# Temporal trends of cumulative risks to phthalate mixtures in the United States from 2005 to 2014

**Jeanette M. Reyes[1] and Paul S. Price[2]**

[1]Oak Ridge Institute for Science and Education, Environmental ... Assessment Group, National Center for Environmental Assessment, U.S. Environmental Protection Agency

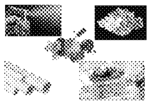
[2]National Exposure Research Laboratory, U.S. Environmental Protection Agency

Jeanette M. Reyes | reyes.jeanette@epa.gov | Paul S. Price | price.paul@epa.gov

## Background

Phthalates

Phthalates (esters of phthalic acid) are used as plasticizers in a wide range of consumer goods. These goods include vinyl flooring, food packaging, outer coating of pills, cosmetics, and food containers.[1] In 2008 the National Academy of Sciences concluded that risks from cumulative exposures should be investigated for phthalates that produce a common adverse outcome. Several phthalates are implicated in the "phthalate syndrome," which is associated with endocrine disruption of male reproductive development. This work investigated di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DIBP), diisononyl phthalate (DINP), butyl benzyl phthalate (BBP), and diisodecyl phthalate (DIDP).



National Health and Nutrition Examination Survey (NHANES)

The National Health and Nutrition Examination Survey (NHANES) collects data of the concentrations of anthropogenic chemicals and their metabolites in biological media such as blood and urine. Unique urinary metabolites of multiple phthalates were measured in nearly 13,000 individuals ages 6 and older from the last five consecutive biennial cycles of NHANES spanning from 2005-2014.

Objective

This research applied previous Reyes and Price[2] methodology to the last five NHANES cycles for which phthalate data exist. The regression analysis of Zota et al.[3] was applied to determine trends in hazards for the entire group and by gender, race/ethnicity, and age. The Maximum Cumulative Ratio[4-6] technique was applied to determine trends in the pattern of relative contribution of individual phthalates to NHANES participants' cumulative risks.

## Methods

Daily Intake (DI) Dose

$DI_j = \left(\left[PhMet_{cr-adj} \cdot CE\right] / \left[F_{UE,j} \cdot 1000\ mg/g\right]\right) \times \left(MW_i / MW_j\right)$; $DI_i = \sum_{j=1}^{n_i}\left(DI_j \times \frac{F_{UE,j}}{\sum_{k=1}^{n_i} F_{UE,k}}\right)$, where $DI_j$ is the daily intake of the $j^{th}$ phthalate; $PhMet_{cr-adj}$ is the phthalate metabolite adjusted for creatinine; $CE$ is the daily creatinine excretion; $F_{UE,j}$ is the fraction urinary excretion; $MW_{i,j}$ is the molecular weights of the phthalate and metabolite; $n_j$ is the number of metabolites from the $j^{th}$ phthalate.

Hazard Quotient (HQ), Hazard Index (HI), and the Maximum Cumulative Ratio (MCR)

HQ and HI are measures of impact for individual chemicals and mixtures, respectively. HQ is the ratio of a dose of a chemical to a dose at which no adverse effects are expected (e.g., Tolerable Daily Intake (TDI)). HI is the sum of the HQs that reach an individual. MCR is a measure of the degree that the impact of an individual's combined exposure is driven by one chemical (Table 1; Table 2).[4-6]

Regression Analysis

We calculated the Least Squares Geometric Mean (LSGM) in a regression analysis adjusted for gender, race/ethnicity, fasting hours, and poverty income ratio (depending on the interaction term) along with the NHANES weighting factors.

| Abrev. | Term | Equation |
|---|---|---|
| HQ | Hazard Quotient | $HQ_i = DI_i/TDI_i$; $HQ_i \in \{HQ_1, HQ_2, \ldots, HQ_N\}$ |
| $HQ_M$ | Maximum Hazard Quotient | $HQ_M = \max_{i \in \{1,\ldots,N\}} HQ_i$ |
| HI | Hazard Index | $HI = \sum_{i=1}^{N} HQ_i$ |
| MCR | Maximum Cumulative Ratio | $MCR = HI/HQ_M \in [1, N]$ |

**Table 1.** Metrics, descriptions, and equations of HQ, HI, and MCR for N chemicals.

| Group | Definition | Description |
|---|---|---|
| I | $HI > 1$ and $HQ_M > 1$ | Single substance driving concern |
| II | $HI \leq 1$ | Low concern |
| IIIA | $HI > 1$, $HQ_M < 1$, $MCR < 2$ | Concern for combined effect dominated by one substance |
| IIIB | $HI > 1$, $HQ_M < 1$, $MCR > 2$ | Concern for combined effect by several substances |

**Table 2.** Name, definition, and description of the Groups in the log(HI) vs log(MCR-1) plot (Figure 3).

## Results and Discussion

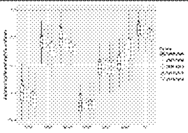


**Figure 1.** Boxplots of the natural log transform of the phthalate-specific HQs and HI of NHANES participants presented by cycle adjusted for the NHANES weighting factor.

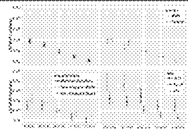


**Figure 2.** Population Least Squares Geometric Means (LSGM) of HI (with 95% confidence intervals) presented by cycle for NHANES participants by gender, race/ethnicity, and age.

- There was a **2.2-fold decrease** in mean HI (0.34 to 0.15) over the last 10 years. This was mostly attributed to a decrease in DEHP and DBP and partially offset by an increase in DINP (Figure 1).
- There was a **7.2-fold decrease** in the number of participants with HI>1 (5.1% to 0.8%). With only a few exceptions, there was no difference in the fraction of participants with HI>1 within the demographics for a fixed NHANES cycle (Table 3).
- In the regression analysis children had a consistently higher average HI values compared with adolescents and adults. With a few exceptions, there were no differences in average HI values in other demographics for a fixed NHANES cycle (Figure 2).
- There was a **1.2-fold increase** in mean MCR (1.7 to 2.1) and the slope between MCR and HI decreased indicating that largest combined exposures are becoming less dominated by one chemical during this time (Figure 3).
- The top HQs among HI>1 changed over time. In the 2005-2006 cycle DEHP, DINP, and DBP comprised **95%** of participants with HI>1, whereas in the 2013-2014 cycle DEHP, DINP, and DIDP comprised **90%** of participants with HI>1 (Table 4).

| | Demographics | 2005/2006 | 2007/2008 | 2009/2010 | 2011/2012 | 2013/2014 |
|---|---|---|---|---|---|---|
| | Total Participants | 2,530 | 2,578 | 2,725 | 2,494 | 2,663 |
| Gender | Male | 6.4[a] | 3.8 | 2.9 | 1.5 | 0.79 |
| | Female | 4.9[a] | 4.2 | 2.2 | 1.7 | 0.78 |
| Race/Ethnicity | Mexican American | 4.5[a] | 4.6 | 2.7 | 0.96 | 0.46 |
| | Non-Hispanic White | 5.2[a] | 3.3 | 2.4 | 1.5 | 0.82 |
| | Non-Hispanic Black | 7.0[a] | 3.9 | 2.3 | 1.4 | 0.66 |
| Age | 6-11 | 7.3 | 7.0 | 2.7 | 1.2 | 1.5 |
| | 12-19 | 5.9 | 4.0 | 2.4 | 1.3 | 1.5 |
| | 20+ | 5.1 | 3.3 | 2.5 | 1.7 | 0.45 |

**Table 3.** Percent of participants within each subgroup with $HI > 1$ presented by demographic. [a]Significant difference in proportions within a demographic for a fixed cycle ($p < 0.05$).

| | | 2005/2006 | 2007/2008 | 2009/2010 | 2011/2012 | 2013/2014 |
|---|---|---|---|---|---|---|
| DEHP | DBP | 115 | 78 | 35 | 13 | 1 |
| DEHP | DINP | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
| DEHP | DIDP | 6 | 3 | 2 | 1 | 2 |
| DBP | DINP | 1 | 0 | 0 | 0 | 0 |
| DBP | DIDP | 0 | 2 | 0 | 0 | 0 |
| [illegible] | [illegible] | 0 | 1 | 0 | 4 | 1 |
| DIDP | DINP | 0 | 0 | 0 | 4 | 3 |

**Table 4.** Frequency of pairs of phthalates that produced the top two Hazard Quotients (HQs) in the participants with $HI > 1$.

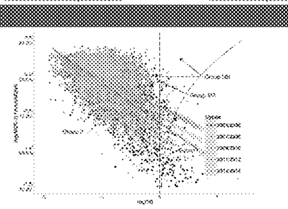


**Figure 3.** Plot of log HI versus $\log(MCR - 1)$ (with $HQ_M/HI$) for all participants from the five NHANES cycles performed over **2005-2014** NHANES cycle identified by corresponding cycle of the participant. Regions correspond to Groups I, II, IIIA, and IIIB and linear regression between log $HI$ with $\log(MCR - 1)$ with 95% confidence interval are presented.

Limitations

- Findings are dependent on toxicity values. Changes in values may occur as new information is produced.
- NHANES did not survey children under the age of six. If infants and small children have sources of exposure that differ from older children, then the these findings may not be relevant for those age groups.
- NHANES is a national survey; thus, small local populations with unique exposure sources may not be reflected in the NHANES data.
- The dose estimation methodology will tend to overestimate doses in the upper tail; thus, the true fraction of the population HI values > 1 could be lower than the values presented here.

## Conclusions

This is the first work to investigate temporal trends of HI and MCR for six phthalates using NHANES biomonitoring data to determine the impact of gender, race/ethnicity, and age on these trends. Due to changing patterns in phthalate exposures over the last 10 years:

- HI values in NHANES participants have decreased, and the decreases are largest for individuals with the highest exposures.
- The declines were also observed in demographics based on age, gender, and race/ethnicity.
- While HQ values decreased, the potential for cumulative exposures of concern became relatively more important as MCR values increased.
- Since phthalate exposures have shown strong secular changes, tracking new phthalates and plasticizers entering the market and biomonitoring for these compounds will remain important tasks.

## References

[1]The National Academy of Sciences. Phthalates and Cumulative Risk Assessment - The Tasks Ahead. 2008.

[2]Reyes, J.; Price, P. An analysis of cumulative risks based on biomonitoring data for six phthalates using the Maximum Cumulative Ratio. *Environ. Int.* 2018, *112*, 77–84.

[3]Zota, A. R.; Calafat, A. M.; Woodruff, T. J. Temporal trends in phthalate exposures: Findings from the national health and nutrition examination survey, 2001-2010. *Environ. Health Perspect.* **2014**, *122* (3), 235–241.

[4]Han X, Price PS. Determining the maximum cumulative ratios for mixtures observed in ground water wells used as drinking water supplies in the United States. *Int J Environ Res Public Health* 2011; 8: 4729–4745.

[5]Price PS, Han X. Maximum cumulative ratio (MCR) as a tool for assessing the value of performing a cumulative risk assessment. *Int J Environ Res Public Health* 2011; 8: 2212–2225.

[6]De Brouwere K, et al. Application of the maximum cumulative ratio (MCR) as a screening tool for the evaluation of mixtures in residential indoor air. *Sci Total Environ* 2014: **479–480**: 267–276.

Conflicts of interest: The authors declare no competing financial interests.

U.S. Environmental Protection Agency
Computational Exposure Division, National Exposure Research Laboratory, Office of Research and Development

*Although this work was reviewed by EPA and approved for presentation, it may not necessarily reflect official Agency policy.*