.ncbi.nlm.nih.gov/pubmed/20797930. This was a study conducted by CDC scientists taking multiple samples from each individual, separate from the NHANES where one sample is taken from each of multiple individuals..

Further, as shown in Figure A-3, spot urine samples will yield a greater distribution of values than a daily or weekly average, because the spot samples include individuals measured at peaks and valleys. The distribution for average daily exposure will be tighter than that of spot samples – both lower than the extreme highs and higher than the extreme lows. The distribution for average weekly exposure would be even tighter (highs and lows closer to the average).

Figure A-3: The distribution of spot samples is larger than the distribution of values for an individual's exposure over time (4 orders of magnitude versus 1 order of magnitude).

A. Distribution of exposures in a single subject



B. Distribution of exposures in multiple subjects

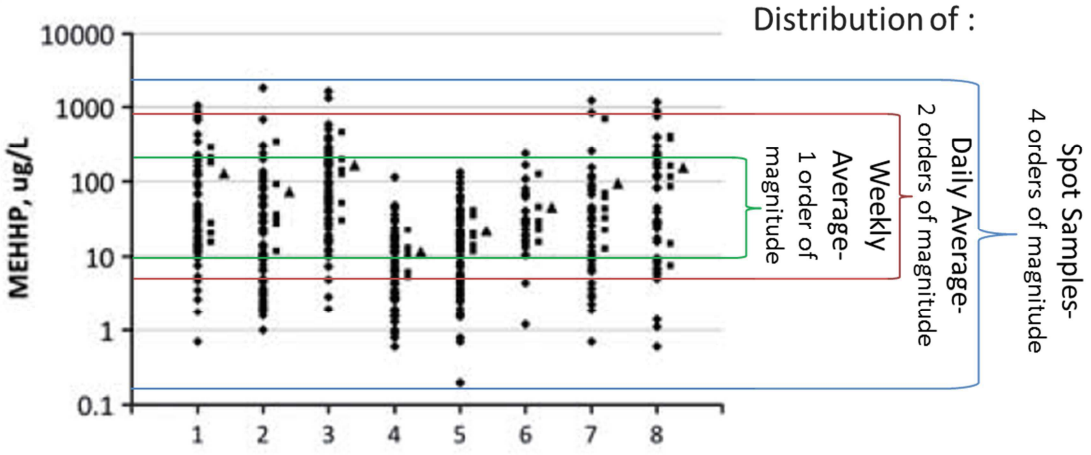
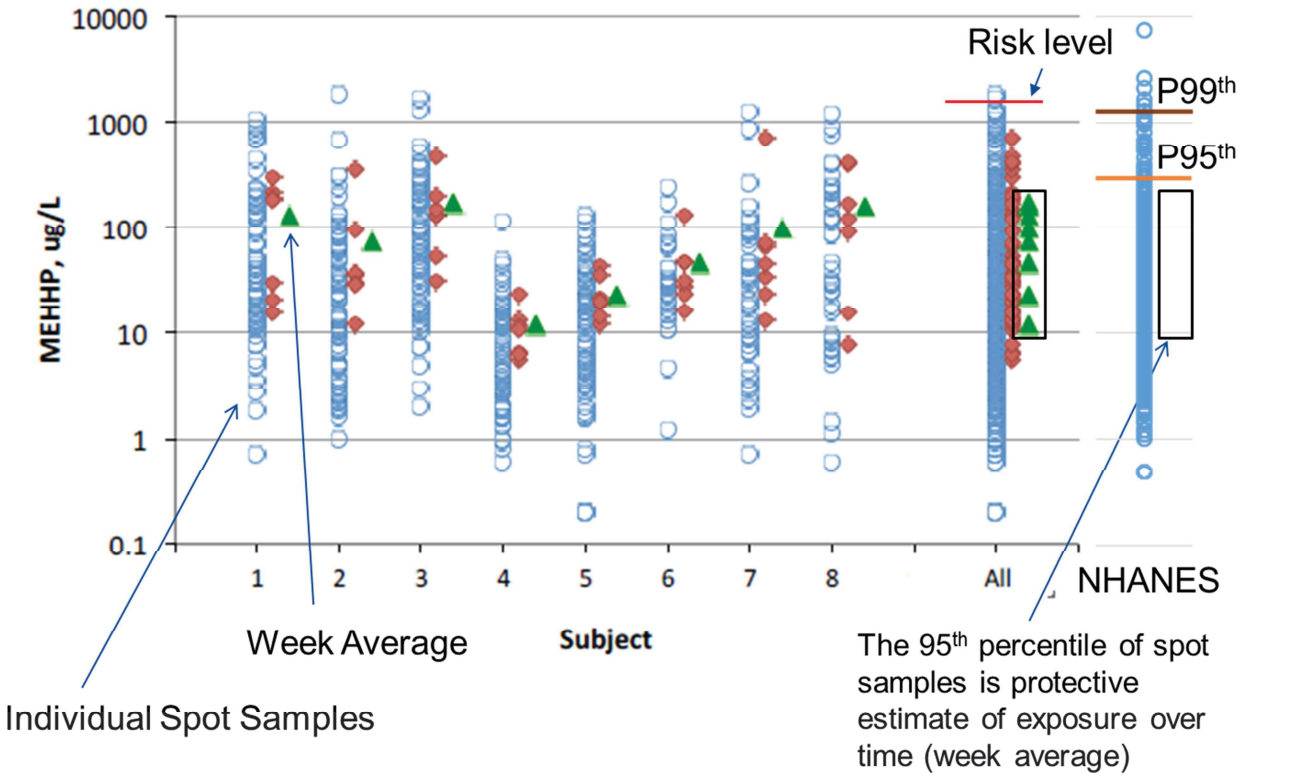


Figure A-3: Adapted from Figure 3 of Aylward et al.,[2] this figure demonstrates how acute exposures relate to chronic exposures. Each number on the x-axis (1 through 8) represents an individual, with the circles depicting spot samples collected multiple times per day across a week for those individuals. As can be seen, the distribution of all the spot samples is wider than the distribution of the daily averages for each individual. The weekly averages for each individual have a yet smaller distribution than all of the daily averages. What NHANES gives is the distribution for spot samples in a population. The susceptible time period during pregnancy covers a period of weeks. What is needed for risk determination are exposures equivalent to the period of susceptibility (repeated exposures). The mean for all of these measures will be the same (i.e., population mean of spot samples = population mean for daily average = population mean for weakly average); however, what will differ is variation away from the mean, with less variation in repeated measures. The distributions of the daily averages and weekly averages demonstrate that repeated exposures trend toward the mean compared to spot samples.

What does this mean for the CHAP cumulative risk assessment? This means that even though spot urine samples cannot accurately estimate an individual's exposure level, they can be used to estimate variation of exposure in the population. This is further illustrated in Figure A-4, below.

Figure A-4: NHANES data are a compilation of acute individual exposure measures which, at the 95th percentile, will be an overestimate of an individual's exposure over time



[2] Aylward, L. L., Kirman, C. R., Adgate, J. L., McKenzie, L. M., & Hays, S. M. (2012). Interpreting variability in population biomonitoring data: role of elimination kinetics. *Journal of Exposure Science and Environmental Epidemiology*, *22*(4), 398-408.

Figure A-4: With a large enough sample of single spot samples from multiple individuals, a reasonable approximation of the distribution of spot samples in the population can be assessed (blue circles on far right). One can be reasonably certain that the population of individuals which generates that distribution will generate a 95th HI that is representative of an HI for the extreme end of exposures over time. Therefore if NHANES spot urine samples of a sufficient number generates a 95th percentile HI<1, that population does not contain any individuals with an individual risk (HI > 1). A population with individuals that have higher exposures over time would have an increased probability of being sampled when urine levels are high and thus would generate a larger population 95th percentile. The CDC provides guidance for what constitutes a large enough sample size, and the size of WORA in the NHANES is large enough to generate a reliable 95th percentile. Additionally, experts in the field have estimated that the 95th percentile of spot urine samples likely overestimates the upper percentiles of multiday average concentrations among individuals (and therefore longer-term average intake rates) for most transient analytes, such as phthalates (Aylward et al. 2016).[3] This makes the 95th percentile sufficiently conservative to estimate potential high end exposures in the population. The 99th percentile would be inappropriate for calculation risk, as it would over estimate high end exposures and is an unstable measure (*see* 2015 CPSC Update).

The 50th percentile of the NHANES data sets estimates the average exposure over time (repeat exposure) for the population. The extreme values present in the spot samples will be higher than the extreme range of chronic exposure values. The reason for using the 95th percentile exposure value to calculate a hazard index is because one can be reasonably certain that the extreme values for the repeat exposure distribution will fall below the 95th percentile of the acute exposure values. Therefore exposure over time for each individual person within that population will fall below the 95th percentile of the measured acute exposures for the population (empty black box next to NHANEs distribution). As can be seen for subject 2 in Figure A-4, even though their NHANES-based HI would fall outside of the 95th percentile of acute exposures, their individual value over time falls below the 95th percentile and they are not at risk (HI<1). The nature of spot urine samples in estimating phthalate exposure, as outlined above, is why it is inappropriate to state that a certain percent of women, or children, in the given population have a HI>1. The percentage in fact cannot be precisely determined from the NHANES data, but is likely zero or very close to zero.

[3] Aylward, L. L., Hays, S. M., & Zidek, A. (2016). Variation in urinary spot sample, 24 h samples, and longer-term average urinary concentrations of short-lived environmental chemicals: implications for exposure assessment and reverse dosimetry. Journal of Exposure Science and Environmental Epidemiology.