**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

# NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) – FURTHER INFORMATION

## Introduction

1. During the horizon scanning discussion at the February 2010 meeting, a Member proposed that it would be useful for the COT to receive an overview of the National Health and Nutrition Examination Survey (NHANES). At the May 2010 meeting, Members discussed paper TOX/2010/09, which provided an introduction to the NHANES, a summary of research undertaken using stored specimens from the survey and findings of a literature search for papers based on NHANES data that addressed the inter-relationship of chemical exposure, biomarkers and health risk. Members raised the following queries which this paper addresses:

- Are researchers allowed access to original data that have not been anonymised?
- If a researcher wanted to undertake a follow up study, based on a trend identified from the NHANES data, (hypothetically) would the researcher be able to identify and follow up participating individuals?
- Have any researchers published papers using NHANES genetic data?
- Have any papers been published where a cumulative exposure assessment has been undertaken using data from the NHANES?
- How are NHANES data used to inform public health decisions?

2. At the June meeting, Committee Members discussed a paper on the Health assessment of endocrine disrupting chemicals – The Danish EPA report and exposure time trends to phthalates (TOX/2010/16). Members noted that no UK biomonitoring data were available for the substances listed in the Danish EPA report and suggested it would be helpful to ascertain if any papers had been published that utilised relevant data from NHANES. This paper provides summary details of the papers identified from the literature search undertaken for each of the endocrine disrupting substances identified in the Danish EPA report that make use of/or compare NHANES data.

## NHANES sensitive data & survey follow up

3. Access to some sensitive data is available through the National Center for Health Statistics (NCHS) Research Data Center (RDC); however the

NCHS promise that "*No names, addresses, or any other item that could directly identify a person or firm are left on internal files unless absolutely needed.*" As the RDC has responsibility for protecting the confidentiality of survey respondents they do not allow the release of any electronic data without making sure that this information is removed.

4. Some sensitive data, for example ethnicity, sexual behaviour and phenotype can be accessed on request. Researchers have to submit a research proposal outlining why they need this more sensitive data. If approved the RDC then works with the research contractor to create a specific dataset using the original NHANES data that is tailored to the proposed research.

5. The RDC does not send out tailored datasets to researchers. To access the datasets the research contractor must work under the supervision of an RDC analyst at one of their facilities in Hyattsville, Maryland or Atlanta, Georgia. Alternatively restricted data can be accessed using a remote access system which allows the researcher to communicate with an automated system via e-mail. Remote access provides the convenience of performing analysis from any computer at any time, but it has several limitations such as not being able to see microdata (individual data records).

6. An item that *could* lead to the identity of a participant is described by the RDC as a "direct identifier". The RDC **cannot** provide access to direct identifiers; furthermore, to reduce the risk of accidental disclosure, data sets accessed through the RDC can **never** be removed from the RDC. Severe penalties (including up to 5 years imprisonment) have been put in place for breaching confidentiality.

## Papers published that utilise NHANES genetic data

7. A literature search was completed to assess the uptake and use of NHANES genetic data, full details of the search strategy are attached in Annex A. The search resulted in the identification of 42 potentially relevant papers. The results were refined to ensure the papers identified were relevant to the use of genetic data from NHANES, this led to the identification of 9 relevant papers, attached in Annex B. Table 1 below provides a brief summary of the relevant papers identified.

| Published Title | Brief Summary |
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| **Prevalence in the United States of selected candidate gene variants: Third National Health and Nutrition Examination Survey, 1991-1994**<br><br>**(Chang *et al.,* 2008)** | The authors used data from the second phase (1991-1994) of NHANES III to evaluate the allele frequency and genotype prevalence of polymorphisms that have known or proposed associations with common diseases in a nationally representative sample of the US population as a resource for future epidemiological studies. |

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| **Genetic variants associated with fasting blood lipids in the U.S. population: Third National Health and Nutrition Examination Survey**<br><br>**(Chang *et al*., 2010)** | The authors used data from the second phase (1991-1994) of NHANES III; they examined associations between 22 polymorphisms in 13 candidate genes and four serum lipids to test for genetic associations for each of the three major race/ethnic groups in the United States.<br><br>The authors reported significant associations of blood lipids with variants and haplotypes in *APOE, ITGB3, NOS3*, and *PON1* in the three main race/ethnic groups. |
| **Association of APOE polymorphism with chronic kidney disease in a nationally representative sample: a Third National Health and Nutrition Examination Survey (NHANES III) Genetic Study**<br><br>**(Chu *et al.,* 2009)** | Apolipoprotein E polymorphisms (APOE) have been associated with lowered glomerular filtration rate (GFR) and chronic kidney disease, with e2 allele conferring risk and e4 providing protection. The authors analyzed 5,583 individuals from NHANES III to determine association with estimated GFR.<br><br>The authors observed a weak association between the APOE e4 allele and low-GFR cases and continuous GFR in non-Hispanic whites, and the APOE e2 allele and continuous GFR in non-Hispanic blacks, but found no association with either measure of kidney function in Mexican Americans. |
| **Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey**<br><br>**(Crawford *et al.,* 2006)** | Increased serum C-reactive protein (CRP) is thought to be an independent risk factor for cardiovascular disease. This study aimed to identify specific *CRP* single-nucleotide polymorphisms (SNPs) and haplotypes associated with raised serum CRP levels in the general population using data from 7159 individuals from the NHANES III.<br><br>The results suggest "genetic variation within *CRP* is associated with serum CRP levels in the general population and may be associated with the prevalence of coronary heart disease." |
| **Gene polymorphisms in association with emerging cardiovascular risk markers in adult women**<br><br>**(Fan *et al.,* 2010)** | The authors used data from the second phase (1991-1994) of NHANES III; they examined fourteen candidate genes for associations with emerging cardiovascular risk markers.<br><br>The authors noted that in covariate-adjusted models, serum C-reactive protein concentrations were significantly associated with polymorphisms in *CRP*, *MTHFR*, and *ADRB3*. Serum homocysteine levels were also significantly associated with polymorphisms in *MTHFR*. |

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| **CRP polymorphisms and progression of chronic kidney disease in African Americans**<br><br>**(Hung *et al.,* 2009)** | 642 participants with chronic kidney disease from the African American Study of Kidney Disease and Hypertension (AASK) were genotyped, with five tag polymorphisms selected for comparison. The authors compared the minor allele frequencies (MAF) of single nucleotide polymorphisms from AASK to MAF's of African Americans from NHANES III.<br><br>The authors reported that MAF was higher for the *rs2808630_G* allele and lower for the *rs1205_A* allele in the AASK compared with NHANES III. The authors concluded C-reactive protein single nucleotide polymorphisms that were associated with higher levels of C-reactive protein did not predict chronic kidney disease progression. |
| **Using DNA fingerprints to infer familial relationships within NHANES III households**<br><br>**(Katki *et al*., 2010)** | The authors aimed to utilise the genetic data from NHANES III in order to ascertain familial relationships within households using DNA fingerprinting methods and two competing statistical methods, the identical by state (IBS) method and the exact method, used by law enforcement agencies.<br><br>The authors reported that both statistical methods usually agreed on the rankings of the most likely familial relationships; however the IBS method underestimated the likelihood ratio by not taking account of the informative value of matching rare alleles. |
| **Lead and cognitive function in VDR genotypes in the third National Health and Nutrition Examination Survey**<br><br>**(Krieg *et al.,* 2009)** | The authors investigated the relationship between blood lead concentration and cognitive function in children and adults with different *VDR* (1,25-dihydroxyvitamin D3 receptor) genotypes who participated in NHANES III. They also investigated the relationship between blood lead and serum homocysteine concentrations.<br><br>No evidence of differences in blood levels between the genotypes of *VDR rs2239185* and *VDR rs731236,* were found, however the authors did notice a difference in cognitive performance between genotypes, varying with age group. The authors postulate the differences may be due to “a difference in the amount or activity of a protein that is regulated by vitamin D3.”<br><br>The authors also reported a variation in the relationship between serum homocysteine and blood lead concentrations by *VDR* genotype. The authors suggested this may be due to “an effect of vitamin D on vitamin B absorption in the intestine”. |

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| **Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank**<br><br>**(Yang *et al.*, 2008)** | Data from the second phase (1991-1994) of NHANES III was used to assess the prevalence of genetic polymorphisms and their relation to serum folate and homocysteine concentrations.<br><br>The authors concluded that the *MTHFR 677C→T* polymorphism was associated with significant differences in serum folate and homocysteine concentrations in the US population before folic acid fortification. The effect of *MTHFR 677C→T* on homocysteine concentrations was reduced by moderate daily folic acid intake. |

*Table 1 - Relevant papers identified which utilise NHANES genetic data*

## Cumulative risk assessment of NHANES data

8. A PubMed literature search was undertaken, and the National Center for Health Statistics (NCHS) contacted, in order to ascertain if any papers had been published which had undertaken a cumulative exposure assessment using data from the NHANES. No papers could be identified that utilised NHANES data, although a paper was identified that sought to undertake a cumulative risk assessment of the intake of organophosphorus and carbamate pesticides in the Danish diet using data from the 1996 – 2001 Danish pesticide residue-monitoring programme. Full details of the search strategy and a copy of the identified paper by Jensen *et al* are attached in Annex C.

## How NHANES data are used to inform public health decisions

9. The following provides a useful summary of how the survey data is used in practice, most of the text is taken directly from the NHANES website at http://www.cdc.gov/nchs/nhanes/about_nhanes.htm

10. "Results of NHANES benefit people in the United States in important ways. Facts about the distribution of health problems and risk factors in the population give researchers important clues to the causes of disease. Information collected from the current survey is compared with information collected in previous surveys. This allows health planners to detect the extent various health problems and risk factors have changed in the U.S. population over time. By identifying the health care needs of the population, government agencies and private sector organizations can establish policies and plan research, education, and health promotion programs that help improve present health status and will prevent future health problems."

11. "Past surveys have provided data to create the growth charts used nationally by paediatricians to evaluate children's growth. The charts have been adapted and adopted worldwide as a reference standard."

12. "Blood lead data were instrumental in developing policy to eliminate lead from gasoline and in food and soft drink cans. Recent survey data indicate the policy has been even more effective than originally envisioned, with a decline in elevated blood lead levels (in the US) of more than 70% since the 1970s."

13. "Overweight prevalence figures have led to the proliferation of programs emphasizing diet and exercise, stimulated additional research, and provided a means to track trends in obesity."

14. "NHANES data have continued to indicate that undiagnosed diabetes is a significant problem in the United States. Efforts by government and private agencies to increase public awareness, especially among minority populations, have been intensified."

15. "National programs to reduce hypertension and cholesterol levels continue to depend on NHANES data to steer education and prevention programs toward those at risk and to measure success in curtailing risk factors associated with heart disease."

16. Information collected in the current survey will be used by the Food and Drug Administration to decide if there is a need to change vitamin and mineral fortification regulations. The current survey will also introduce new measures of lung function to further understanding of respiratory disease and better describe the burden of asthma in the United States.

## NHANES data on endocrine disrupting chemicals

17. A literature search was undertaken to identify published papers that utilised relevant data from NHANES and referred to the endocrine disrupting substances examined as part of the survey and health assessment of the exposure of 2 year-olds to chemical substances in consumer products undertaken by the Danish EPA. Only one significant paper was identified that sought to comprehensively analyse the NHANES data for time trends in exposure. Full details of the literature search strategy and a copy of the identified paper by Wittassek *et.al.,* 2007 are included in Annex D.

Table 2 provides a brief summary of all the relevant papers identified relating to substances identified by the Danish EPA as having endocrine disrupting effects in animal studies. It should be noted that as phthalates and bisphenol A (BPA) tend to be rapidly cleared in humans the data available from the NHANES are only indicative of recent exposure. Conversely PCBs and dioxins tend to accumulate in human adipose tissue and have much longer half lives, therefore the NHANES data for these substances will reflect longer term exposure.

| PHTHALATES | |
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| Paper Title | Brief Summary |
| **Dietary intake is associated with phthalate body burden in a nationally representative sample**<br><br>**(Colacino *et al.,* 2010)** | This study assessed the contribution of different food types to phthalate exposure using a multiple linear regression model to analyse data collected as part of the 2003-2004 NHANES.<br><br>Metabolites of DEHP and high-molecular-weight phthalate metabolites were associated with the consumption of poultry. Monoethyl phthalate, a metabolite of diethyl phthalate (DEP), was associated with vegetable consumption, specifically tomato and potato consumption. |
| **A simple pharmacokinetic model to characterize exposure of Americans to di-2-ethylhexyl phthalate**<br><br>**(Lorber *et al.,* 2010)** | The authors developed and applied a simple pharmacokinetic model to predict concentrations of five metabolites of DEHP in serum and urine. The model was calibrated using data from an individual who dosed himself with 48.5 mg DEHP, and then took blood and urine samples over a 44-h period. The calibrated model was used in two applications: (i) on a set of individuals whose exposure to DEHP was through PVC medical devices in a blood platelet donation procedure, and (ii) on background exposures in the United States taken from the 2001-2002 NHANES.<br><br>The 2001-2002 NHANES data indicate the median US background urine concentrations of the DEHP metabolites MEHP, 5OH-MEHP, and 5oxo-MEHP are 4.1, 20.1, and 14.0 microg/l, respectively. The authors used creatine and urine volume-correction approaches to backcalculate an average daily dose of DEHP in the range of 0.6-2.2 µg/kg per day.<br><br>A "background cohort" including 8 individuals and 57 complete days of urination were assumed to be exposed to 1.5 µg/kg per day, spread out in equal doses of 0.3 µg/kg per day at 0900,1200, 1500, 1800, and 2100 h. The average predicted urine concentrations were 4.6, 15.9, and 9.4 µg/l for MEHP, 5OH-MEHP, and 5oxo-MEHP.<br><br>These results are similar, but the two secondary metabolites are slightly lower than medians found in NHANES. The authors postulate this could have been due to differences in metabolism between the individual who provided the calibration data (61-year-old Caucasian male) and the general US population. |

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| **Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999-2000**<br><br>**(Silva *et.al.,* 2004)** | This study examined urinary monoester metabolites of seven commonly used phthalates in approximately 2,540 samples collected from participants of the 1999-2000 NHANES.<br><br>Detectable levels of metabolites monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), and mono-(2-ethylhexyl) phthalate (MEHP) were found in > 75% of the samples, suggesting widespread exposure in the United States to diethyl phthalate, dibutyl phthalate or diisobutylphthalate, benzylbutyl phthalate, and di-(2-ethylhexyl) phthalate, respectively.<br><br>Mono-isononyl phthalate, mono-cyclohexyl phthalate, and mono-n-octyl phthalate were detected less frequently suggesting that human exposures to di-isononyl phthalate, dioctylphthalate, and dicyclohexyl phthalate, respectively, are lower than those listed above, or the pathways, routes of exposure, or pharmacokinetic factors such as absorption, distribution, metabolism, and elimination are different.<br><br>The authors highlighted that females of all ages had significantly higher concentrations of the reproductive toxicant MBP than did males of all ages; however, women of reproductive age (i.e., 20-39 years of age) had concentrations similar to adolescent girls and women 40 years of age. |
| **Internal phthalate exposure over the last two decades:- a retrospective human biomonitoring study**<br><br>**(Wittassek *et.al.,* 2007)** | This retrospective human biomonitoring study analysed 24h urine samples taken from 634 subjects who participated in the German Environmental Specimen Bank for Human Tissues (ESBHum) for concentrations of primary and/or secondary metabolites of di-n-butyl phthalate (DnBP), di-iso-butyl phthalate (DiBP), butylbenzyl phthalate (BBP), di(2-ethylhexyl) phthalate (DEHP) and di-iso-nonyl phthalate (DiNP).<br><br>In over 98% of the urine samples metabolites of all five phthalates were detectable indicating a ubiquitous exposure of the German population to all five phthalates throughout the last 20 years.<br><br>The authors used the urinary phthalate metabolite levels to estimate the daily intakes of the parent phthalates. Compared to data from NHANES, median exposure levels of the dibutyl phthalates were generally higher in the German study population, while levels of BBP were somewhat lower. Over the years the authors noted a pronounced decline in exposure to DnBP with the median value for 2003 being 3 times lower than from 1988. Overall, for 14% of the subjects observed daily DnBP intakes were above the EFSA tolerable daily intake (10 µg/kg bw/d). However, the frequency of exceedance decreased during the years. From 1988 to 1993 there were 63 daily intakes above the TDI; whereas between 1996 and 2001 only 27 exceedances were noted, dropping to only 1 subject in the most recent (2003) subset. A similar pattern of decline in exposure was noted with DEHP. The authors also noted slightly decreasing values for BBP exposure over the timecourse.<br><br>By contrast both DiBP and and DiNP showed an increasing trend over time with DiNP values in 2003 amounting to twice their 1988 value. |

| PCB's (POLYCHLORINATED BIPHENYLS) | |
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| **PCB body burdens in US women of childbearing age 2001-2002: An evaluation of alternate summary metrics of NHANES data**<br><br>**(Axelrad *et al.,* 2009)** | The authors aimed to provide a robust method to track and summarise PCB exposure over time using NHANES data. They considered 6 different metrics consisting of different combinations of the 9 most frequently detected congeners.<br><br>The authors concluded the 4-congener metric (the sum of PCB-118, PCB-138, PCB-153 & PCB-180) and total PCB's metric (the sum of the 9 most frequently detected congeners) were the most promising approaches for tracking changes in PCB body burden over time and for comparing body burdens of different population subgroups.<br><br>It should be noted that the authors made no attempt to actually track changes in body burden using the approaches they identified. |
| **Association of polychlorinated biphenyls with hypertension in the 1999-2002 National Health and Nutrition Examination Survey**<br><br>**(Everett *et al.,* 2008)** | This study used data from the NHANES (1999-2002) to investigate the association of 11 PCB's with hypertension.<br><br>After adjustment for a number of potential confounders the authors identified 7 of the 11 PCB's as significantly associated with hypertension. |
| **Association between serum concentrations of persistent organic pollutants and insulin resistance among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002**<br><br>**(Lee *et al.,* 2007)** | The association between exposure to POPs and insulin resistance among non-diabetic adults, a frequent pathogenic precursor of type 2 diabetes was investigated. Data were taken from the 1999-2002 NHANES on 749 non-diabetic participants aged > or = 20 years. Serum concentrations of POPs and homeostasis model assessment of insulin resistance (HOMA-IR) were investigated cross-sectionally.<br><br>Organochlorine (OC) pesticides were most strongly associated with HOMA-IR. Associations with elevated HOMA-IR appeared to be specific to oxychlordane and trans-nonachlor. Associations were also found for two nondioxin-like PCBs. The association between OC pesticides and HOMA-IR tended to strengthen as waist circumference increased, with no apparent association in the lowest quartile of OC pesticide concentrations.<br><br>The authors concluded that OC pesticides and non-dioxin like PCBs may be associated with type 2 diabetes risk by increasing insulin resistance, and POPs may interact with obesity to increase the risk of type 2 diabetes. |

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| **Age-specific reference ranges for polychlorinated biphenyls (PCB) based on the NHANES 2001-2002 survey**<br><br>**(Nichols *et al.,* 2007)** | The serum concentrations of many persistent organochlorine compounds are strongly age dependent. Data were analyzed from the NHANES 2001-2002 sampling cycle to identify age-specific reference ranges for the measured PCB congeners on a lipid-adjusted serum basis. In addition, reference ranges were estimated for the sum of the 34 measured PCB congeners. Many congeners were frequently non-detectable, so estimates were used to calculate summed PCB levels. The effect of non-detects on the summed congeners totals is particularly strong for younger ages.<br><br>The authors noted that the NHANES 2001-2002 PCB serum data demonstrate strong age-related trends, with older individuals displaying higher concentrations of most congeners and of summed PCB congeners. |
| DIOXINS | |
| **Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999-2002**<br><br>**(Ha *et al.,* 2007)** | This study aimed to examine associations of serum concentrations of POPs with self-reported history of cardiovascular disease (CVD). Cross-sectional associations of serum POPs concentrations with the prevalence of self-reported CVD were investigated in 889 adults ≥ 40 years of age in the 1999-2002 NHANES.<br><br>Dioxin-like PCBs, non-dioxin-like PCBs, and organochlorine pesticides were positively associated with the prevalence of CVD only among females. PCDDs showed positive trends with the prevalence of CVD in both males and females. The authors suggested these findings should be interpreted with care due to the cross-sectional design of the study and use of self-reported CVD. |
| **Association between serum concentrations of persistent organic pollutants and prevalence of newly diagnosed hypertension: results from the National Health and Nutrition Examination Survey 1999-2002**<br><br>**(Ha *et al.,* 2009)** | The authors investigated associations of serum persistent organic pollutant (POP) concentrations with the prevalence of newly diagnosed hypertension in 524 adult participants of the NHANES (1999-2002).<br><br>Serum concentrations of PCDD's and PCDF's were associated with hypertension among women, but not men, whilst serum concentrations of PCB's were associated with hypertension amongst men only. The authors suggested these findings should be interpreted with care due to the cross-sectional design of the study. |

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| **Perspective on serum dioxin levels in the United States: an evaluation of the NHANES data**<br><br>**(LaKind *et al.,* 2009)** | This study utilised the serum PCDD/F data from the NHANES sampling periods spanning 1999-2004 to assess whether there were discernable temporal trends in the United States, either for the overall population or by age. The authors also compared population serum data to bio-monitoring equivalents (BEs) derived for PCDDs/Fs/PCBs.<br><br>The serum PCDD/F data provides evidence that levels in the US population are declining, mirroring international trends, although the lower levels are principally observable in the 2003-2004 time period.<br><br>PCDD/F serum levels decreased by 56% for the 12-to 19-year-old group and by 38% for the 20-to 39-year olds. A slight non-significant decrease was observed for 40-to 59-year olds and a slight statistically significant increase was found for 60+ year olds.<br><br>The population mean PCDD/F/PCB TEQ is approximately equal to the BE (based on the Agency for Toxic Substances and Disease Registry's Minimum Risk Level) and is approximately 2-4 times lower than the remaining BEs, placing the population mean at the border between medium and low priority levels. However, certain segments of the population have levels at the medium/high priority level (e.g., the 95th percentiles for ages 60 years and older). |
| **Evaluation of background exposures of Americans to dioxin-like compounds in the 1990s and the 2000s**<br><br>**(Lorber *et al.,* 2009)** | This study provides an update to the US Environmental Protection Agency's 2004 Dioxin Reassessment whose evaluation utilised data generated in the mid-1990s.<br><br>Studies conducted in the 2000s suggest declines in the average background dose and body burden, however a precise quantification of the decline, much less a conclusion that a decline has indeed occurred, could not be made because of the inconsistency of study design and data sources, and the treatment of non-detects in the generation of congener average concentrations.<br><br>The average background intake of the reassessment was 61.0 pg TEQ/day, however using more current data, the average background intake dropped to 40.6 pg TEQ/day.<br><br>The average body burden from the surveys in the mid-1990s was 22.9 pg TEQ/g lipid weight. Data from the 2001-2002 NHANES, suggest an adult average at 21.7 pg/g TEQ lipid weight.<br><br>A more detailed examination of beef and pork data from similarly designed national statistical surveys show that declines in pork were statistically significant while the beef concentrations appeared to have remained constant between the time periods. |

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| **Serum dioxin levels in residents of Calcasieu and Lafayette parishes, Louisiana with comparison to the US population**<br><br>**(Wong *et al.,* 2008)** | This cross-sectional, population-based, study aimed to determine if serum dioxin toxic equivalent (TEQ) levels of a population-based representative sample of Calcasieu Parish residents aged 15 years and older were elevated relative to Lafayette Parish, whose residents have a similar demographic with less industrial activity.<br><br>The study findings indicated that dioxin TEQ levels are similar in both parishes. However when the Calcasieu and Lafayette Parish data were compared by age group to the 2001-2002 NHANES data, the geometric means for the dioxin levels in the combined Parish data set were significantly lower than the NHANES data in all age groups except the oldest age group where the significance level was marginal. |
| BPA (BISPHENOL A) | |
| **Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004**<br><br>**(Calafat *et al.,* 2008)** | This study aimed to assess exposure to BPA and 4-tertiary-octylphenol (tOP) in the U.S. general population using the total (free plus conjugated) urinary concentrations of BPA and tOP in 2,517 participants ≥ 6 years of age in the 2003-2004 NHANES.<br><br>BPA and tOP were detected in 92.6% and 57.4% of the participants, respectively. Least square geometric mean (LSGM) concentrations of BPA were significantly lower in Mexican Americans than in non-Hispanic blacks and non-Hispanic whites. Females had statistically higher BPA LSGM concentrations than males. Children had higher concentrations than adolescents, who in turn had higher concentrations than adults. LSGM concentrations were lowest for participants in the high household income category (> $45,000/year).<br><br>The authors concluded that urine concentrations of total BPA differed by race/ethnicity, age, sex, and household income. |
| **Bisphenol A (BPA) daily intakes in the United States: estimates from the 2003-2004 NHANES urinary BPA data**<br><br>**(LaKind & Naiman 2008)** | This study used nationally representative data on urinary levels of BPA in the United States from the 2003-2004 NHANES to estimate daily intake of BPA, assuming steady-state excretion.<br><br>Distributions of intakes for the US population were determined for (i) all NHANES participants with urinary BPA data; (ii) participants by the following age groups: 6-11 years, 12-19 years, 20-39 years, 40-59 years, and 60+ years; and (iii) participants by gender.<br><br>On the basis of the NHANES urinary BPA data and the assumptions made by the authors, daily BPA intakes for male participants appeared to be higher than for female participants, there were also statistically significant differences in daily BPA intakes according to age groups, with the oldest group having the lowest estimated intakes. Median intake was approximately three orders of magnitude below health-based guidance values of 50 µg/kg bodyweight /day. |

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| **Daily intake of bisphenol A and potential sources of exposure: 2005-2006 National Health and Nutrition Examination Survey**<br><br>**(LaKind *et al.,* 2010)** | Nationally representative data on urinary levels of bisphenol A (BPA) and its metabolites from the 2005-2006 NHANES were used to estimate daily BPA intakes. The NHANES data were also examined to identify associations between urinary BPA levels and potential sources of BPA exposure.<br><br>The authors calculated that 34 ng/kg bw/day was the approximate daily BPA intake for the overall population. They also identified median daily BPA intakes for men were higher than for women with a significant decrease in daily BPA intake with increasing age.<br><br>Estimates of daily BPA intake decreased when compared with the 2003-2004 NHANES. However the authors suggest it is premature to draw conclusions regarding trends at this time, as there is no indication that BPA use declined from 2003 to 2006.<br><br>The authors also concluded that the consumption of soda, school lunches, and meals prepared outside the home (but not bottled water or canned tuna) were associated with higher levels of urinary BPA. |
| **Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults**<br><br>**(Lang *et al.,* 2008)** | The authors undertook a cross sectional analysis to examine associations between urinary BPA concentrations and adult health status using data from 1455 individuals obtained from the 2003-2004 NHANES.<br><br>It was noted that higher BPA concentrations were associated with diagnoses of cardiovascular disease and diabetes. Associations were also found between higher BPA concentrations and clinically abnormal concentrations of the 3 liver enzymes examined, namely GGT, alkaline phosphatase, and lactate dehydrogenase.<br><br>The authors concluded that “higher BPA exposure, reflected in higher urinary concentrations of BPA, may be associated with avoidable morbidity in the US community-dwelling adult population.” |
| **Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06**<br><br>**(Melzer *et al.,* 2010)** | This study used a cross sectional analysis of data from the 2005-2006 NHANES and data pooled across a number of collection years to estimate associations between urinary BPA concentrations and health measures.<br><br>The authors noted that higher BPA concentrations were associated with coronary heart disease in the 2005-2006 data and in the pooled data. Associations with diabetes did not reach significance in 2005-06, however pooled estimates remained significant. There was no overall association with gamma glutamyl transferase concentrations, but pooled associations with alkaline phosphatase and lactate dehydrogenase remained significant.<br><br>The authors concluded that higher BPA exposure, reflected in higher urinary concentrations of BPA, is consistently associated with reported heart disease in the general adult population of the USA. |

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| **Within person variability in urinary bisphenol A concentrations: measurements from specimens after long-term frozen storage**<br><br>**(Nepomnaschy *et al.,* 2009)** | The study aimed to evaluate the stability of BPA in specimens after years of storage and to measure short term within-person temporal variability in urinary BPA.<br><br>Total BPA concentration was measured by mass spectrometry in first-morning urine samples from 60 premenopausal women. Three specimens per woman were selected at approximately 2-week intervals to include both follicular and luteal phase samples. Seven metabolites of five phthalates were measured by mass spectrometry. Temporal variability was assessed using mixed model regression and correlations.<br><br>The authors concluded that although the same samples have not been measured both before and after long-term storage, their results suggest that the measurement of phthalate metabolites after long-term sample storage yield generally similar distributions and temporal reliability as those reported for recently collected specimens. The similar distribution to NHANES samples and correlation of BPA levels taken at 2-week intervals provide indirect evidence that BPA is relatively stable during long-term freezer storage. |
| **Bisphenol A data in NHANES suggest longer than expected half-life, substantial non-food exposure, or both**<br><br>**(Stahlhut *et al.,* 2009)** | It is thought that food is the predominant source of exposure to BPA and that it is rapidly and completely cleared from the body. The authors suggest that if this is correct, BPA levels in fasting individuals should decrease with increased fasting time.<br><br>The authors set out to investigate the relationship between urine BPA concentration and fasting time in a population-based sample. They modelled log BPA urine concentration as a function of fasting time, adjusted for urine creatinine and other confounders, in 1,469 adult participants from the 2003-2004 NHANES.<br><br>The authors reported that overall, BPA levels did not decline rapidly with fasting time in this sample, suggesting substantial non-food exposure or accumulation in body tissues such as fat, or both. |

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| **Levels of metabolites of organophosphate pesticides, phthalates, and bisphenol A in pooled urine specimens from pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa)**<br><br>**(Ye *et al.*, 2009)** | Average levels of metabolites of organo-phosphate pesticides, phthalates and BPA were measured in 10 pooled urine samples representing 110 pregnant women who participated in the Norwegian Mother and Child Birth Cohort (MoBa) study in 2004. Daily intakes were estimated and compared with health based guidance values. The results were also compared to findings from the Dutch Generation R study (a population-based birth cohort study in the city of Rotterdam) and data from pregnant women in the NHANES.<br><br>MoBa pregnant women had the highest mean BPA concentrations. Mean total dialkyl phosphate metabolite concentrations in the pregnant women in MoBa were lower than in Generation R, but higher than in NHANES. Compared with women in NHANES, MoBa participants had higher concentrations of the primary DEHP metabolite MEHP; but lower concentration of the secondary metabolites, MEHHP and MEOHP. The largest difference was found between the two European studies and NHANES for MiBP, a metabolite of DiBP. The unadjusted mean MiBP concentration in the European studies was more than *10* fold higher than that in NHANES.<br><br>The authors note that unlike the NHANES women, the pregnant women in MoBa and Generation R were not selected to represent the whole study population nor all pregnant women in the two countries. Thus, the data presented in their paper do not necessarily reflect the national exposure levels in Norway or the Netherlands. |

*Table 2: Published papers that utilise NHANES data and refer to endocrine disrupting substances investigated as part of the survey and health assessment of the exposure of 2 year-olds to chemical substances in consumer products undertaken by the Danish EPA*

18. In addition to the papers published in Table 2, the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics have recently published The Fourth National Report on Human Exposure to Environmental Chemicals (based on data taken from the NHANES) which provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals (including those substance identified as endocrine disrupters by the Danish EPA). A copy of the executive summary is attached in Annex E. The full report is available at http://www.cdc.gov/exposurereport/

## Questions on which the views of the Committee are sought

19. Members are invited to comment on the information provided and consider the following questions:

i. Do Members have any comments on the published use of NHANES data and health assessment of endocrine disrupting chemicals?

ii. Do Members consider the papers described suggest major concerns regarding the potential health impact of any of the chemical substances, such as would require a full COT evaluation?

**Secretariat**
**September 2010**

**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

# NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) – FURTHER INFORMATION

## *Genetic Data Literature Search Strategy*

This Annex presents the search strategy undertaken to identify papers that have used genetic data from NHANES.

**Secretariat**
**September 2010**

**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

# NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) – FURTHER INFORMATION

## *Published Papers that Utilised Genetic Data from NHANES*

This Annex provides copies of the Nine (9) relevant papers identified from the NHANES genetic data search as detailed below:


- Chang *et al*, (2008) *Prevalence in the United States of selected candidate gene variants: Third National Health and Nutrition Examination Survey, 1991-1994.* Am J Epidemiol. 2009 Jan 1;169(1):54-66. Epub 2008 Oct 20.
- Chang *et al*, (2010) *Genetic variants associated with fasting blood lipids in the U.S. population: Third National Health and Nutrition Examination Survey.* BMC Med Genet. 2010 Apr 20;11:62.
- Chu *et al*, (2009) *Association of APOE polymorphism with chronic kidney disease in a nationally representative sample: a Third National Health and Nutrition Examination Survey (NHANES III) Genetic Study.* BMC Med Genet. 2009 Oct 23;10:108Katki *et al*, (2010) *Using DNA fingerprints to infer familial relationships within NHANES III households.* J Am Stat Assoc. 2010 Jun 1;105(490):552-563.
- Crawford *et al*, (2006) *Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey.* Circulation. 2006 Dec 5;114(23):2458-65. Epub 2006 Nov 13.
- Fan *et al*, (2010) *Gene polymorphisms in association with emerging cardiovascular risk markers in adult women.* BMC Med Genet. 2010 Jan 15;11:6.
- Hung *et al*, (2009) *CRP polymorphisms and progression of chronic kidney disease in African Americans.* Clin J Am Soc Nephrol. 2010 Jan;5(1):24-33. Epub 2009 Dec 3.
- Katki *et al,* (2010) *Using DNA fingerprints to infer familial relationships within NHANES III households*. J Am Stat Assoc. 2010 Jun 1;105(490):552-563.
- Krieg *et al*, (2010) *Lead and cognitive function in VDR genotypes in the third National Health and Nutrition Examination Survey.* Neurotoxicol Teratol. 2010 Mar – Apr; 32(2):262-72. Epub 2009 Dec 18.
- Yang *et al*, (2008) *Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank.* Am J Clin Nutr. 2008 Jul;88(1):232-46.


**Note:** For copyright reasons the papers in the Annexes are not included in the published version on the COT website. The bibliographic details of the annexed material are listed above. The documents are all in the public domain and individuals can obtain them by application to appropriate sources.

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**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

# NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) – FURTHER INFORMATION

## *Literature search strategy for papers relating to* cumulative exposure assessment using data from the NHANES

This Annex presents details of the literature search strategy to identify papers that undertook a cumulative exposure assessment using data obtained from NHANES. It also includes a copy of the paper by Jensen *et al* as listed below:

- Jensen *et al,* (2003) *Cumulative risk assessment of the intake of organophosphorus and carbamate pesticides in the Danish diet.* Food Addit Contam. 2003 Aug;20(8):776-85.

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**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

# NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) – FURTHER INFORMATION

## *Literature search strategy for papers relating to the health assessment of endocrine disrupting chemicals and NHANES data*

This Annex presents details of the literature search strategy to identify papers that utilised relevant data from NHANES and referred to the endocrine disrupting substances examined as part of the survey and health assessment of the exposure of 2 year-olds to chemical substances in consumer products undertaken by the Danish EPA. It also includes a copy of the paper by Wittassek *et.al* as listed below:

- Wittassek *et.al* (2007) *Internal phthalate exposure over the last two decades: a retrospective human biomonitoring study".* Int J Hyg Environ Health. 2007 May;210(3-4):319-33. Epub **2007** Mar 30.

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**September 2010**

**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

# NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) – FURTHER INFORMATION

***The Fourth National Report on Human Exposure to Environmental Chemicals – Executive Summary***

This Annex provides a copy of the executive summary of The Fourth National Report on Human Exposure to Environmental Chemicals.

This document is available from:

http://www.cdc.gov/ExposureReport/pdf/FourthReport_ExecutiveSummary.pdf

**Note:** For copyright reasons the papers in the Annexes are not included in the published version on the COT website. The bibliographic details of the annexed material are listed above. The documents are all in the public domain and individuals can obtain them by application to appropriate sources.

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**September 2010**