The CDC Fourth National Report on Human Exposure to Environmental Chemicals: What it Tells Us About our Toxic Burden and How it Assists Environmental Medicine Physicians

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Abstract
The Centers for Disease Control (CDC) conducts ongoing assessments of the levels of environmental chemicals in the U.S. population. This ongoing study utilizes lab samples from the individuals who are part of the National Health and Nutrition Examination Survey (NHANES). The NHANES samples from the years 1999-2000, 2001-2002, and 2003-2004 (each representing about 2,400 individuals) were used for the CDC's national reports. In the CDC Fourth National Report on Human Exposure to Environmental Chemicals (“the fourth report”) complete data from the above sample years were included. Each year additional chemicals are measured; the fourth report contains information on 75 previously untested compounds, for a total of 212 compounds measured. In the fourth report, blood and urinary levels of eight different forms of arsenic are reported. The fourth report, for the first time, also includes levels of solvents (30 different compounds) and provides adult rather than juvenile values for mercury. In the majority of individuals tested, acrylamides, cotinine, trihalomethanes, bisphenol A, phthalates, chlorinated pesticides, triclosan, organophosphate pesticides, pyrethroids, heavy metals, aromatic hydrocarbons, polybrominated diphenyl ethers, benzophenone from sunblock, perfluorocarbons from non-stick coatings, and a host of polychlorinated biphenyls and solvents were found. This review provides many of the ranges for xenobiotic toxins so a clinician can identify a patient’s current exposure and toxic load compared to the national averages and monitor the effectiveness of prescribed treatments.


Background
The Centers for Disease Control (CDC) has been conducting ongoing laboratory assessment of human samples from the National Health and Nutrition Examination Survey (NHANES) in order to quantify the level of xenobiotic compounds present in the average U.S. resident. NHANES is designed to collect data on the health and nutritional status of the U.S. population and in 1999 became a continuous survey with data released in two-year cycles.

As stated in the CDC Fourth National Report on Human Exposure to Environmental Chemicals (herein referred to as "the fourth report"), the overall purpose of this work is to "provide unique exposure information to scientists, physicians, and health officials to help prevent exposure to some environmental chemicals."1

The goals of the CDC’s assessment include:

❖ Determination of chemicals found in the U.S. population and at what concentrations.
❖ For chemicals with known toxicity levels, to determine the prevalence of individuals with levels exceeding the safe limit (e.g., a blood level ≥10 mcg/dL).
❖ To establish reference values that can be used by physicians and scientists to determine whether a person or group has an unusually high exposure. This information is especially helpful to identify population groups that merit further assessment of exposure sources or health effects.

Additional Chemicals Tested for in the Fourth Report
Using mass spectroscopy, samples of urine, blood, and serum collected from NHANES participants were tested for the presence of 212 environmental chemicals or their metabolites. Of these 212 compounds, 75 were new additions to the fourth report. All compounds found indicate exposure only and are not provided as markers for disease states. The 75 additional compounds in the fourth report include:
two acrylamide adducts

⇒ total arsenic and levels of seven different arsenic species
⇒ four trihalomethanes (from chlorinated water)
⇒ four phenols (including triclosan)
⇒ three additional non-dioxin-like polychlorinated biphenyls (PCBs)
⇒ perchlorate
⇒ 12 perfluorinated compounds
⇒ one additional phthalate metabolite (MECPP)
⇒ 11 polybrominated diphenyl ethers (PDBE) and polybrominated biphenyls (all flame retardants)
⇒ 31 different volatile organic compounds (VOCs)

Data Reporting

Values are reported with geometric means and percentiles (50th, 75th, 90th, and 95th) by age group, gender, and race or ethnicity. The fourth report does not provide information on the percentage of participants who demonstrated exposure to the various compounds; hence, it cannot be unequivocally stated that compound X was found in 98 percent of the individuals tested. However, the appearance of a compound in all of the percentile groups does suggest it is detectable in the majority of study samples; i.e., found ubiquitously.

Compounds measured in the urine are reported in levels per total urine volume as well as per gram of creatinine. The latter allows more accurate monitoring of toxin levels for individuals with either very dilute or concentrated urine. For dioxins, furans, PCBs, and chlorinated pesticides, levels are reported both per whole weight of serum and per gram of total blood lipids. Because these compounds are lipophilic they are typically only present with lipids in the serum. When levels are reported per total blood lipids they become reflective of the total amount of the compound stored in body fat. Since many published studies report the levels of these same compounds on a per-lipid-weight basis, comparison with levels that may have health implications becomes easier. In addition, some laboratories now offer this method of measurement, allowing easy reference points for clinicians to determine where a patient falls on an average national scale for each compound.

Some Ubiquitous Xenobiotics

Acrylamides

Acrylamides, used to make polymers, are found in foods, cosmetics, and cigarette smoke. Most U.S. exposure comes from French fries, potato chips, and cosmetics. Acrylamides are measured in the fourth report as hemoglobin adducts, rather than individual compounds, because they rapidly bind covalently with hemoglobin. These compounds were found in the majority of samples, with the highest average level found in 20- to 59-year-olds (62.5 pmol/g hemoglobin). These compounds are toxic to mitochondria, a likely neurotoxic mechanism.

Cotinine

Although cotinine remains a ubiquitous xenobiotic, levels have dropped approximately 70 percent in the last decade of NHANES. Since NHANES only measures cotinine levels in non-smokers, the reported levels are reflective of secondhand smoke exposure. With a plasma half-life of 16 hours, this means the majority of individuals are still exposed to environmental tobacco smoke, albeit a lower burden.

Trihalomethanes (THMs)

THMs are produced when the water disinfectants chlorine and bromine bind with other organic materials in the water. Exposure to these disinfectant by-products comes from showering, washing dishes or clothes, or swimming in chlorinated pools. The four most common THMs are bromodichloromethane, dibromochloromethane, tribromomethane, and trichloromethane (also known as chloroform). Of the four, bromodichloromethane and chloroform are ubiquitous, with chloroform demonstrating the highest average levels – 10.2 pg/mL for adults in the 2003-2004 survey. Chloroform is an effective anesthetic and can also cause mitochondrial dysfunction and hepatotoxicity.

Bisphenol A (BPA)

BPA is a plasticizer used to make polycarbonate bottles (recycle #7), as an epoxy resin (inside food cans), in thermal paper (no-carbon required receipts), and in other products. It has been associated with the development of breast tumors in animals, as well as protecting the tumors from the effects of chemotherapy. In utero exposure to BPA may lead to obesity and behavior issues in offspring.

Bisphenol A is metabolized through glucuronidation and is mostly excreted within 24 hours of exposure. Its consistent finding in NHANES indicates ongoing routine exposure. The creatinine adjusted average for adults was reported as 2.39 mcg/g creatinine, but the highest mean value (4.32 mcg/g creatinine) was found in children ages 6-11 years. BPA is also a potent mitochondrial toxin.
Environmental Medicine

Triclosan
Triclosan is an antimicrobial agent used in personal care products (soaps, toothpastes, shampoos, etc.) and is impregnated into some kitchen utensils, toys, and medical devices. It also appears to be one of the two primary antimicrobial components in grapefruit seed extracts. It has been reported to be present in over half of U.S. streams, another sign of its widespread use. Triclosan is a mitochondrial toxin. Urinary triclosan was highest in persons over age 20, with a mean level of 13.4 mcg/g creatinine.

Chlorinated Pesticides
The chlorinated pesticide levels in the fourth report are similar to levels previously reported in this journal, with a few exceptions. For the first time, hexachlorobenzene was commonly found. The fourth report suggests this finding is due either to “improvements in analytical measurement or recognition of an analytical issue (e.g., the presence of an interference).” New ranges for the total levels of individual chlorinated pesticides based on the NHANES 2003-2004 survey are reported in Table 1. For a full listing of the differences among age groups, genders, and ethnic groups consult the fourth report (www.cdc.gov/exposurereport/).

As can be observed in Table 1, four organochlorine pesticides are found in the majority of the population: oxychlordane, trans-nonachlor, dichlorodiphenyldichloroethylene (DDE), and hexachlorobenzene. For a more complete discussion of the adverse health effects of these compounds, refer to an earlier review in this journal.

Organophosphate Pesticides
Organophosphate pesticides are water soluble and fairly rapidly cleared through the urine. Their presence in urine typically indicates recent exposure (within the previous few days). They are not biologically persistent, but are one of the major classes of pesticides in current use today. Organophosphate pesticides show up with some regularity in the fourth report because the greatest source is non-organic versions of the “dirty dozen” most toxic foods and vegetables (the list can be found at www.foodnews.org).

Pyrethroid Pesticides
Pyrethroid pesticide residues were found with some regularity. Exposure is typically airborne from dust contaminated with these pesticides from home or outdoor use. The metabolite most commonly found is 3-phenoxy-benzoic acid, a metabolite of cypermethrin, deltamethrin, and permethrin. The mean value (mcg/g creatinine) was 0.316, with a 75th percentile reading of 0.580 and a 95th percentile of 3.10.

Carbamate pesticides and the herbicides tested for were only rarely found in the NHANES population. Thus, it appears that exposure of U.S. residents to these toxicants is rare.

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Table 1. Chlorinated Pesticides from NHANES 2003-2004

<table>
<thead>
<tr>
<th>Compound</th>
<th>Geometric mean</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dieldrin (ng/g lipid)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>9.00</td>
<td>14.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Dieldrin (ppb)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>0.059</td>
<td>0.098</td>
<td>0.138</td>
</tr>
<tr>
<td>Oxychlordane (ng/g lipid)</td>
<td>9.37</td>
<td>10.3</td>
<td>18.0</td>
<td>29.0</td>
<td>37.7</td>
</tr>
<tr>
<td>Oxychlordane (ppb)</td>
<td>0.057</td>
<td>0.063</td>
<td>0.119</td>
<td>0.204</td>
<td>0.269</td>
</tr>
<tr>
<td>Heptachlor epoxide (ng/g lipid)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>13.4</td>
<td>18.9</td>
</tr>
<tr>
<td>Heptachlor epoxide (ppb)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>0.094</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>Trans-nonachlor (ng/g lipid)</td>
<td>14.7</td>
<td>14.8</td>
<td>30.2</td>
<td>49.0</td>
<td>68.3</td>
</tr>
<tr>
<td>Trans-nonachlor (ppb)</td>
<td>0.089</td>
<td>0.094</td>
<td>0.191</td>
<td>0.324</td>
<td>0.470</td>
</tr>
<tr>
<td>p,p-DDT (ng/g lipid)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>11.9</td>
<td>19.5</td>
</tr>
<tr>
<td>p,p-DDT (ppb)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>0.078</td>
<td>0.128</td>
</tr>
<tr>
<td>p,p-DDE (ng/g lipid)</td>
<td>238</td>
<td>203</td>
<td>509</td>
<td>1170</td>
<td>1860</td>
</tr>
<tr>
<td>p,p-DDE (ppb)</td>
<td>1.45</td>
<td>1.26</td>
<td>3.16</td>
<td>7.07</td>
<td>12.1</td>
</tr>
<tr>
<td>Hexachlorobenzene (ng/g lipid)</td>
<td>15.2</td>
<td>14.9</td>
<td>19.0</td>
<td>24.4</td>
<td>28.9</td>
</tr>
<tr>
<td>Hexachlorobenzene (ppb)</td>
<td>0.092</td>
<td>0.090</td>
<td>0.120</td>
<td>0.157</td>
<td>0.186</td>
</tr>
<tr>
<td>Beta-HCH (ng/g lipid)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>14.1</td>
<td>32.1</td>
<td>56.5</td>
</tr>
<tr>
<td>Beta-HCH (ppb)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>0.092</td>
<td>0.216</td>
<td>0.372</td>
</tr>
<tr>
<td>Mirex (ng/g lipid)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>8.40</td>
<td>13.2</td>
</tr>
<tr>
<td>Mirex (ppb)</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>0.054</td>
<td>0.093</td>
</tr>
</tbody>
</table>

NA=not applicable; LOD=level of detection
Heavy Metals

Heavy metals are well represented in the fourth report, including arsenic, which was glaringly absent from the first three national reports, partly because arsenic is found in over 200 different forms. The fourth report provides levels of seven different arsenic species along with totals for all of them. The fourth report includes levels of the organic arsenic compounds arsenobetaine, arsinecholine, and trimethylarsine oxide, the inorganic arsenic compound arsenous III acid, and the metabolites monomethylarsonic and dimethylarsinic acids.1

The inorganic arsenic species of arsenous and arsenic acids occur naturally in groundwater sources and are considered carcinogenic.18 The highest natural levels of these arsenics in groundwater occur in the West, Midwest, and Northeast regions of the United States.19 Inorganic arsenics are also found in flour and rice – higher in rice that has been cooked in high-arsenic water.20 Poultry and seafood are the primary sources of organic arsenics, which are considered to have very low toxicity.21 Inorganic arsenics are metabolized in the body and excreted as either monomethylarsonate (MMA) or dimethylarsinate (DMA).22 The body’s ability to metabolize inorganic arsenics to either MMA or DMA can have a profound effect on health, as MMA is associated with cancers and cardiovascular problems.23,24 Table 3 shows the total amounts of the various arsenic species in the fourth report.1 Note that most inorganic arsenic is metabolized into DMA rather than MMA, which is a positive finding. For individuals with elevated total urinary arsenic, the greatest source is arsenobetaine, most likely from seafood sources.

For the first time, adult levels of mercury (both blood and urine) are reported; both blood levels of total and inorganic mercury are provided.1 The vast majority of blood mercury is from organic sources (typically seafood), as shown in Table 4. The figures in Table 4 reflect the data from the 2003-2004 NHANES and are given in mcg/L.

Table 5 is an update on the total averages for heavy metals currently measured by those laboratories that test for urinary heavy metals. These levels from the fourth report provide clinicians who utilize such tests a national scale against which they can compare non-flushed (baseline) urine tests. Since the urinary levels of these metals are mostly reflective of current exposure, the clinician can easily spot a patient with likely current exposure. For more details on pre- and post-challenge urine heavy metal testing, see articles in previous volumes of this journal.25,26

Table 2. Organophosphate Pesticides in NHANES (mcg/g urinary creatinine)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Geometric mean</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylphosphate</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>4.42</td>
<td>9.02</td>
<td>13.2</td>
</tr>
<tr>
<td>Dimethylphosphate</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>3.86</td>
<td>9.54</td>
<td>14.6</td>
</tr>
<tr>
<td>Diethylthiophosphate</td>
<td>1.97</td>
<td>&lt;LOD</td>
<td>0.700</td>
<td>1.47</td>
<td>2.63</td>
</tr>
<tr>
<td>Dimethylthiophosphate</td>
<td>1.75</td>
<td>5.21</td>
<td>15.7</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td>Dimethyldithiophosphate</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>0.500</td>
<td>2.14</td>
<td>5.27</td>
</tr>
</tbody>
</table>

NA=not applicable; LOD=level of detection

Table 3. Arsenic Species Reported in NHANES (mcg/g creatinine)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Geometric mean</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenous (III) acid</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>Arsenic (V) acid</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>MMA</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>1.33</td>
<td>2.22</td>
<td>2.86</td>
</tr>
<tr>
<td>DMA</td>
<td>3.69</td>
<td>3.37</td>
<td>5.71</td>
<td>9.09</td>
<td>13.0</td>
</tr>
<tr>
<td>Arsenobetaine</td>
<td>1.55</td>
<td>1.00</td>
<td>5.20</td>
<td>16.8</td>
<td>35.0</td>
</tr>
<tr>
<td>Arsenocholine</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>Trimethylarsine oxide</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>Total arsenic</td>
<td>8.24</td>
<td>7.04</td>
<td>14.1</td>
<td>30.4</td>
<td>50.4</td>
</tr>
</tbody>
</table>

NA=not applicable; LOD=level of detection

Table 4. Mercury Levels from 2003-2004 NHANES (mcg/L)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Geometric mean</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Blood Hg</td>
<td>0.797</td>
<td>0.800</td>
<td>1.70</td>
<td>3.30</td>
<td>4.90</td>
</tr>
<tr>
<td>Inorganic Blood Hg</td>
<td>NA</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>0.600</td>
<td>0.700</td>
</tr>
</tbody>
</table>

NA=not applicable; LOD=level of detection
Environmental Medicine

Table 6 provides blood levels of mercury, lead, and cadmium for clinicians utilizing blood testing. These levels are much lower than established lab reference ranges for these three heavy metals, as the reference ranges are based on acute toxicity data (and are typically derived from industrial exposure data).

**Phthalates**

Phthalates provide flexibility and resilience in numerous plastic products. They are also found in adhesives, automotive plastics, detergents, flooring, raincoats, personal care products (cosmetics, shampoos, fragrances, etc.), plastic bags, and garden hoses. Typically, the more flexible the plastic, the higher the amount of phthalates. Because phthalates are not chemically bound to the plastics they are added to they are easily released into the environment. Since they are rapidly excreted from the body their presence in urine indicates current exposure. Table 7 lists the commonly found phthalates.

**Polybrominated Diphenyl Ethers**

Polybrominated diphenyl ethers (PBDEs), flame retardants impregnated into many household materials, total approximately 25 percent of all flame retardants. They are highly persistent, meaning they resist being broken down in the environment and mammals, and are found in mother’s milk and farmed salmon and other fish. Several PBDEs were measured in the fourth report and reported as lipid adjusted values (ng/g lipid). Table 8 lists only those found ubiquitously.

**Benzophenone-3**

Benzophenone-3 is a common compound found in sun-blocking formulas. The fourth report indicates it is found ubiquitously. In Table 9, note the large difference between the mean levels and the upper percentiles.
Perfluorochemicals
Perfluorochemicals are used for waterproofing, flameproofing, and other protective coatings on a variety of clothes, furniture, and household items. One compound, polytetrafluoroethylene, is the primary component of non-stick coatings on cookware, but was not among the compounds measured in the fourth report. Of 12 perfluorochemicals tested in NHANES, only four were found ubiquitously: perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), and perfluorooctane sulfonic acid (PFOS) (Table 10).1

Polychlorinated Biphenyls
PCBs comprise a large family of industrial chemicals now found throughout the entire world. They were used extensively a generation ago as coolants and lubricants for electrical transformers and many other industrial uses. In the United States, production of PCBs ceased in 1977 because it was found these compounds accumulated in the environment and were associated with severe health problems. Over 200 different PCBs were made, and some consumer products manufactured before 1977 may yet contain PCBs, including fluorescent lighting fixtures, electrical devices or appliances containing PCB capacitors, microscope oil, and hydraulic fluids.

In the Environmental Working Group (EWG) study, 48 different PCBs were tested for in the blood of the nine volunteers who submitted for blood testing by the EWG.27 PCBs have contaminated the food chain and, because of their lipophilic nature, are especially high in many fish and in fat-containing foods such as butter.28-30 The CDC is also measuring PCB levels in NHANES, and the fourth report has expanded to measure 38 of these compounds. With the CDC’s updated analytical ability, 34 of the 38 PCBs were found in virtually all persons tested.1 Of the 38 PCBs, the six with known published health effects are represented in Table 11, which is far from a complete list of the average U.S. resident’s total PCB load.

Polycyclic Aromatic Hydrocarbons
Polycyclic aromatic hydrocarbons are products of combustion, and individuals living in urban areas are heavily exposed to these compounds. In the fourth report, four of these compounds and their urinary metabolites are reported.1 Not surprisingly, they are also found ubiquitously. The levels of these compounds are not provided here because no laboratory tests are available to the clinician to help them utilize these statistics. The interested reader is referred to the fourth report for specifics.1

Volatile Organic Compounds
Volatile organic compounds or solvents are also represented for the first time in the fourth report.1 Of the 29 solvents measured in NHANES, only nine were regularly found in persons tested (Table 12). Of these nine, ethylbenzene, methyl tert-butyl ether, toluene, and xylene were ubiquitous. Since these are rapidly cleared from the blood (the half-life of most is counted in hours), their presence would indicate current airborne exposure.

Summary
The ongoing NHANES provides a continuing database for the CDC to gather information about...
the toxic load in the average U.S. resident. This research is published periodically in a series of national reports, and with each successive report the CDC measures participants’ blood and urine for (and is finding) a greater number of xenobiotics, most of which are considered toxic. In this fourth report, acrylamides, cotinine, trihalomethanes, bisphenol A, phthalates, chlorinated pesticides, triclosan, organophosphate pesticides, pyrethroids, heavy metals, aromatic hydrocarbons, polybrominated diphenyl ethers, benzophenone from sunblock, perfluorocarbons from non-stick coatings, and a host of polychlorinated biphenyls and solvents were found commonly in the NHANES population (the average U.S. resident).

For the first time, the fourth report provides comprehensive information about arsenic presence. The report differentiates between organic and elemental (inorganic) forms of arsenic and reports arsenic metabolites. It also provides information about the level of organic and total mercury in the blood.

Many of the ranges for these xenobiotic toxicants are provided so the clinician can compare a patient’s readings against national percentiles. This data will help the clinician identify current exposures and monitor the effectiveness of prescribed treatments.

**References**


