U.S. Consumer Product Safety Commission

LOG OF MEETING

SUBJECT: Phthalates.

DATE: March 16, 2015.

TIME: 1:00pm to 3:00pm.

PLACE: U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, Maryland 20850.

ENTRY SOURCE: Kent R. Carlson, HSTR.

COMMISSION REPRESENTATIVE: Kent R. Carlson, HSTR and attached.

NON FEDERAL REPRESENTATIVES: Attached.

SUMMARY: The meeting was requested by the American Chemistry Council (ACC). The purpose of the meeting was to hear BASF and ExxonMobil Biomedical Sciences, Inc. (EMBSI) present information on human biomonitoring, how National Health and Examination Survey (NHANES) biomonitoring data could be used to estimate human exposure to phthalates, and their results from a quantitative reanalysis of the 2005-2006 NHANES data using methods presented in the CHAP report. Results from the additional analyses of 2007-2008, 2009-2010, and 2011-2012 NHANES data were also presented. The presentations were followed by clarifying questions on the analyses and results from the CPSC staff. Both the BASF and EMBSI presentations are attached.

March 16th 2015

Presentation to CPSC Science Staff on Analyses of NHANES data

Methodology for replication of CHAP process – building Excel spreadsheet

Download metabolite data files using SAS viewer and transfer to Excel spreadsheet – Excel tab "Metabolites"

Download demographics data – Excel tab "Demographics"

Download fasting data – Excel tab "Fasting"

Information on each tab of spreadsheet was linked to subject SEQN

Generate excel tab "Constants"

- Fue – as reported in Table D-1 CHAP 2014
- MW for Parents and Metabolites – as reported in Table D-1 CHAP 2014
- Mage equations – as reported in Mage et al. 2008 - indicated on pg Appendix D – 3 these were used by CHAP
- "PEAA"s for three Cases – as reported in Table D-8 CHAP 2014

Methodology for replication of CHAP process – CE calculation

In demographics sheet calculate CE (mg/kg/day) –

use Mage equations to calculated mg creatinine/d

- assigned equation based on age for Females
- assigned equation based on age and height for Males
- Race identified as Black or Other for purpose of equation
- subjects w/o height data could not calculate and were removed from further analyses

divided mg/creatinine/d (Mage) by weight to get CE (mg/kg/d)

- subjects w/o weight data could not calculate and were removed from further analyses

Methodology for replication of CHAP process – DI calculation

In metabolite sheet convert metabolite data from ng/ml to ug/g

Metabolite (ng/ml) * Creatinine (mg/dl) = Metabolite (ug/g)

Created new tab "working data"

imported information from other data tabs using VLOOKUP command anchored to SEQN number

- Metabolites (ug/g)
- Demographic information (age, gender, height, weight)
- Fasting (h)
- CE (mg/kg/day)

calculated DI (ug/kg/day) – equation pg Appendix D - 3

- SUM UE (Metabolites (ug/g)/MW metabolite)
- Metabolites used as indicated in Table D1
  - DIBP – MIBP
  - DBP – MBP
  - BBP – MBZP
  - DEHP – SUM (MEHP, MEHHP, MEOHP, & MECPP)
  - DINP – cx-MINP (MCOP)

$$DI(\mu g/kg_{bw}/day) = \frac{UE_{sum}(\mu mole/g_{crt}) \times CE(mg_{crt}/kg/day)}{F_{UE} \times (1000 mg_{crt}/g_{crt})} \times MW_{parent}(g/mole)$$

Selection of population of interest

Sample size of pregnant women declined in later datasets women of reproductive age fluctuates but remained robust

NHANES	Phthalate metabolite data published	Pregnant Women*	Women of Reproductive Age (15-45)*
2005/2006	February, 2010	130	618
2007/2008	October, 2010	19	516
2009/2010	September, 2012	23	568
2011/2012	October, 2014**	18	493

*Number of women identified as pregnant or in the appropriate age range with metabolite data and sufficient data to calculate CE using Mage's equations.
**update was published

Evaluated appropriateness of using women of reproductive age as surrogate

- sensitive time window in humans is 1st trimester, food consumption increases in 2nd and 3rd trimester, should not impact exposure
  - only a subsample of "pregnant women" represent sensitive exposure window (1st trimester)
- Woodruff et al. analyzed phthalate exposures between pregnant women and women of reproductive age given considerations that could effect exposure differences
  - no statistical differences between exposure of two populations
    - this was also noted in the CHAP

Women of reproductive age is an appropriate surrogate for exposure to male fetuses during the 1st trimester of pregnancy

Derivation of percentile information

Used SAS-Callable SUDAAN to incorporate appropriate sampling weight for analyses of percentile information. Data for entire population needs to be uploaded into software to appropriately account for sample design. Output parameters are designated in program

Women of reproductive age:

- Variance Estimation Method: Taylor Series (WR)
- For Subpopulation: RIAGENDR = 2 AND RIDAGEYR > 14 AND RIDAGEYR < 46
- by: Variable, SUDAAN Reserved Variable One, Percentiles.
- for: Variable = DiBP

Pregnant women – DiBP example:

- Variance Estimation Method: Taylor Series (WR)
- For Subpopulation: RIAGENDR = 2 AND RIDAGEYR > 14 AND RIDAGEYR < 46 AND RIDEXPRG = 1
- by: Variable, SUDAAN Reserved Variable One, Percentiles.
- for: Variable = DiBP

Note - Percentiles for pregnant women used RIDEXPRG – Code value 1 - Yes, positive lab pregnancy test or self-reported pregnant at exam – did not cross reference to URXPREG

Confirmed replication of DI for 2005/2006

Table D-2 Summary statistics for estimated daily intake of phthalate diesters in adults of reproductive age (ages:15–45 yrs) from NHANES (2005–06) and SFF (prenatal, postnatal, and infants) biomonitoring data, estimated from exposure modeling (Wormuth *et al.*, 2006) and as given in Kortenkamp and Faust (2010).

Daily Intake Estimates (µg/kg - d)	BBP[a]	DBP	DEHP	DEP[b]	DMP	DiBP	DiDP	DiNP
Median Estimates from Biomonitoring Data (NHANES, 2005–06; 15<=Age<=45) (CDC, 2012b)								
Adults (represents 123M)	0.29	0.66	3.8	3.3	0.03	0.19	1.5	1.1
Pregnant Women (represents 5M)	0.30	0.63	3.5	3.4	0.05	0.17	1.5	1.0
99th Percentile Estimates from Biomonitoring Data (NHANES, 2005–06; 16<=Age<=45) (CDC, 2012b)								
Adults	2.5	5.5	203	118	0.80	1.9	19	35
Pregnant Women	2.7	6.4	366	357	0.68	2.0	11	27
Median Estimates from Biomonitoring Data (Sathyanarayana *et al.*, 2008a)								
Prenatal	0.51	0.88	2.9	6.6	0.06	0.15	2.3	1.1
Postnatal	0.44	0.62	2.7	3.7	0.06	0.14	1.7	0.63
Infants	1.2	1.7	5.5	4.8	0.12	0.31	6.0	3.5
99th Percentile Estimates from Biomonitoring Data (Sathyanarayana *et al.*, 2008a)								
Prenatal	4.2	5.1	69	307	0.67	1.7	28	7.6
Postnatal	4.1	4.7	45	171	0.60	1.8	68	8.1
Infants	22	13	110	217	2.1	2.9	70	24

Daily Intake* (ug/kg-d) Pregnant Women

Year	Label	Percentile	Estimate
2005/2006	BBP	50%	0.30
2005/2006	DBP	50%	0.63
2005/2006	DEHP	50%	3.5
2005/2006	DiBP	50%	0.17
2005/2006	DINP (MCOP)	50%	1.0
2005/2006	BBP	99%	2.7
2005/2006	DBP	99%	6.4
2005/2006	DEHP	99%	366
2005/2006	DiBP	99%	2.0
2005/2006	DINP (MCOP)	99%	27

*Values provided for 2005/06-2011/12 data sets for pregnant women and women of reproductive age as Appendix to ExxonMobil submission Sept 2014

Could not replicate SFF values

The methodology outlined in the CHAP was also applied to the SFF infant data and could not replicate Table D-2

Table D-2 Summary statistics for estimated daily intake of phthalate diesters in adults of reproductive age (ages:15–45 yrs) from NHANES (2005–06) and SFF (prenatal, postnatal, and infants) biomonitoring data, estimated from exposure modeling (Wormuth *et al.*, 2006) and as given in Kortenkamp and Faust (2010).

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Not clear how CHAP handled missing data. For example only a subset of mother-child pairs have reported DINP metabolite data.

- BBP/DBP/DiBP/DINP approximate median
- DEHP large derivation at median 5.5 reported vs. 0.84 calculated
- 99th percentiles deviate for all

Percentile	BBP	DBP	DEHP	DiBP	DINP*
50th	1.2	1.7	0.84	0.30	3.4
99th	17	12	18	2.9	19

- Based on analyses HI's well below 1 at all percentiles
  - 0.68% of children exceed HI of 1, not "up to 5%" as indicated in CHAP

PDF of data supplied as supplementary file on CPSC site. Difficult to transfer into spreadsheet. Request data in excel format to repeat analyses

Application of recent NHANES

Applied validated replication methodology to all subsequent NHANES datasets

2005/2006

2007/2008

2009/2010

2011/2012

- data was removed in Aug and then made available again in Oct
  - removal was due to errors in sampling weights
  - re-analyzed percentiles based on Oct release

Did not combine NHANES cycle years based on analyses of trend in phthalate exposures

Derivation of HQ/HI

Used CHAP PEAAs for Cases 1, 2, and 3 to derive HQ's and HI's for each individual, as well as HQ's based on the DI percentiles derived for each HQ

Graphical representation of HI's

Deviated from CHAP's method to depict HI's

- CHAP generated percentiles based HI's calculated for each individual
  - method does not allow visualization of contribution of each HQ
- Used summed HQ's derived from 95th percentile DI to depict HI
  - method is more conservative that the CHAP's method but allows visualization of estimated contribution of each HQ
- Both methods derived similar HI's for Case 1 and 3
  - DEHP was major contributor for both Cases therefore 95ht percentile HI was essentially 95th percentile DEHP HQ
- Methods derived different HI's for Case 2
  - Case 2 "modeled" PEAA's which increased the potency estimates for other phthalates
    - inflated contribution of other phthalates to HI and therefore final 95th HI deviated from 95th HQ DEHP

Risk considerations

95th percentiles derived based on spot urine samples are a conservative estimate of average exposure over time and appropriate for derivation of HQ's/HI's for determination of risk.

Spot urine concentrations of MEHHP from CDC study (Figure from Preau et al., 2010).

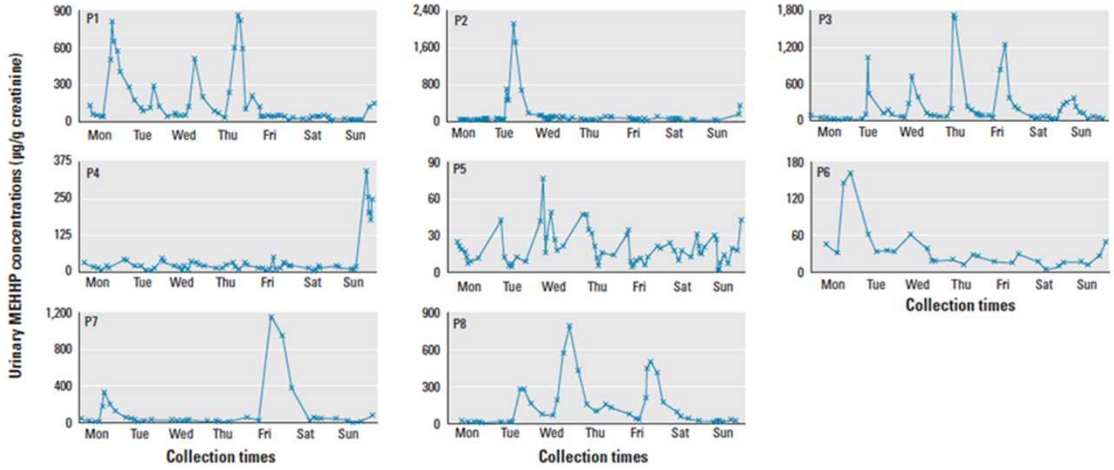


Figure 2. Creatinine-corrected concentrations of MEHHP (µg/g creatinine) for all study participants (P1–P8) during 1 week.

The 95th percentile of concentration of MEHHP in spot urine samples in the CDC study over estimated the maximum of longer term average (the 7-day average for each of the eight individuals in the CDC study) concentrations of MEHHP by a factor of 2.8.

95th Percentile Daily Intake Across NHANES surveys

Daily Intake

Daily Intake (ug/kg-d) Pregnant Women

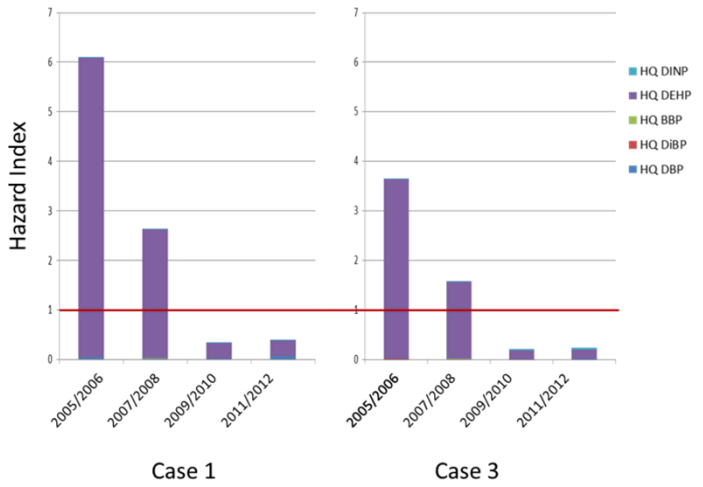
	DBP	DiBP	BBP	DEHP	DINP
2005/2006	3.49	1.02	1.27	181.34	11.14
2007/2008	1.64	0.77	1.81	77.94	7.11
2009/2010	1.44	0.57	0.69	9.23	13.30
2011/2012	6.02	0.75	2.23	9.31	18.97

Daily Intake (ug/kg-d) Women of Reproductive Age

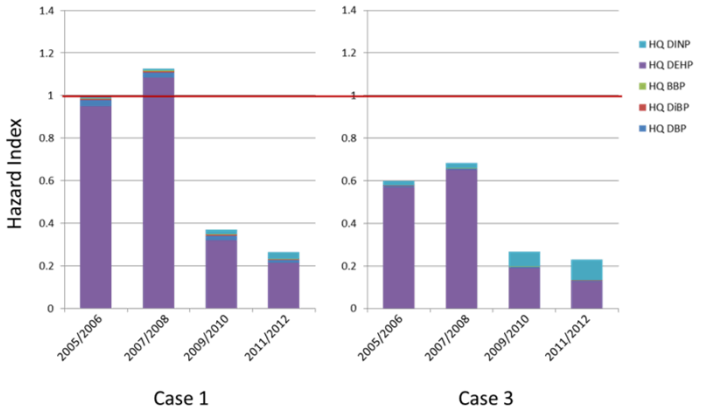
	DBP	DiBP	BBP	DEHP	DINP
2005/2006	2.79	0.89	1.14	28.51	9.83
2007/2008	2.45	0.94	1.67	32.54	11.79
2009/2010	2.10	0.94	0.96	9.56	34.32
2011/2012	1.34	0.88	0.80	6.38	48.38

Effect on HI's

Pregnant women



Women of reproductive age (15-45) – Oct 2014 update for 2011/2012 data



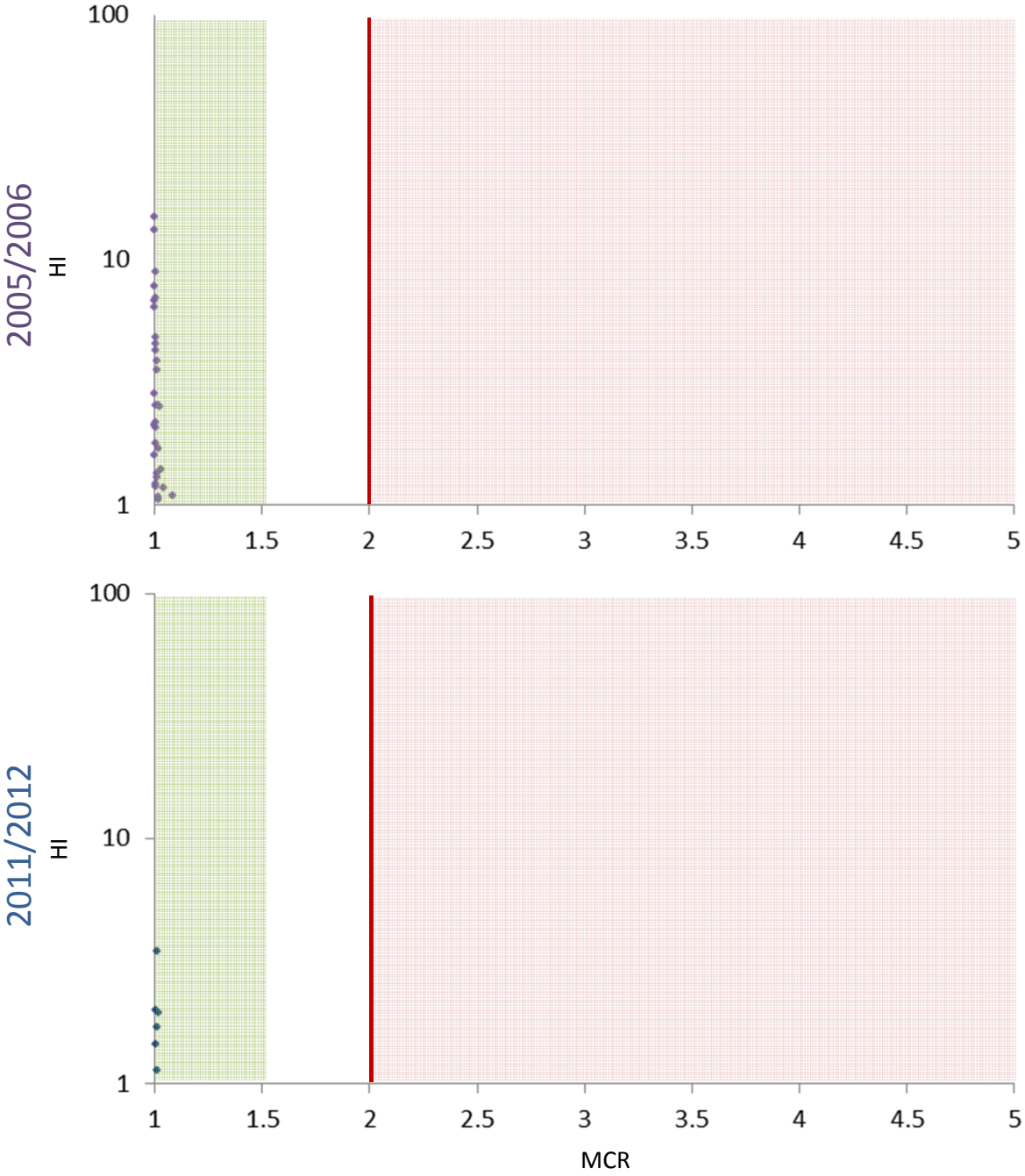
Interpretation of Cumulative Risk Assessment

In many cases the outcome of a cumulative risk assessment (CRA) is driven by a single chemical

- Maximum cumulative ratio (MCR) is a method to determine relative contribution[1]
  - MCR = HI/Max HQ
- As MCR values approach 1 cumulative risk assessment (CRA) is being driven by a single chemical
- A threshold MCR value of 2 has been proposed[2,3]
- Risk management for all components of CRA approach only necessary when HI > 1 and MCR > 2
  - MCR < 2 indicates a single substances is responsible for 50-100% of the risk

Risk identified by CRA of phthalates is primarily due to a single phthalate (DEHP)

- see MCR analyses on follow slides



Case 1

MCR = 5
(20% due to highest chemical exposure)
equal contribution of all phthalates

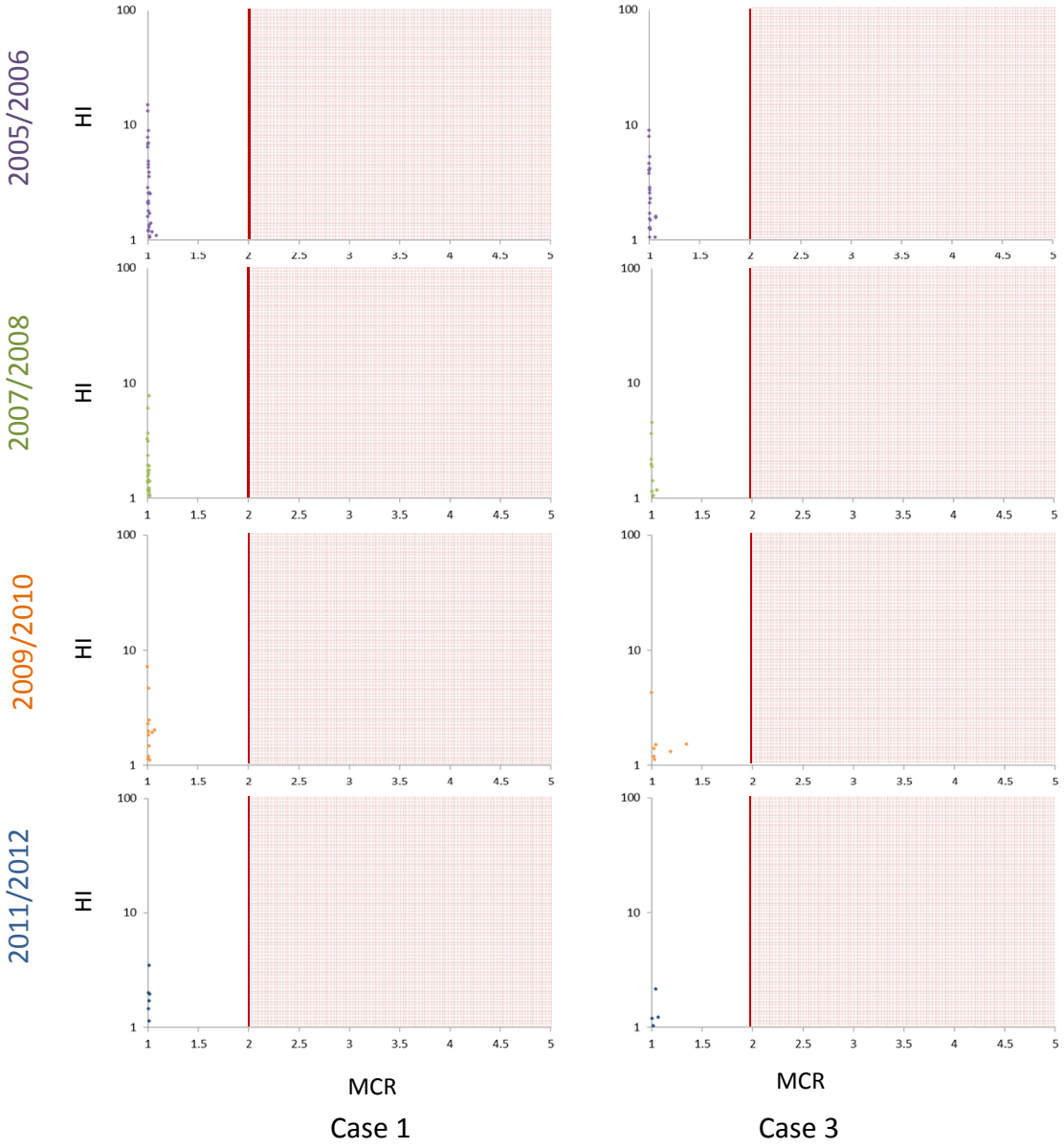
MCR = 1
(100% due to highest chemical exposure)
all risk contributed by single phthalate

red zone 50% - 20% single phthalate

green zone 67-100% single Phthalate

CRA for five phthalates indicates risk is due to single phthalate

No values HI>1 and MCR>2 (pink shaded region)



MCR all approach 1 - (100% due to highest chemical exposure)

Data points represent women of reproductive age (15-45) from NHANES data sets indicated

Comments?

Additional Questions?

March 16, 2015

Biomonitoring data to estimate exposure – using the latest NHANES data

American Chemistry Council

Agenda

The method

The trends

The impact of fasting

Exposure of pregnant women

The method

American Chemistry Council

The method

The method used by ACC is the same method used by CHAP.

Based on formula published by David (2000) and adopted by Koch and others (Koch *et al.*, 2003; Wittassek *et al.*, 2011).

$$DI(\mu g/kg_{bw}/day) = \frac{UE_{sum}(\mu mole/g_{crt}) \times CE(mg_{crt}/kg/day)}{F_{UE} \times (1000 mg_{crt}/g_{crt})} \times MW_{parent}(g/mole)$$

From CHAP Report, p. 35

The method

Formula allows exposure to be back-calculated from urinary concentrations that can be influenced by other factors such as consumption of water.

Variables:

Creatinine excretion rate is constant allowing normalization of concentrations per unit volume. (excretion changes with age of population or pregnancy)

Molar excretion fraction that is determined experimentally

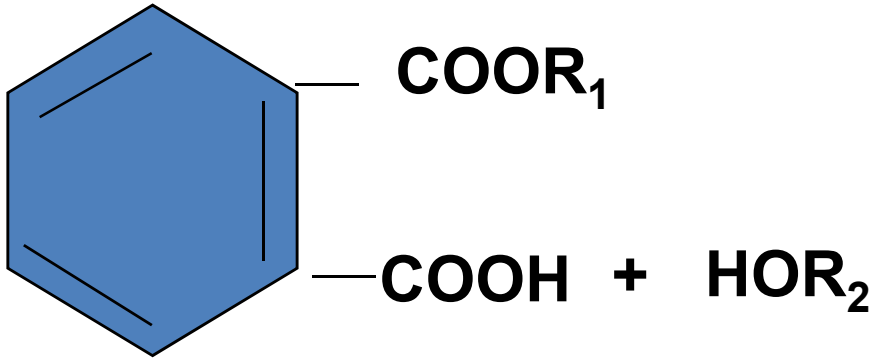
The method

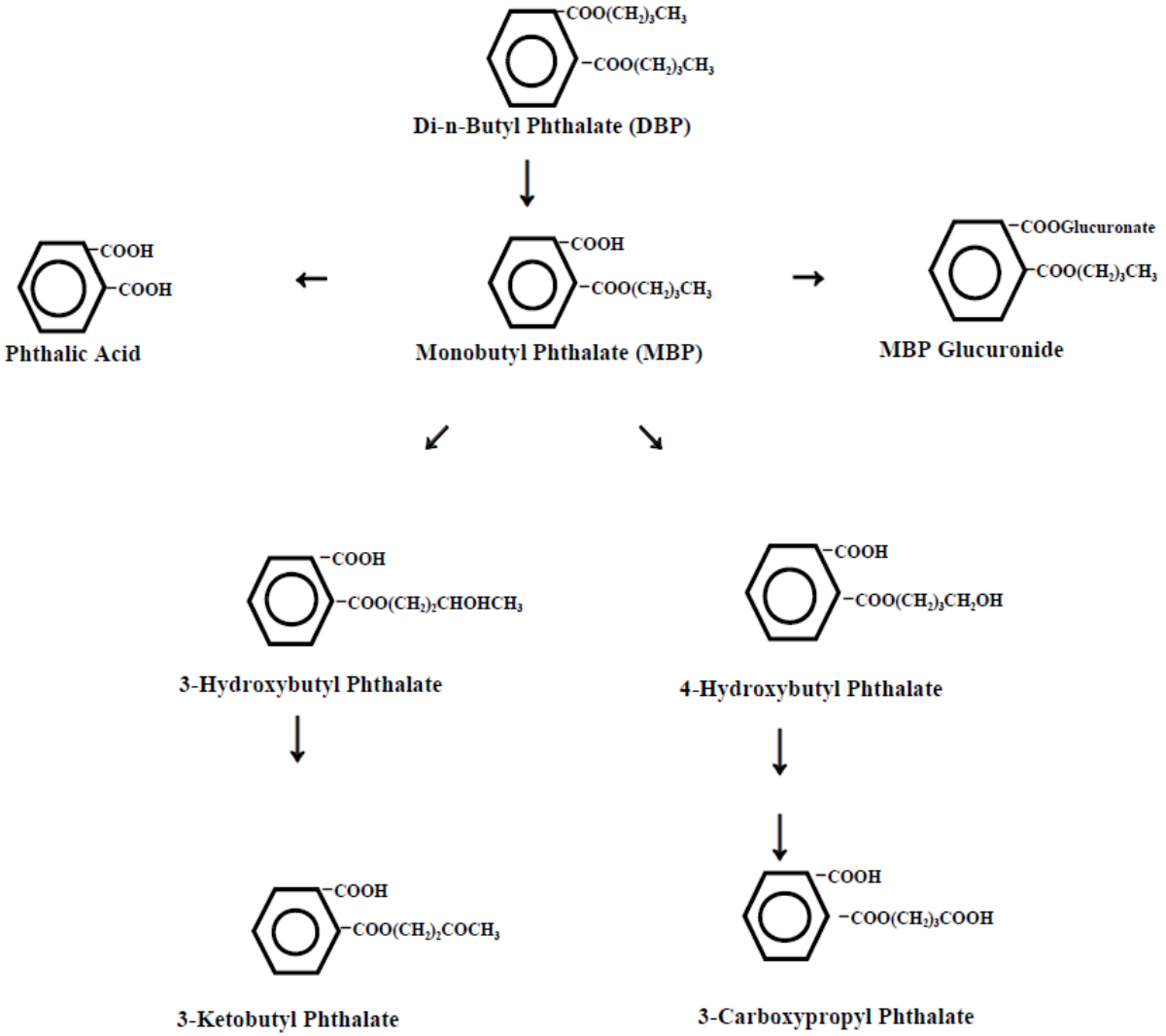
Molar excretion fraction is determined in humans knowing the oral dose and measuring the urinary concentration of metabolites.

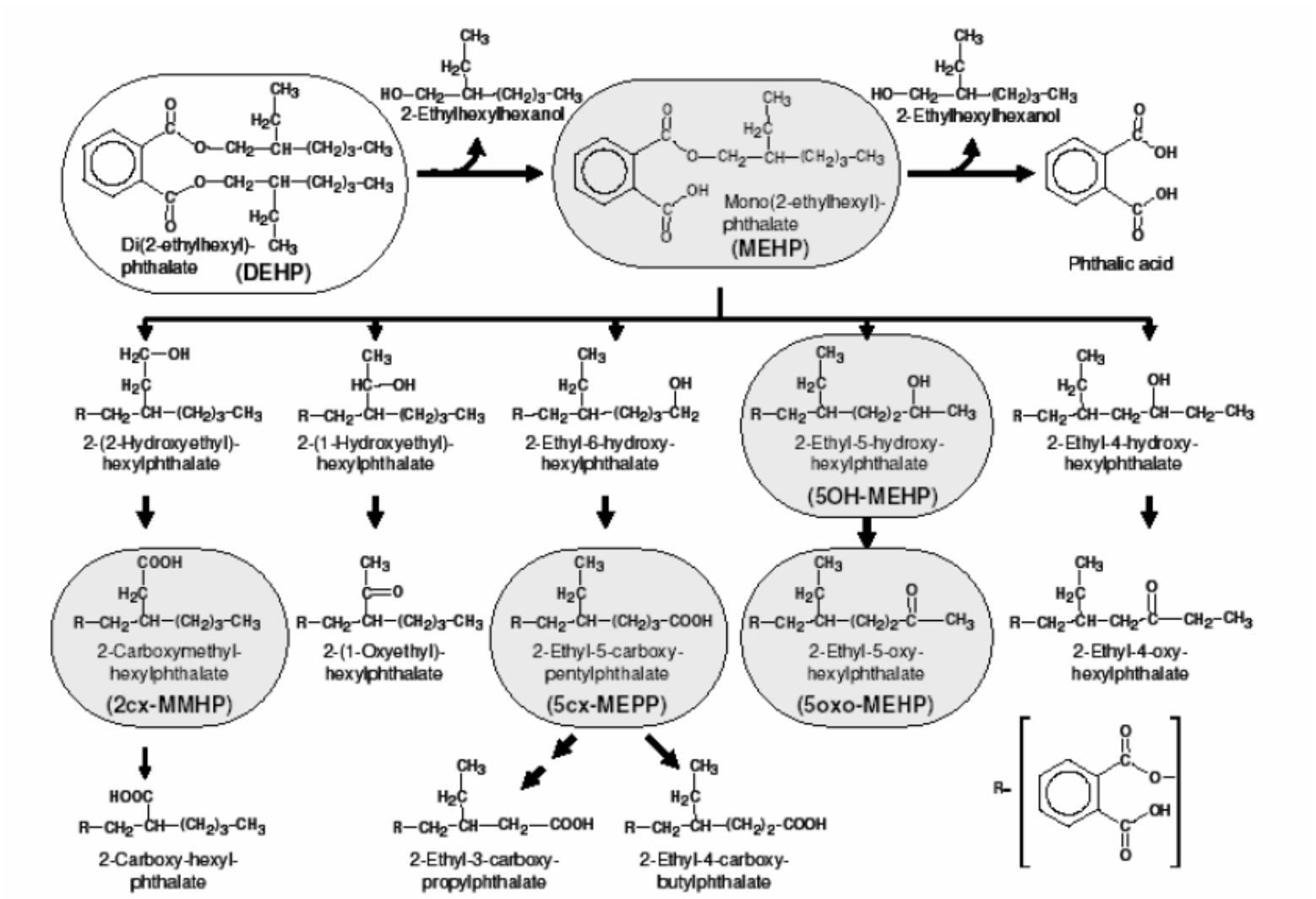
Common metabolite for all phthalate esters is the mono-ester.

The method

Phthalate esters are di-acid esters. First step in absorption/metabolism is hydrolysis of one ester bond to yield a mono-ester.




COO(CH2)3CH3
COO(CH2)3CH3
Di-n-Butyl Phthalate (DBP)
COOH
COOH
Phthalic Acid
COOH
COO(CH2)3CH3
Monobutyl Phthalate (MBP)
COOGlucuronate
COO(CH2)3CH3
MBP Glucuronide
COOH
COO(CH2)2CHOHCH3
3-Hydroxybutyl Phthalate
COOH
COO(CH2)3CH2OH
4-Hydroxybutyl Phthalate
COOH
COO(CH2)2COCH3
3-Ketobutyl Phthalate
COOH
COO(CH2)3COOH
3-Carboxypropyl Phthalate


Di(2-ethylhexyl)-phthalate (DEHP)
2-Ethylhexylhexanol
Mono(2-ethylhexyl)-phthalate (MEHP)
2-Ethylhexylhexanol
Phthalic acid
2-(2-Hydroxyethyl)-hexylphthalate
2-(1-Hydroxyethyl)-hexylphthalate
2-Ethyl-6-hydroxy-hexylphthalate
2-Ethyl-5-hydroxy-hexylphthalate (5OH-MEHP)
2-Ethyl-4-hydroxy-hexylphthalate
2-Carboxymethyl-hexylphthalate (2cx-MMHP)
2-(1-Oxyethyl)-hexylphthalate
2-Ethyl-5-carboxy-pentylphthalate (5cx-MEPP)
2-Ethyl-5-oxy-hexylphthalate (5oxo-MEHP)
2-Ethyl-4-oxy-hexylphthalate
2-Carboxy-hexyl-phthalate
2-Ethyl-3-carboxy-propylphthalate
2-Ethyl-4-carboxy-butylphthalate

The method

Schmidt and Schlatter (1985) were among the first to measure the urinary metabolites in man following exposure to DEHP.

Anderson *et al*. reported coefficients for 12 (2001) and 20 (2011) individuals exposed to one of several phthalates.

Wittasek *et al*. (2007) report coefficients for one or two humans exposed to DIDP.

The CHAP and ACC used the same coefficients to calculate exposure.

The method

The original method was validated by comparison to other calculations.

David (2000) exposures were compared with Kohn *et al*. (2000) who used a slightly different method. The results were almost identical (see CHAP report, p. 45, Table 2.7).

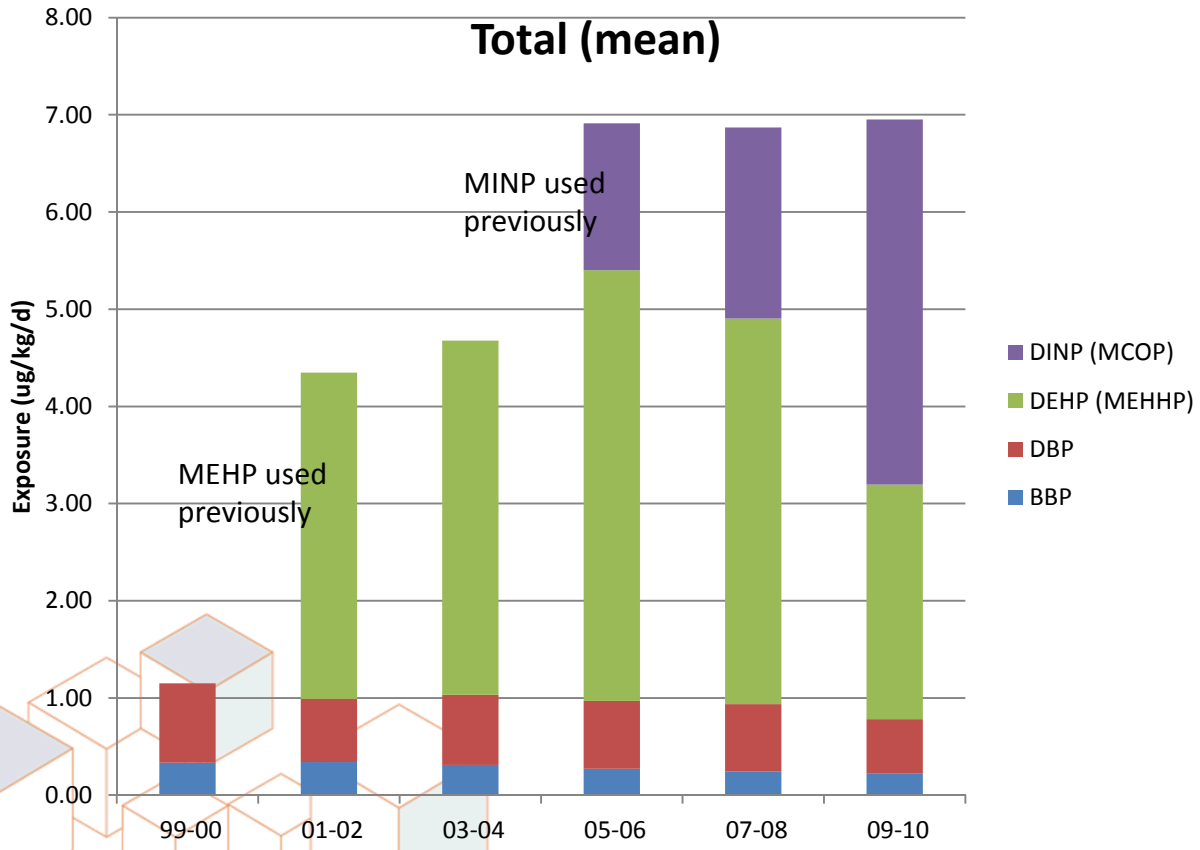
The trends

American Chemistry Council

Trends

ACC compiled the NHANES data over the last decade. While the CHAP reported that the collection protocol had changed in 2005 (CHAP, p. 35) and could not be lumped with earlier data, the comparison is interesting and consistent with production levels.

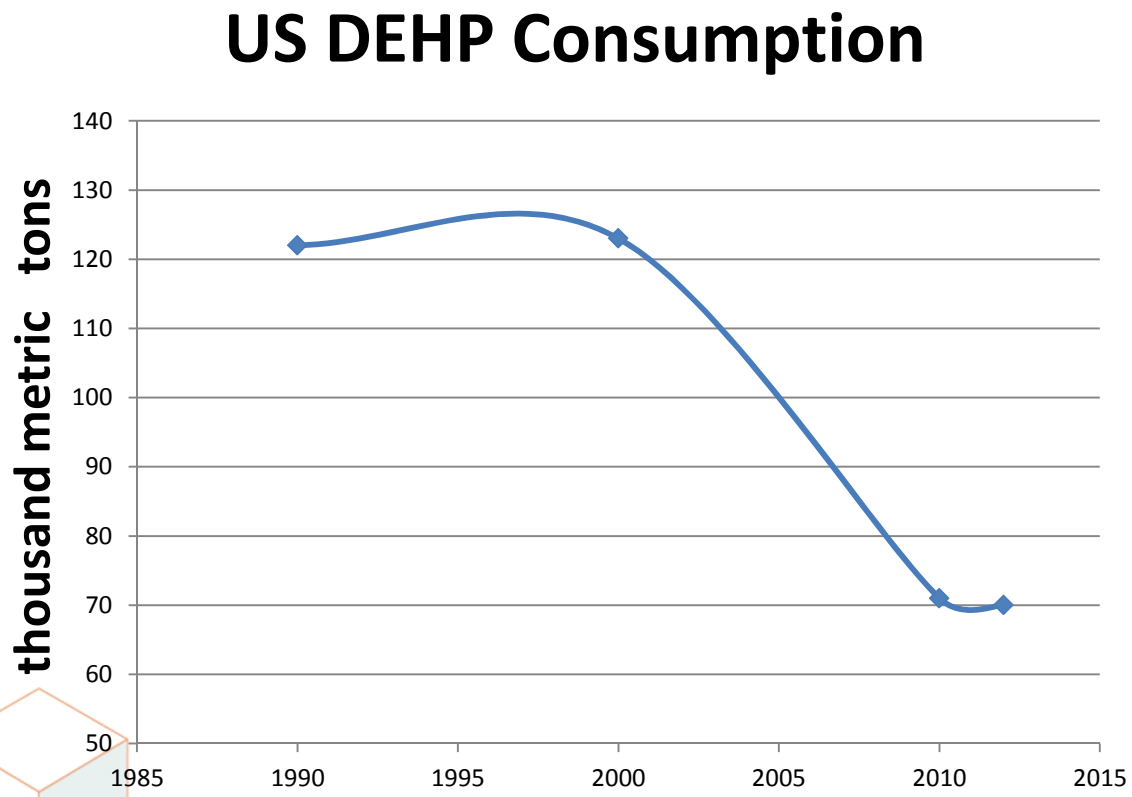
Trends

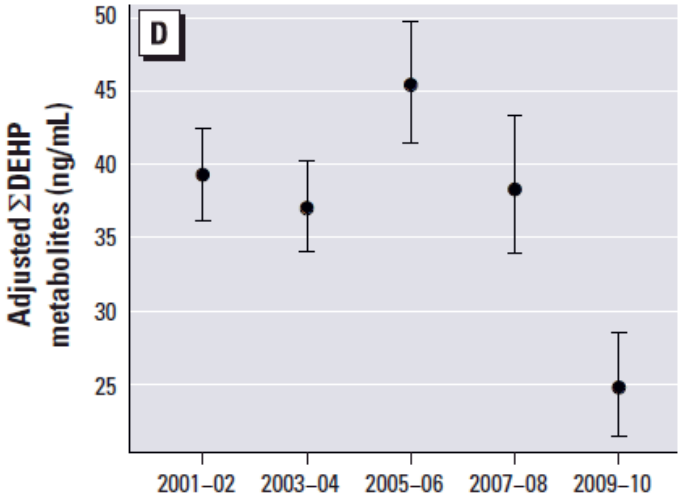


CDC 4th Report, Revised tables

Trends

Source: 2013 IHS Chemical Economics Handbook





From Zota *et al*., 2014

Trends

Thus, even the NHANES data since 2005 show a decrease in exposure levels that is consistent with a decrease in US consumption.

These observations are consistent with those published by others. For example, Zota *et al*. (2014) showed a trend toward lower exposure to DEHP and higher DINP.

It is appropriate to use the most recent NHANES data for the assessment rather than from previous years because it reflects the current situation.

Fasting

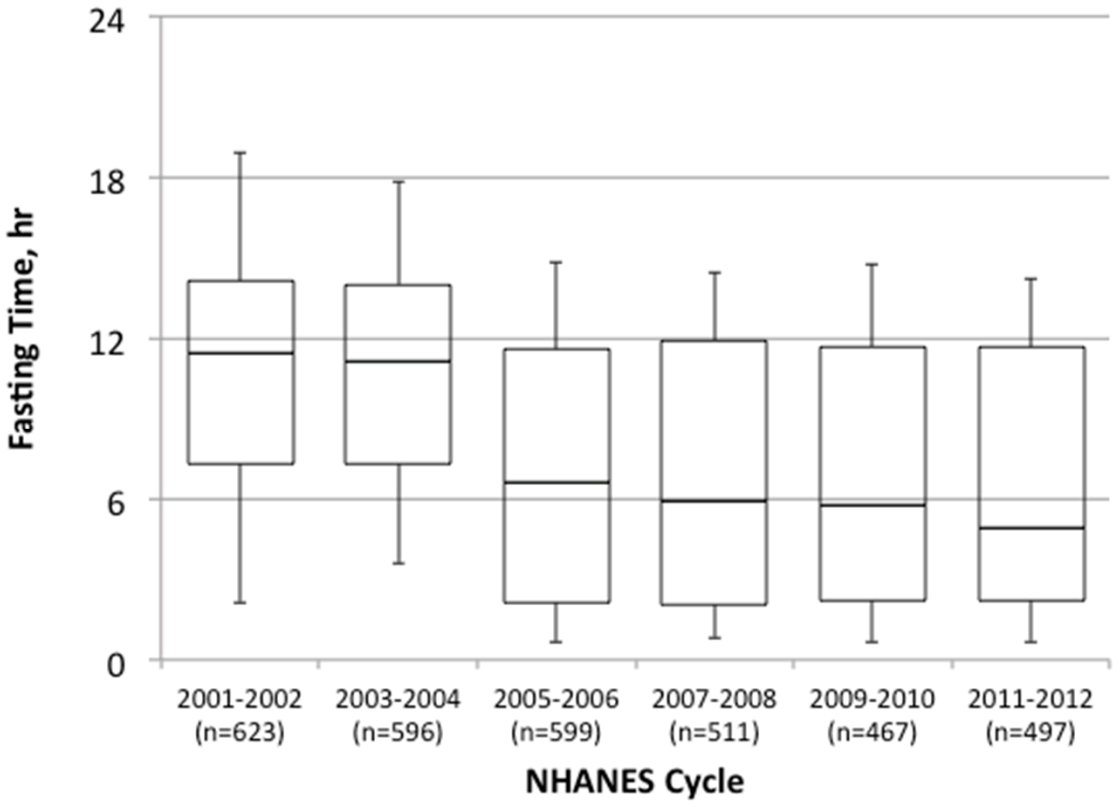
American Chemistry Council

Fasting

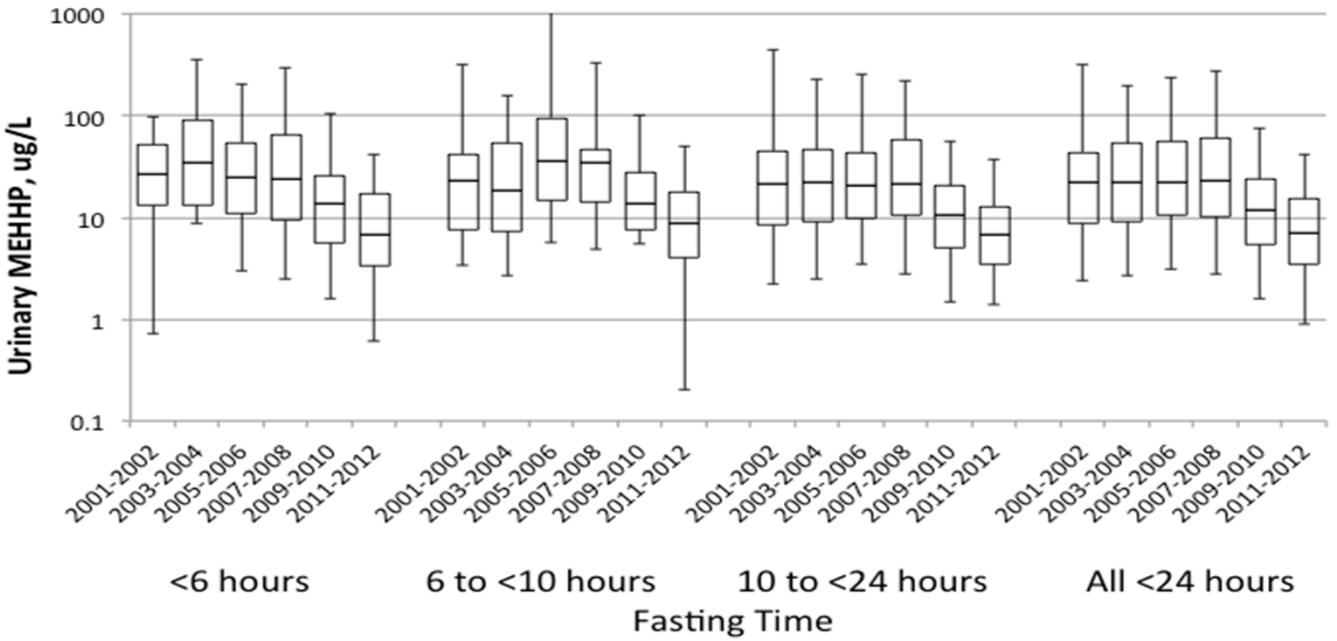
CHAP report suggests that fasting might have an impact on urinary levels and calculated exposure (CHAP, p. 4)

However, fasting had little impact on urinary concentrations and the urinary concentrations are consistent with consumption.

Fasting

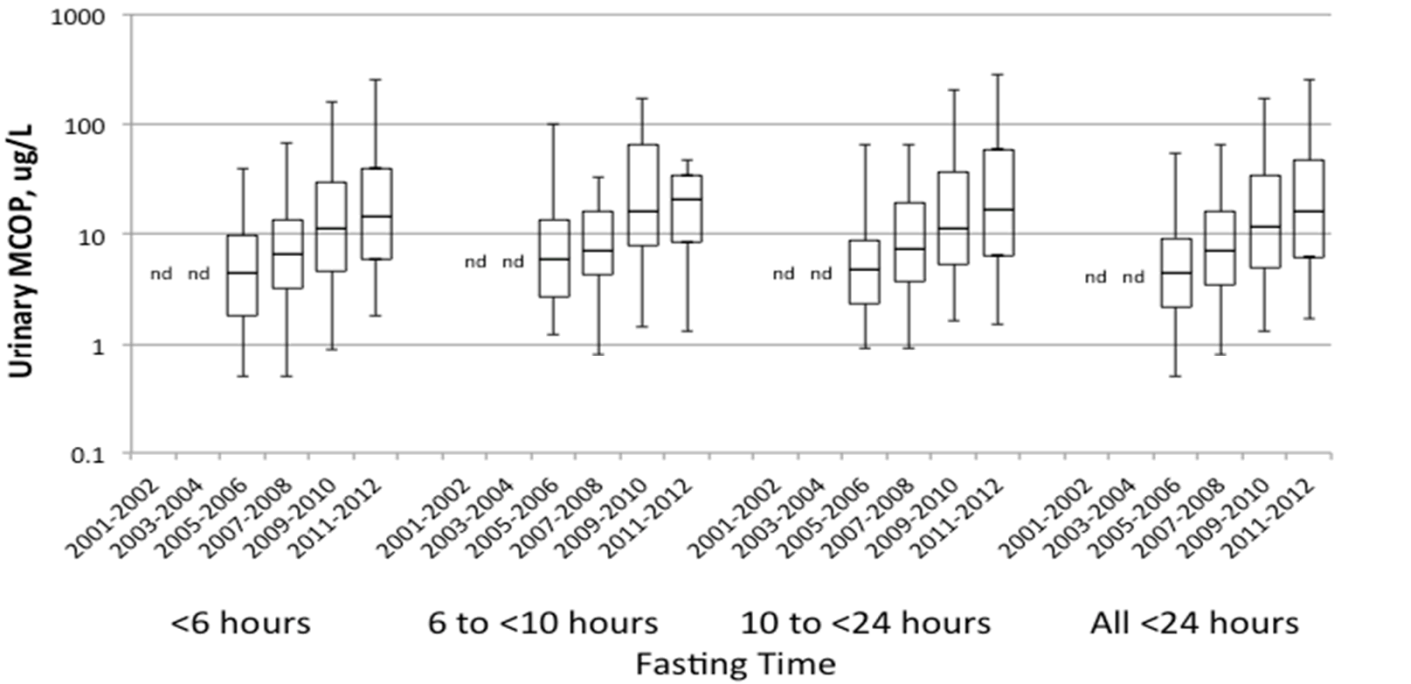

24
18
12
6
0
Fasting Time, hr
2001-2002 (n=623)
2003-2004 (n=596)
2005-2006 (n=599)
2007-2008 (n=511)
2009-2010 (n=467)
2011-2012 (n=497)
NHANES Cycle

Fasting



Distribution of urinary MEHHP concentrations in six NHANES cycles in women ages 15 to 45 by fasting time. Participants reporting fasting times greater than 24 hours were omitted from the analysis

Fasting



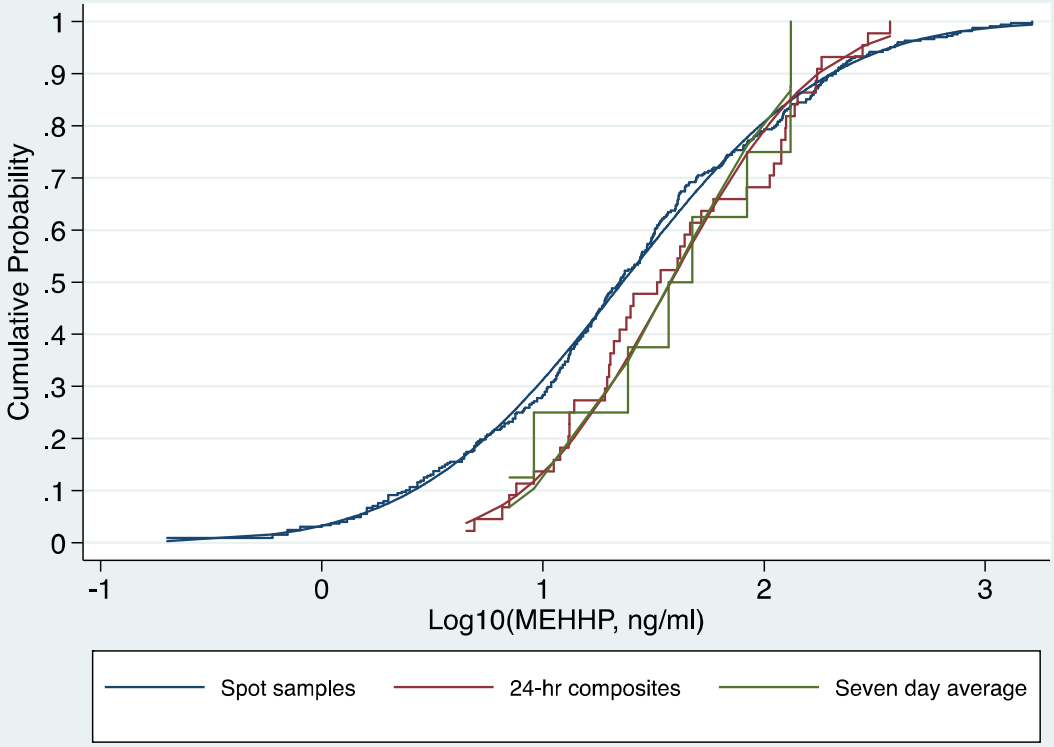
Distribution of urinary MCOP concentrations in five NHANES cycles in women ages 15 to 45 by fasting time. Participants reporting fasting times greater than 24 hours were omitted from the analysis. MCOP was not analyzed in the 2001-2002 and 2003-2004 cycles ("nd", no data).

Fasting

These data are consistent with NHANES values as a whole and with consumption levels of DEHP in North America.

Furthermore, spot samples are as predictive as 24-hour samples.

Fasting


Cumulative Probability
1
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
-1
0
1
2
3
Log10(MEHHP, ng/ml)
Spot samples
24-hr composites
Seven day average

Exposure of pregnant women

American Chemistry Council

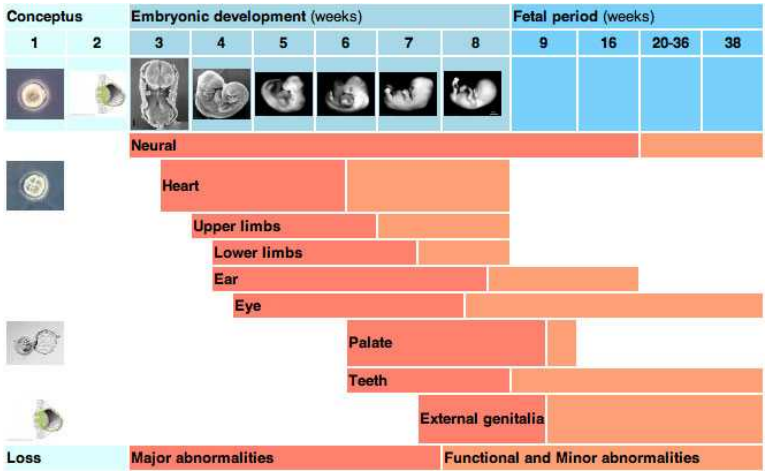
Year	Number of Women
99-00	1326
01- 02	1411
03-04	1355
05-06	1278
07-08	1310
09-10	1350

Pregnant women

CPSIA requires "*examine the likely levels of children's, pregnant women's, and others' exposure to phthalates ..*"

4th CDC Report had reduced number of pregnant women due to cessation of supplemental collection.

However, the number and percentage of women included in the 4th Report was unchanged.



Pregnant women

Proposed mode of action is most likely confined to first trimester when pregnancy may not be confirmed (Jost *et al.*, 1970; Bendsen *et al.*, 2003).

Using the data from the 4th CDC Report does not eliminate any population. Rather, it provides more up-to-date information that is consistent with changes in the market.

Also, there is no difference between exposure of pregnant and non-pregnant women.

Pregnant women

NHANES cycle	n by pregnancy status		MEHHP GM , ng/ml			MCOP GM , ng/ml		
	Yes	No	pregnant	non-pregnant	p	pregnant	non-pregnant	p
01-02	96	483	18.3	17.3	0.77	NM	NM	--
03-04	74	463	21.9	19.5	0.49	NM	NM	--
05-06	110	440	16.9	21.4	0.42	3.1	4.5	0.07
07-08	20	358	29.7	22.6	0.62	5.5	6.7	0.31
09-10	26	410	5.6	11	0.01	7.5	12.5	0.04
11-12	18	358	7.5	7	0.82	15.4	17.2	0.66

Summary

Method used by CHAP was developed by industry and both groups used the same approach.

Trends in levels of DEHP – the main driver for the HI – in NHANES are consistent with production levels.

Fasting has less of an impact than CHAP suggests. Rather, decreases in NHANES levels are consistent with production.

It is more appropriate to use most recent NHANES data for exposure estimate rather than 10-year old data that do not reflect current situation.