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Commentary on CDC National Center for Environmental Health's "Third National Report on Human Exposure to Environmental Chemicals"

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Introduction

The *Third National Report on Human Exposure to Environmental Chemicals*, released in July 2005, represents the ongoing efforts of the Centers for Disease Control and Prevention to study the exposure of the US population to a number of environmental chemicals. Using state-of-the-art analytical techniques, the Environmental Health Laboratory uses biomonitoring to assess environmental chemical exposure. Biomonitoring is a method of measuring human exposures to natural and synthetic chemicals that is based on sampling and analysis of an individual's tissues and fluids. As a result of these efforts, information on an increasing number of chemicals is available to scientists, policymakers, and the public.

This commentary provides an introduction to the information contained in the *Third Report* and highlights key concepts that may be useful when attempting to interpret the information contained therein. More specifically, it focuses on the utility and limitations of the data contained within the *Report* and how these considerations affect the interpretation of this data.

Appendices A-C focus on three environmental chemicals included in the *Third Report* (lead, mercury, phthalates) that illustrate how the information in the report can be used. Appendix A considers the public health success represented by the continued decline in population blood lead measurements and raises questions about current research concerning low-intensity lead exposure effects. Appendix B focuses on population measurements of blood mercury. The discussion on environmental mercury exposure conveys the importance of considering dose in the context of human exposures and the challenges of communicating risk accurately to the public. Appendix C presents the developing story on phthalates. This compound is an example of the role of biomonitoring in providing some perspective to an environmental exposure experienced by the majority of the U.S. population.

Overview

The Third Report

The National Center for Environmental Health (NCEH) of the US Centers for Disease Control and Prevention (CDC) provides very accurate and technically reproducible laboratory analyses through the Division of Laboratory Sciences. The NCEH has served as our nation's standard setting laboratory for years in the measurement of blood lead, newborn screening, cholesterol and lipid measurements, and other laboratory tests; and is a global leader in pioneering analytical methodologies.

Beginning in 1999, the NCEH has undertaken the task of measuring and reporting the concentrations of an increasing variety of environmental chemicals in the blood and urine of a sample of the American population. The *Third National Report on Human Exposure to Environmental Chemicals*, released in July 2005, further expands these efforts (<http://www.cdc.gov/exposurereport/>). This report provides the average blood and/or urine concentration (geometric mean) of 148 environmental chemicals for the civilian, non-institutionalized U.S. population. The *Third Report* includes data from samples obtained during 2001-2002 and reflects an expanded survey from the 116 chemicals evaluated in the *Second Report*. As with the previous two reports, the *Third Report* provides results in tabular format. The overall average concentration is listed along with results sorted according to age, gender, and race/ethnicity. Selected percentiles, sample size, and results from the *Second Report* (when available) are also displayed. A brief narrative summary is provided for each chemical or family of chemicals. Each summary contains an overview of the chemical(s), physical characteristics, routes of exposure, and known or potential adverse health effects associated with exposure. Chemicals chosen for inclusion were identified according to a number of criteria, including relevance of the chemical exposure to the U.S. population, availability of adequate analytical methodology, and the cost of performing the analyses. The chemicals to be included in future *Reports* as well as a list of all “nominated substances” are available on the CDC website at: http://www.cdc.gov/exposurereport/chemical_nominations.htm.

Utility

How can the information in the *Third Report* be used?

The biomonitoring information contained in these reports serves several important purposes:

- 1) Identifying actual exposures of the U.S. population to various substances, rather than relying on exposure models and assumptions;
- 2) Tracking exposure trends over time, particularly as they relate to changes in the generation, use, disposal, and regulation of specific substances;
- 3) Providing benchmark biomonitoring data, both for population estimates and laboratory reproducibility;
- 4) Identifying substances or populations for further study.

Limitations

What are some limitations of the *Third Report*?

While the *Third Report* represents an extensive and powerful data set, it is important to understand its limitations so that the results can be interpreted appropriately. As the CDC states in the document, and has repeatedly stated in other forums, “the measurement of an environmental chemical in a person’s blood or urine does not by itself mean that the chemical causes disease.” “Advances in analytical methods allow us to measure lower

and lower levels of environmental chemicals in people, but separate studies of varying exposure levels and health effects are needed to determine which blood or urine levels result in disease.” Consequently, the *Report* itself does not provide any conclusion regarding possible health effects from current chemical exposures.

There are several reasons for this limitation regarding conclusions on health effects:

- 1) Although these samples were collected as part of the larger National Health and Nutrition Examination Survey (NHANES), which includes a health questionnaire and physical exam, the study is not designed and does not attempt to draw conclusions about specific compounds and health effects;
- 2) The concentrations of various chemicals for most of the population is well below that associated with any clinical health effects;
- 3) Although the population sample is weighted so that certain minorities and at-risk groups (African Americans, Mexican Americans, adolescents, elderly, and recently, low-income whites) are adequately represented, targeted analysis of known high risk groups for any particular compound or any particular health outcome was not done;
- 4) Samples were taken at a single point in time so they represent a snapshot of exposure and cannot be used to determine exposure over a longer time period. This may be especially important for substances that are rapidly metabolized and excreted, such as phthalate esters (discussed in more detail below), where blood levels are known to decrease rapidly following termination of exposure.

Interpretation

Interpreting the data in the *Third Report*

As mentioned above, individual substances and chemical classes are chosen for analysis based on multiple criteria. It is reasonable to consider the following questions when evaluating results for a particular chemical or chemical class:

- 1) *What are the analytical limitations to testing a given chemical of interest?*

While this question is purely a practical one, it is not trivial. The NCEH continues to expand its laboratory capacity while maintaining scrupulous attention to quality control. This is evident in the rigor applied to their test procedures and reporting, as well as by the continued improvement in their limits of detection, now routinely at the parts per billion and often parts per trillion range (http://www.cdc.gov/exposurereport/3rd/pdf/appendix_a.pdf). These test procedures fully take into account the principles of sound laboratory practice, including adequate sample volume, specimen integrity, and testing of sample blanks and sampling equipment to identify background levels of contamination. These procedures are all very important steps in assuring the validity of the results; the methodology used by the NCEH serves as a benchmark for other laboratories attempting to provide biomonitoring test services.

- 2) *Is the substance known to cause adverse human health effects, and at what dose(s) does it cause those effects?*
 - a) *How do these dose levels relate to the concentration of the substance in blood or urine measured in the Report?*
 - b) *Has a health criterion or safe level of exposure been set for the substance?*

The results of the *Third Report* provide reason for optimism when one considers some substances in the environment that are known to cause adverse human health effects. The measured concentrations of many such substances continue to decline. Examples include lead (see [Appendix A](#)), certain dioxins, and cotinine (a metabolite of nicotine).

Mercury is a biopersistent chemical that is of concern because in sufficient doses it is a potent neurotoxin, particularly to the fetus and neonate. Several large-scale public health disasters have provided information on what doses of methylmercury cause adverse health effects in humans. This information can be used to compare these high-level exposures to current population estimates and guide rational policy development (see [Appendix B](#)).

The information in the *Reports* also allows comparisons with other parts of the world where significant exposures occur routinely. Biomonitoring of arsenic provides one comparison. Groundwater from deep wells naturally high in arsenic content in India and Bangladesh can contain >500 µg/L arsenic, compared with U.S. drinking water concentrations that rarely approach 50 µg/L. Overt arsenic-related health effects are prominent in Southeast Asia, but not in the U.S. (Rahman, 2005)

An analytical challenge for NCEH is the development of robust biomarkers for other problematic environmental issues such as diesel exhaust. Although measurements of polycyclic aromatic hydrocarbons, such as 1-hydroxypyrene, have been used as surrogates for measurement of diesel exhaust, further refinements to adjust for confounders or development of alternative markers are needed.

- 3) *Has the substance been demonstrated to cause adverse health effects in an animal model?*
 - a) *If so, how does that model relate to human health?*
 - b) *What is the margin of exposure (“distance”) between the lowest adverse effect level in the animal model and the levels of human exposure provided in the Report?*

Although the *Report* does not address possible differences in response to chemicals between animal models and humans, it does provide ranges of exposure that can be used to compare with those utilized in experimental studies. As noted below in the discussion of phthalates ([Appendix C](#)), these dose comparisons are important but sometimes difficult to interpret.

- 4) *Is the substance suspected or known to be biopersistent, bioaccumulated, bioconcentrated, or biomagnified? What trends over time are evident for these substances?*

Measurements of substances that are of environmental health concern because of their biopersistence, such as the organochlorine insecticide DDT and the polychlorinated dibenzo-*p*-dioxins and dibenzofurans, continue to show declines in the U.S. population. DDT was used widely until it was banned in this country more than 30 years ago. Trace amounts of this compound are detected in <5% of the U.S. population at a limit of detection in blood of <20ng/g lipid (parts per billion). A longer-lived metabolite of DDT, DDE is detected in the majority of the population at concentrations 10-15% higher in 2001-2002 than in 1999-2000. Significant differences between ethnic groups continue to be noted, with Mexican-Americans having more than twice the concentration of this metabolite than non-Hispanic blacks and whites. This raises questions regarding subgroups of the population with differing intake or metabolism of environmental chemicals, and suggests the need for further study.

The dioxins represent a large group of chemical compounds formed as industrial byproducts or released in fires. An increasing number of these and other polychlorinated cyclic compounds are being analyzed by the NCEH. Comparisons regarding health effects are difficult as there is a large variation (more than 10,000 fold) in the likely toxicity between these compounds. However, the most potent compound is considered to be 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD). The *Third Report* notes that blood concentrations of this dioxin have decreased more than 80% in the last 30 years. Currently, even with improved detection limits in blood (lower than 10 pg/g lipid = parts per trillion), most of the population has no detectable TCDD. This should be reassuring when considering possible carcinogenic and reproductive/developmental effects that have noted in animal studies or suggested in humans at much higher levels of exposure.

- 5) *Is there a high exposure prevalence in the population sampled? If so, is the substance prevalent in the environment naturally or as a result of human activity?*

Other compounds are receiving increased attention in environmental research because of advances in analytical techniques which permit scientists to measure smaller and smaller quantities of an expanding number of substances. These advances have led to the recognition of the widespread presence of manmade substances at low levels in the environment and their subsequent uptake by humans; biomonitoring for these substances is the focus of increasing analytical and interpretive work, including better understanding of routes of exposure and any potential health effects.

One category of substances receiving increased attention includes compounds suspected of causing modification of endocrine (primarily sex steroid) response. Included in this group are a variety of industrial and naturally occurring compounds,

such as phthalates (discussed in more depth in [Appendix C](#)) and some of the isoflavones, respectively. It should be standard for published research regarding potential clinical effects of these and other classes of chemicals identified as having endocrine effects in animal models to include reference to population estimates of current human exposure such as is provided in the *Reports*. This comparison would allow proper interpretation and application of results from large dose animal or human catastrophic exposure studies to background exposure or potential high-risk groups. A more informed discussion regarding risk and benefit can then ensue. One would hope that such efforts as these would allow a more informed discussion on allocation of resources – mitigating environmental release of those industrial chemicals that actually pose a risk of environmental or human health adverse effects, while avoiding fear and expensive sophistry about inconsequential substances or exposures.

Conclusions

The data in the *Third Report* documents low and decreasing exposures to a variety of environmental chemicals in a sample of the U.S. population. The number and variety of compounds analyzed will increase in future *Reports*. As research continues into a wide array of environmental chemical compounds, appropriate use of the benchmark data contained in the *Reports* will allow us to better interpret and apply new findings as they become available. The information contained in the *Third Report* provides a solid foundation to identify future trends in human exposure to environmental chemicals. As such, this information should prove useful to a broad cross-section of stakeholders: industry groups, environmental advocacy groups, research scientists and physicians, and public health agencies charged with policy development. The data in the *Report* also provide a framework to compare the exposures commonly seen in the U.S. population with those of particular high-risk groups within the U.S., and to contrast these results with exposures associated with real threats to health in other areas of the world. While the U.S. public should be reassured regarding our populations' exposure to a variety of environmental chemicals, we should not ignore the impact that these same chemicals may have on those with greater exposures and fewer resources with which to respond.

Additional References:

Agency for Toxic Substances and Disease Registry

<http://www.atsdr.cdc.gov/toxpro2.html>

Access point for ATSDR Toxicological Profiles-containing detailed information on more than 250 chemical substances including very useful graphical summaries of animal and human health studies by dose, route, and duration of exposure.

Rahman MM, Sengupta MK, Ahamed S, et al: Arsenic contamination of groundwater and its health impact on residents in a village in West Bengal, India. *Bulletin of the World Health Organization*. vol. 83, issue 1, pages 49-57, 2005.

<http://www.scielosp.org/pdf/bwho/v83n1/v83n1a13.pdf>

U.S. Environmental Protection Agency: National Center for Environmental Assessment website.

<http://cfpub.epa.gov/ncea/>

Provides access to EPA Risk Assessments on a variety of environmental chemicals, as well as access to risk tools, such as Benchmark Dose software.

Pengchai P, Nakajima F, Furumai H: Estimation of origins of polycyclic aromatic hydrocarbons in size-fractionated road dust in Tokyo with multivariate analysis. *Water Science Technology*. Vol. 51, pages 169-175, 2005.

Useful Web Resources

Centers for Disease Control

<http://www.cdc.gov/exposurereport/>

Link to the full text version of the "Third National Report on Human Exposure to Environmental Chemicals".

Agency for Toxic Substances and Disease Registry

<http://www.atsdr.cdc.gov/toxpro2.html>

Access point for ATSDR Toxicological Profiles-containing detailed information on more than 250 chemical substances including very useful graphical summaries of animal and human health studies by dose, route, and duration of exposure.

U.S. Environmental Protection Agency: National Center for Environmental Assessment website.

<http://cfpub.epa.gov/ncea/>

Provides access to EPA Risk Assessments on a variety of environmental chemicals, as well as access to risk tools, such as Benchmark Dose software.

National Toxicology Program Center for Evaluation of Reproductive Risks

<http://cerhr.niehs.nih.gov/reports/index.html>

Link to NTP monographs on the reproductive risk of several environmental chemicals.

Appendix A: Lead

General

Lead is a ubiquitous contaminant in the environment, with multiple commercial and industrial uses still prevalent. Examples include lead-acid (e.g. automotive) battery manufacture and recycling, solder in computer parts manufacture, ammunition, as well as many others. Uncommon household sources of exposure include ethnic medicines, lead-glazed cookware or glassware, and leaching into water supplies from lead soldered pipes. Lead was previously used in indoor house paint and as an anti-knock compound in gasoline (tetraethyl lead). This latter product was readily bioavailable by the inhalation route, accounting for the majority of the populations' exposure. Lead was phased out of household paint beginning in the 1970s, with indoor and outdoor house paint now required to contain less than 0.06% lead by weight (compared to 1% in the mid-1950s and as much as 50% earlier than that). Leaded paint may still be used in bridge paint and marine applications. Leaded gasoline was banned in 1996, with reductions beginning in the 1970s. Currently, significant exposure is restricted to certain occupational, avocational, and socioeconomic settings. Whole blood levels have been declining in the U.S. human population since the 1970s. While mean childhood (1-5 year olds) lead concentrations were 15 $\mu\text{g}/\text{dl}$ in 1980, the *Third Report* documents a mean of 2.2 $\mu\text{g}/\text{dl}$ in 1999-2000 and 1.7 $\mu\text{g}/\text{dl}$ in 2001-2002 data collections. These changes are largely attributable to the removal of lead from gasoline.

Toxicity

Lead disrupts numerous cellular enzymes, primarily affecting the bone marrow, central and peripheral nervous systems, and kidneys. In *in vitro* models, enzyme effects can be identified at very low lead exposure concentrations. Research into human health effects of lead has resulted in progressive lowering of the CDC's level of concern from 70 $\mu\text{g}/\text{dl}$ whole blood in 1960's to 10 $\mu\text{g}/\text{dl}$ in 1991. Recent research has suggested that even this body burden of lead in very young children is associated with decrements in intellectual functioning and concern has been raised about "low-level" lead effects on chronic renal function. The *Reports* provide important information with which to evaluate these claims. If the CDC's sampling is an accurate reflection of the population at risk from lead exposure, more than 95% of children today have blood lead concentrations lower than 90% of current middle-aged people when they were children. In the absence of any current renal function or intelligence crisis among the middle-aged, it will be difficult to demonstrate risk from the markedly lower exposures to lead among today's children. It is more likely that what are now considered "relatively high" lead determinations (e.g. 7 $\mu\text{g}/\text{dl}$ range) are confounders for other socioeconomic, dietary or environmental issues; these latter issues should be the focus of public health attention, not the former.

Conclusions

Biomonitoring data in the *Reports* demonstrates that the U.S. population has had a remarkable decline in blood lead concentrations as large scale exposure to environmental lead has been eliminated. Current research findings that suggest significant health effects from very low-intensity exposure or even from more moderate occupational exposure should be interpreted cautiously against these historical trends. The belated success of environmental lead reduction in the U.S. should be recognized and attention turned to other public health issues.

Additional References

Agency for Toxic Substances and Disease Registry Tox FAQs

<http://www.atsdr.cdc.gov/tfacts13.html>

Provides a summary of environmental lead in non-technical language and has link to a Toxicological Profile for lead that provides more detailed information.

Garcon G, Leleu B, Zerimech F, et al: Biologic markers of oxidative stress and nephrotoxicity as studied in biomonitoring of adverse effects of occupational exposure to lead and cadmium. *Journal of Occupational and Environmental Medicine*, vol. 46, issue 11, pages 1180-6, 2004.

Identifies small changes in biomarkers of oxidative stress (few resulting in changes outside reference range) in workers exposed to lead and cadmium, with average whole blood lead measurements of 30 µg/dl.

Lin JL, Lin-Tan DT, Hsu KH, Yu CC: Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. *New England Journal of Medicine*, vol. 348, issue 4, pages 277-86, 2003.

A sample of patients in Taiwan with mean estimated creatinine clearances of 40 ml/min and mean whole blood concentrations of 5.3 µg/dl were followed for 24 months then randomized to chelation with Ca-Na²-EDTA or no chelation, resulting in immediate 20% improvement in estimated creatinine clearance vs. continued decline in renal function.

The results are attributed to effects of lead on renal function and its amelioration with chelation therapy.

Koller K, Brown T, Spurgeon A, Levy L: Recent developments in low-level lead exposure and intellectual impairment in children. *Environmental Health Perspectives*, vol. 112, issue 9, pages 987-94, 2004.

Review article suggesting that low-level lead and health findings are largely attributable to confounders, rather than toxic effects of lead.

Vaziri ND, Sica DA: Lead-induced hypertension: role of oxidative stress. *Current Hypertension Reports*, vol. 6, issue 4, pages 314-20, 2004.

Review of literature on lead effects on blood pressure emphasizing multifaceted nature, including role of reactive oxygen species and lead-induced enzyme alterations.

Appendix B: Mercury

General

Mercury is an element that has a long history of use in industry, medicine, and dentistry. Although volcanic activity, erosion and fire have always released mercury into the environment, over the last century industrial activity has contributed more than one-half of the content of mercury currently found in water and surface soil. Mercury's health effects depend both on the form of mercury encountered and the route of exposure. From a public health perspective, inhalation of elemental mercury and ingestion of organic mercury (particularly methylmercury) are the main concerns. The former is an infrequent occurrence resulting from the inappropriate handling of elemental mercury; the consumption of methylmercury occurs primarily through ingestion of fish and seafood.

Mercury is biopersistent - once an organism incorporates the metal, elimination is slow or incomplete. Mercury may be bioconcentrated, bioaccumulated, and biomagnified. Bioconcentration and bioaccumulation are characteristics of all persistent compounds that are incorporated into organisms low on the food chain, which higher predators then consume. Aquatic anaerobic bacteria convert the elemental form of mercury into organic methylmercury, a potent neurotoxin; thus, these organisms biomagnify the effect of mercury. All of these features have raised concern regarding the effects of environmental mercury on human health and have formed the basis for a variety of regulations and health advisories regarding the disposal of elemental mercury and fish consumption by at-risk populations such as pregnant women and infants.

Toxicity

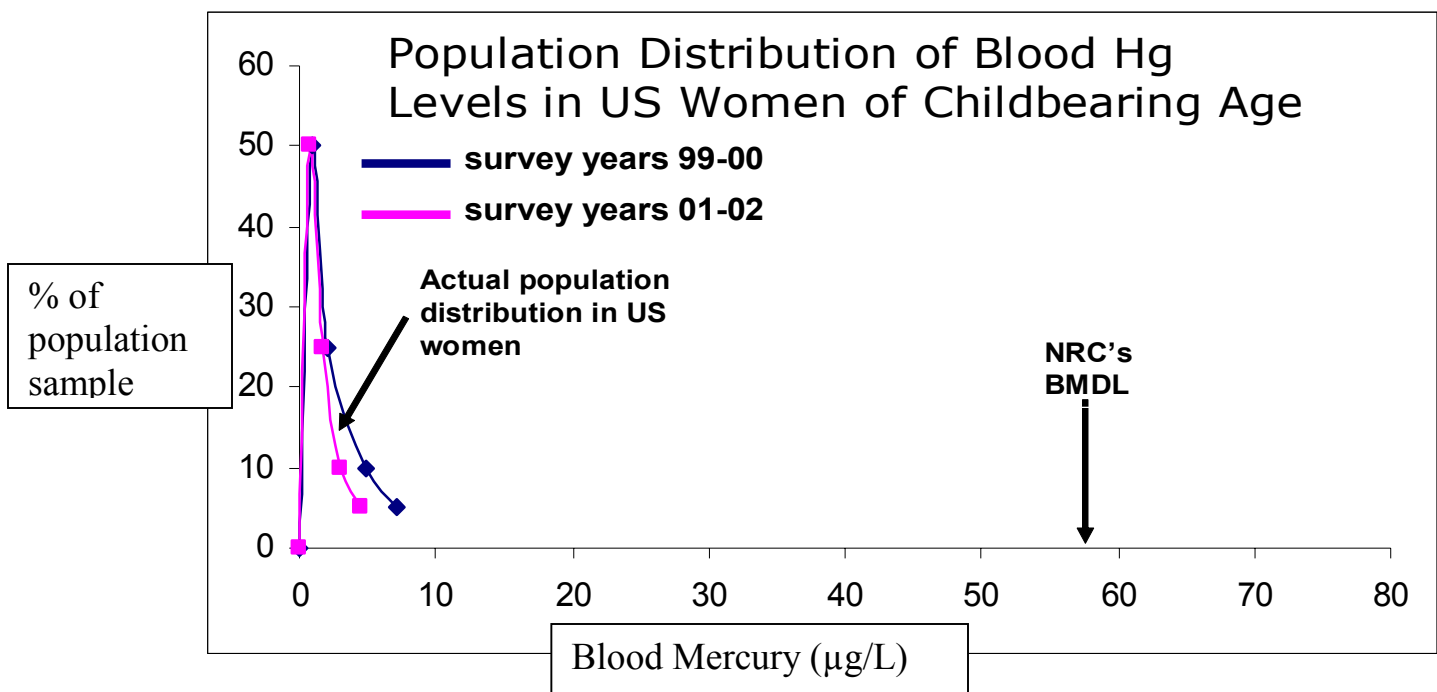
Tragic, large-scale public health mercury disasters have defined the neurological effects of methylmercury. Oft-cited examples are the consumption of fish contaminated by industrial chlor-alkali effluent in Minamata Bay, Japan in the 1950s and the consumption of methyl-mercury fungicide treated seed grain during the Iraqi famine in the 1970s. Children exposed *in utero* to large doses display cerebral palsy, microcephaly, psychomotor retardation, ataxia and seizures. Delayed achievement of developmental milestones is seen at lower levels of exposure. However, it is not known how these short-term, high-level exposures translate to the very low level exposures typically seen in maternal-fetal pairs with low-moderate fish consumption. For that reason, epidemiologic studies have attempted to correlate neurodevelopment in children with maternal ingestion of methylmercury from high-fish content diets. The two largest, and continuing studies, have shown conflicting results. This probably reflects the varying amount and intensity of consumption, as well as underlying nutritional and social factors and differences in neurobehavioral testing. Studies from the Seychelle Islands indicate that low levels of mercury consumption are actually associated with improved testing results (presumably attributable to the beneficial aspects of fish consumption). Studies from the Faroe Islands, where episodic consumption of pilot whale containing 10-100 times the amount

of mercury found in the typical U.S. diet (as well as large amounts of PCBs) occurs, suggest small decrements in some test scores.

The clinically evident effects have been correlated with biomonitoring data of mercury in hair and blood. For the most part, blood mercury reflects the organic mercury contribution from dietary sources. Methylmercury is concentrated in the red blood cell and eliminated with a half-life of 40-50 days in the adult, somewhat shorter in the child. Hair mercury concentrations likewise reflect primarily organic mercury compounds.

In the Iraqi famine in the 1970s, delayed onset to walking was seen with maternal hair mercury concentrations above 20 ppm, while ataxia, dysarthria, deafness and death were outcomes associated with concentrations progressively above 100 ppm (correlating to maternal blood concentrations of 400 ug/L). Statistical analysis of the Faroe Island child development data suggests that abnormalities on neurophysiological testing could become evident at maternal blood mercury concentrations of approximately 58 ug/L.

FIGURE 1: CDC's 2005 National Exposure Report



BMDL: the lower statistical bound (95% confidence interval) dose level (58 ug mercury/L blood) corresponding to a 10% increase in the probability of an adverse health effect, in this case neurologic injury.

Based on these studies, a committee of the National Research Council (NRC) designated a benchmark dose for methylmercury consumption of less than 0.1 $\mu\text{g}/\text{kg}$ body weight per day for maternal-fetal pairs to avoid neurologic injury. This conservative dietary allowance has led to health advisories regarding the consumption of fish during pregnancy and breastfeeding in nearly all states. Using the data from the *Third Report*, it is evident that none of the sampled U.S. population has mercury exposure in this range (see Figure 1 for a graphical representation of this comparison). It is anticipated that analysis in future *Reports* will present speciated mercury concentrations, allowing direct assessment of methylmercury concentrations.

It is reasonable to ask why there are fish consumption health advisories when none of the population demonstrates mercury exposures (presumably methylmercury) in a range that is statistically likely to cause an adverse health effect? This can be explained by the difference between “individual health risk” and “public health concern.”

There is no individual who will be clinically poisoned by mercury from usual dietary exposures. However, public health concern for the entire breadth of the population leads some to contend that there is too narrow a margin of safety for the most highly exposed proportion of the population. If high-risk individuals (in this case, pregnant women or very young infants) with unusually high fish consumption patterns and perhaps, individual or genetic predisposition to abnormally high gastrointestinal mercury absorption, or unusually low mercury detoxification ability, consumed fish high in methylmercury content, they might be harmed during a very vulnerable neurodevelopmental period. Unfortunately, such advisories are often taken to mean that any fish consumption by anyone is likely to cause harm. This presents a challenge to clinicians and public policy makers to do a better job of risk communication, targeting both the population potentially at risk and portraying that risk in an understandable fashion.

Risk Communication

Unfortunately, mercury provides us with many examples of risk communication gone awry. Exposure to ethylmercury in the form of thimerosal-containing preservatives in vaccines has generated intense debate regarding a possible risk of neurological injury. Exposure to ethylmercury from a full series of childhood vaccines (200 μg) over a period of six months could have exceeded the EPA’s conservative “reference dose” for consumption of methylmercury (0.1 $\mu\text{g}/\text{kg}/\text{day}$) for that time period. Even though ethylmercury and methylmercury are distinctly different compounds, the U.S. Public Health Service and the American College of Pediatrics recommended caution in administering thimerosal-containing vaccines to children and encouraged vaccine manufacturers to remove this preservative. This recommendation resulted in a marked drop in neonatal Hepatitis B vaccination in July 1999, which had not recovered even a year later. (MMWR, 2001)

While some case reports and epidemiological studies have raised the possibility of an association between childhood vaccinations and persistent developmental delay/autistic

spectrum disorders, a longitudinal study of children in Denmark, where thimerosal was removed from vaccines in 1992, demonstrates no change in the incidence of autistic spectrum disorders. The Institute of Medicine also evaluated the evidence and found that although developmental effects from ethylmercury are biologically plausible, there is no evidence of causality (Institute of Medicine. Immunization Safety Review: Vaccines and Autism <http://www.nap.edu/catalog/10997.html>). On the other hand, children have developed Hepatitis B and died because of lack of neonatal vaccination (MMWR, 2001). Nonetheless, there is still much political and emotional opinion regarding this association. A reasonable individual risk communication approach would emphasize the: 1) very small dose of mercury delivered in vaccines compared with those known to cause harm; 2) dissimilarity of ethylmercury effects to those of methylmercury; and 3) significant real (as opposed to theoretical) risks associated with failure to vaccinate.

Conclusions

The mercury data in the *Third Report* is reassuring. Even those individuals in the sampled U.S. population with the highest blood mercury measurements have mercury levels that are many fold lower than those associated with neurologic impairment in the highest-risk group; and still more of a distance from those with clinically evident mercury toxicity. Furthermore, there is a downward trend in the mercury concentration in the population. Future *Reports* will focus on specific methylmercury measurements, allowing some more precision in identifying likely sources of mercury exposure.

Additional References

Agency for Toxic Substances and Disease Registry Tox FAQs

<http://www.atsdr.cdc.gov/tfacts46.html>

Provides a summary of environmental mercury in non-technical language and has link to a Toxicological Profile for mercury that provides more detailed information.

EPA Fish Advisories

<http://www.epa.gov/ost/fish/>

Provides the EPA's recommendations regarding fish consumption for women of childbearing age, pregnant women, nursing mothers, and young children.

Notice to Readers: Thimerosal in vaccines: A joint statement of the American Academy of Pediatrics and the Public Health Service. *Morbidity Mortality Weekly Report* vol. 48, issue 26, pages 563-5, 1999. www.cdc.gov/mmwr/preview/mmwrhtml/mm4826a3.htm
Text indicates that benefits of vaccination outweigh any theoretical risk of harm from mercury, but then recommends delay in some early childhood vaccinations.

Impact of the 1999 AAP/USPHS joint statement on thimerosal in vaccines on infant hepatitis B vaccination practices. *Morbidity Mortality Weekly Report* vol. 50, issue 6, pages 94-7, 2001.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5006a3.htm>

Surveys in several states demonstrated a >50% decline in neonatal Hepatitis B vaccination, which still had not recovered to pre "joint statement" levels after one year. Failure to vaccinate was associated with infant chronic Hepatitis B infections and death.

Ball LK, Ball R, Pratt RD: An assessment of thimerosal use in childhood vaccines.

Pediatrics vol. 107, issue 5, pages 1147-54, 2001.

Discusses the precautionary approach taken in evaluating childhood mercury exposure from vaccines.

Clarkson TW: The toxicology of mercury-current exposures and clinical manifestations.

New England Journal of Medicine vol. 349, issue 18, pages 1731-7, 2003.

Review of large scale mercury disasters, epidemiological studies and case/control series of mercury biomonitoring.

Appendix C: Phthalates

General

Esters of phthalic acid, commonly referred to as “phthalates,” are a group of chemicals used as industrial solvents, as additives in personal care products, and as additives in the manufacture of plastics. Phthalates are classified as “plasticizers” because they are additives and are not covalent members of the plastic polymer. Phthalate content serves to customize the physical and optical properties of the plastic.

Phthalates are used in such diverse products as wire and cable insulation, floor coverings, synthetic leather products, garden hoses, loose-leaf binders, clothing, toys, toothbrushes, cosmetics, and car interiors. Human exposure to phthalates occurs through ingestion, inhalation, and dermal contact with products as well as from certain medical procedures, devices, and therapies. Residents of developed nations are exposed to phthalates on a daily basis through their use in plastics, such as polyvinyl chloride (PVC). Di(2-ethyl hexyl) phthalate (DEHP) is the most common phthalate used in PVC manufacturing and, because of its prevalence, is probably the most relevant in terms of human exposure. The DEHP content in PVC plastics varies, but can exceed 40% of the plastic polymer by weight. Phthalates such as DEHP are used because they impart several desirable characteristics to the PVC materials, including flexibility, optical clarity, and thermal stability. Because phthalates are not part of the base polymer, they can leach out of the plastic and into materials in contact with the plastic. Contact with fatty substances (e.g. dairy products, infant formula, meats, oils, blood products) increases the rate at which phthalates leach from the plastic polymer matrix.

DEHP is metabolized to a number of compounds including mono-2-ethylhexyl phthalate (MEHP), which is considered to be a toxic metabolite of DEHP. Its concentration in the urine of the U.S. population, as reported in the *Second* and *Third Reports* has remained roughly the same, 3.43 µg/L and 4.27 µg/L, respectively. For the *Third Report*, two additional metabolites were evaluated, mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP). In general, children 6 to 11 years of age and women have higher concentrations of these metabolites. The relative toxicity of these metabolites is not known, nor is the significance of higher metabolite concentrations in certain sub-groups. For example, higher urine concentrations in children might reflect higher environmental exposure, more efficient absorption and/or metabolism of the parent compound, or better renal excretion of the metabolite. Explanations for these findings in the *Third Report* will require further study.

Toxicity

Concern over potential phthalate toxicity following chronic exposure centers around three basic effects: carcinogenicity, developmental toxicity and reproductive toxicity. These effects have been noted primarily in rodents receiving very large doses of phthalates, rendering extrapolation to typical human exposures difficult, if not impossible. For

example, the *Report* cites published studies reporting higher blood levels of phthalate esters in rodents than in non-human primates that are given equivalent doses due to greater absorption in rodents or possibly more rapid breakdown and excretion in primates. As stated in the *Third Report*, even if humans were exposed to the same high doses as used in the rodent studies, “it would be difficult to translate the effects observed in animals to health effects in people.” Another challenge in attempting to determine risk in humans is that the estimated average daily intake for humans is far less than that used in the animal studies. The available information suggests that human exposure from dietary sources is 3 to 4 orders of magnitude (thousands to tens of thousands) lower than the doses reported to cause harm in laboratory animals. This is consistent with the usual margin of safety required by regulatory agencies for non-cancer health effects, suggesting low risk.

Safety factors for cancer are more difficult to estimate because of the question of the relevance of the animal studies to human cancer. For example, although liver tumors have occurred in some mouse and rat studies following high doses of phthalates, the proposed mechanism of tumor induction (binding to peroxisome proliferation-activated receptor alpha, or PPAR α) is not considered to be relevant in human exposures (see Additional References below). On this latter point there is no agreement among regulatory agencies. The U.S. Department of Health and Human Services (DHHS) classifies phthalates as probable human carcinogens. On the other hand, the International Agency for Research on Cancer (IARC) deems phthalates unclassifiable as to potential for human carcinogenicity due to the lack of cancer information in humans.

A recent multicenter study has raised some concerns regarding the antiandrogenic effects of phthalates in humans (Swan, 2005). For this study, the anogenital distance (distance between the center of the anus and the anterior base of the penis) of boys aged 2 to 36 months was measured and correlated with maternal urinary concentrations of 9 phthalate metabolites obtained during pregnancy. In rodent studies, the anogenital distance has been shown to reflect prenatal antiandrogen exposure. The phthalate metabolites were measured by the NCEH Division of Laboratory Sciences. The concentrations of MEHP, MEHHP, and MEHOP were somewhat lower than the *Third Report* cohort. More importantly, the investigators found that the urinary concentration of four phthalate metabolites were inversely correlated with anogenital distance, which suggests that phthalates may have antiandrogenic effects in humans. Of course, this association does not prove causation and potential confounders need to be evaluated, as well as the range of normal infant anogenital distance defined; nevertheless, this study does raise some important public health concerns that will need to be investigated further. In future studies it will be important to ascertain whether the novel association reported by Swan et al. is indeed robust, reproducible and dose-dependent, whether there is clinical health significance to the endpoint measured, and whether humans are more sensitive, less sensitive or on par with rodents in terms of the associations between exposure levels and effects.

On a societal scale, the debate regarding the safety of phthalates is likely to continue. Plastics are an integral part of the products and services on which industrialized nations

rely. As a result, some argue that in the absence of proven human risk, limiting or discontinuing use of phthalates is not warranted and unnecessarily deprives society of the benefits of these products. Others counter that the animal data, the emerging human data, and the current extent of exposure in people represent sufficient cause for immediate action because the general population exposure to these chemicals is so pervasive that it could pose a significant health burden if they are later shown to cause adverse health effects. Under an extreme precautionary approach, all phthalate usage would be eliminated until safety can be conclusively demonstrated.

Ideally, there would be some level of safety, or lack of risk, that would satisfy proponents of both points of view; however, individuals within these groups are often philosophically different, roughly divisible into “risk tolerant” and “risk averse”. Because these differences are based on philosophical beliefs, science alone cannot resolve this policy debate. Nonetheless, a number of expert panels have evaluated the available evidence concerning phthalate safety (see [Additional References](#)), concluding that the available evidence “...does not support current adverse health effects from background exposure to these compounds.” However, there is widespread agreement that further studies involving human subjects should be undertaken so that these concerns can be addressed in a rigorous and balanced manner, particularly in regards to high-risk groups.

Medical Equipment

DEHP is the most common phthalate found in medical devices and equipment, such as endotracheal tubes, intravenous tubing, and blood storage bags. Because DEHP is not covalently bound to PVC it does leach out and is infused or diffuses into the bloodstream. A number of medical procedures and therapies can result in phthalate exposure: blood product transfusions, total parenteral nutrition, extra-corporeal membrane oxygenation, and hemodialysis. Particular concerns have been raised for certain patient populations, namely, critically ill neonates because of the potential high exposure relative to body mass and hemodialysis patients because of the chronic, long-term nature of the exposure. Extra-corporeal membrane oxygenation (ECMO) has been estimated to result in doses of 10-34.9 mg/kg for 3 to 10 day courses of treatment (Karle, 1997). On the other hand, hemodialysis is estimated to result in doses of 0.1 to 2.2 mg/kg/day. But because it is a chronic exposure, extending for decades in some cases, the cumulative exposure is undoubtedly the highest experienced among individuals exposed to phthalates in the course of medical treatment (Kavlok, 2002). At this time, no specific health effects have been conclusively linked to phthalate exposure related to medical procedures or products, even with the more extraordinary dose ranges.

The U.S. Food and Drug Administration conducted a safety assessment on phthalate exposure from medical devices, concluding that there was potential risk to neonates undergoing ECMO and multiple medical procedures typical of neonate intensive care units but low risk from other medical procedures. The assessment noted that:

“This safety assessment should be viewed as a first step in this process. Other factors, such as the availability and safety of alternatives to DEHP

and PVC, must also be considered in developing a risk management strategy to address this issue.”

Conclusions

As noted above, philosophical viewpoints will interact with available scientific data, leading individuals to differing responses to the same information. Hopefully, these differences will be reduced as more data becomes available. For the moment, it is reasonable to continue investigations into possible long-term effects of phthalate exposure, while continuing to benefit from the products they are in. The expanded phthalate data in the *Reports* will provide the quantitative sampling to compare exposures in various portions of the population with subjects in research studies.

Additional References

Agency for Toxic Substances and Disease Registry Tox FAQs

<http://www.atsdr.cdc.gov/tfacts9.html>

Provides a summary of diethyl phthalate in non-technical language and has link to a Toxicological Profile for diethyl phthalate that provides more detailed information.

Consumer Product Safety Commission

<http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf>

Expert panel review of the use of diisononyl phthalate in toys.

FDA Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices

<http://www.fda.gov/cdrh/ost/dehp-pvc.pdf>

FDA panel review modeling potential exposures to medical devices containing DEHP in high-risk patient groups, yielding estimated doses in various clinical situations. This is compared to “tolerable intake” based on safety factor extrapolations from animal data of adverse effects.

National Toxicology Program Center for Evaluation of Reproductive Risks

<http://cerhr.niehs.nih.gov/reports/index.html>

Expert panel review of several phthalates.

Huber W, Grasl-Kraupp B, Shulte-Hermann R: Hepatocarcinogenic potential of di(2-ethylhexyl) phthalate in rodents and its implications on human risk. *Critical Reviews in Toxicology* vol. 26, pages 365-481, 1996.

Karle V, Short B, Martin GR, et al: Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethylhexyl) phthalate. *Critical Care Medicine* vol.25, pages 696-703, 1997.

Kavlok R, Boekelheide K, Chapin R, et al: NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di(2-ethylhexyl) phthalate. *Reproductive Toxicology* vol. 15, pages 529-653, 2002.

Klaunig, JE, Babich, MA, Baetcke, KP, et al: PPAR α Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance. *Critical Reviews in Toxicology* vol.33, pages 655-780, 2003.

A comprehensive review and analysis of the scientific literature on the relevance to human health of tumors in rodents induced by the peroxisome proliferation-activated receptor agonist mechanism of action conducted by the International Life Sciences Institute (ILSI), with funding from the US EPA and Health Canada.

Swan S, Main K, Liu F, et al: Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environmental Health Perspectives* vol. 113, pages 1056-61, 2005.