

## WRITTEN TESTIMONY OF

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### Introduction

Good morning, Mr. Chairman and Members of the Subcommittee. My name is Dr. L. Earl Gray Jr., and I am a senior reproductive biologist and toxicologist in the Reproductive Toxicology Division of EPA's National Health and Environmental Effects Research Laboratory in the Office of Research and Development. I have been employed by EPA for almost 30 years. During my tenure I have published more than 180 peer reviewed journal articles and book chapters. My co-authors and I have published in *Nature* and *Science* as well as several other prestigious journals. I have received more than 15 EPA Scientific and Technological Achievement Awards for research publications and two gold and 6 bronze medals from the EPA for my work. I also am listed as a Highly Cited scientist by Citations Indices and my work has been presented at numerous national and international symposia and several legislative hearings held by various governmental agencies.

My research has focused on the effects of chemicals, including endocrine disrupters (EDCs), on the cellular and molecular modes of action leading to abnormal reproductive development in male and female rodents – an acceptable model for predicting potential effects in humans.

\*The views presented in my testimony today represent my personal views as a scientist and do not necessarily reflect the position of EPA or the Administration.

Research in my laboratory has included examining the effects of exposure to environmental estrogens, antiestrogens, androgens, antiandrogens, dioxins and polychlorinated biphenyls (PCBs), phthalates, germ cell toxicants and chemicals that inhibit steroid hormone synthesis. The estrogens that we have studied include ethinyl estradiol (found in birth control pills), methoxychlor (a pesticide), and bisphenol A (BPA). In these studies, animals were exposed during critical developmental stages of life in pregnancy (*in utero*) to determine the latent effects later in life. Currently, we are focusing on how mixtures of phthalates and pesticides interact when administered *in utero*.

Data from these studies have been used by the EPA and other regulatory agencies in chemical-specific risk assessments. The findings from our studies on mixtures of phthalates are currently being reviewed, along with those from other studies, by a National Academy of Sciences panel. Later this year, the panel will provide the EPA with recommendations about conducting cumulative risk assessments on the phthalates.

In today's testimony I will discuss phthalates, and their toxicity. Then I will contrast this discussion with one on the toxicity of BPA. Much of what we know about the toxicity of these chemicals is based on studies that have been conducted in laboratory studies using animal models. Studies using laboratory animal models, when well-conducted by well-accepted standards, can provide valuable information for use in hazard assessments to predict potential toxicity in humans. Both phthalates and BPA produce toxicity by mechanisms that interfere with the endocrine or hormone system. Many pathways in the endocrine system are very similar across species and, therefore, there is strong concern about the potential hazard to humans from any chemical that interferes with hormones. However, the levels of exposure that are needed to elicit toxicity are also critical.

## **Phthalates**

Phthalates are a high-production-volume class of chemicals that are used in many consumer products including toys, baby products and lotions, cosmetics, personal care products, fragrances, air fresheners, medical tubing and devices, blood bags, PVC pipe and flooring, pharmaceuticals, and automobile parts. They are ubiquitous in our daily environment and most people, including pregnant women and their fetuses, are exposed to multiple phthalates at a time.

Several studies have shown that although phthalate exposures in humans are generally low -- basically near the limit of detection -- a small percentage of people are exposed to higher levels of phthalates. This information is based on the level of phthalate metabolites identified in the urine of some pregnant women <sup>1</sup> and in human amniotic fluid <sup>2</sup>. In rats, at certain levels of exposure, phthalates can cause liver cancer<sup>3</sup>, spontaneous abortions <sup>4</sup>, and reproductive tract malformations in male and female offspring. The adverse<sup>a</sup> reproductive effects seen in the male offspring, described as the “Phthalate Syndrome,” are currently the focus of regulatory agencies since this syndrome occurs at lower dosage levels than other toxicities.

<sup>a</sup> **adverse effect:** change in morphology, physiology, growth, development, or life span of an organism, which results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other environmental influences

Although there are literally thousands of studies on phthalates, the Phthalate Syndrome in male rats was not described until 1999 and these studies focused on only a few of the phthalates. The effects of phthalates on female offspring, which include partial to complete absence of the uterus, are only mentioned in one sentence in two papers, one from my laboratory <sup>5</sup> and the other from Dr. Paul Foster's laboratory <sup>6</sup>, currently of the NIEHS, NTP. The limited data that are available indicate that Phthalate Syndrome can be induced by phthalate diesters with linear side chains of 4-6 carbons on adjacent side chains and not with phthalate diesters with shorter or longer linear side chains. Thus not all phthalates have equal toxicity.

### **Mode of Action of Active Phthalate Diesters**

Phthalates act by inhibiting fetal rat testis function during a critical stage of life *in utero*. This results in reduced androgen (male hormone) and other hormone levels, hormones that are necessary for normal development of the male reproductive tract. Male offspring exposed to high doses of phthalates *in utero* often display undescended testes and malformations of the penis and internal reproductive tract. This disrupted process in rats, known as sexual differentiation, is common to all mammals and disruption of this pathway in human males also causes profound abnormalities<sup>7</sup>.

The levels of the monoester metabolites of dibutyl- (DBP) and diethylhexyl- (DEHP) phthalate measured in the amniotic fluid of rats during sexual differentiation <sup>8</sup>, from pregnant rats treated with dosage levels that produce low incidence of statistically significant adverse reproductive effects in male rat offspring, are only about 5 fold (DBP <sup>9</sup>) and 24 fold (DEHP <sup>10</sup>) higher, respectively, than the highest levels of the same metabolites seen in the amniotic fluid from a study of 54 women <sup>2</sup>.

This indicates that the margin of exposure (MOE<sup>b</sup>) is not as great as one would generally like.

In addition, the scientific literature is consistent in indicating that phthalates show adverse effects in offspring that are produced by disrupting a hormonal signaling pathway common to all mammals including humans.

It is worth noting that there is considerable agreement in the scientific community about the mode of action of phthalates on the fetal male rat. Studies from industry, government and academic laboratories have all found similar effects. Some of the same laboratories reporting adverse effects of phthalates<sup>5,6,11-14</sup> on reproductive development have, in contrast, not detected any low-dose effects caused by BPA<sup>15,16</sup>.

<sup>b</sup> **margin of exposure:** ratio of the no-observed-adverse-effect level (NOAEL) to the estimated exposure dose in humans

## Phthalate Mixtures

Since most humans are exposed to multiple phthalates, it is critical to understand the biological effects of mixtures of phthalates. Studies in rats show that combining phthalates with other phthalates<sup>13,14</sup> or with pesticides<sup>14,17</sup> can produce cumulative, additive, adverse effects. They do not act independently. The following table describes the relative potencies of several phthalates compared to di(n)ethylhexyl phthalate (DEHP). The estimated potencies describe the potential of each phthalate to disrupt testicular function and/or produce malformations in male rat offspring.

<b>Phthalate</b>	<b>DEHP</b> diethyl hexyl-	<b>DBP</b> dibutyl-	<b>DiBP</b> di-iso butyl-	<b>BBP</b> benzyl Butyl-	<b>DINP</b> di-iso nonyl-	<b>DPP</b> dipentyl-	<b>DEP</b> diethyl-	<b>DMP</b> dimethy-	<b>DOtP</b> dioctyl- ter-
<b>Estimated Relative Potency</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>0.15</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Reference</b>	<b>13,14,18</b>	<b>6,13,14</b>	<b>14,19</b>	<b>12,14,17,18</b>	<b>18,20</b>	<b>14,21</b>	<b>18</b>	<b>18</b>	<b>18,22</b>

## **Concerns about Phthalates**

Following the scale used by the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction (NTP CERHR) (scale: negligible, minimal, some concern, concern, serious concern) I have "serious concern" about the potential effects in children exposed to phthalates from medical interventions<sup>23,24</sup> where serum levels can reach parts per million concentrations<sup>24</sup> and "concern" for exposure to children and women of childbearing age since the currently available data<sup>1,2,8-10,25</sup> indicate that the margin of exposure can be low for the most highly exposed individuals.

- The mode of action is highly conserved, being common among mammals, including humans,
- While most of the human population appears to be exposed to low levels of phthalate metabolites, some individuals are exposed to very high levels,
- Humans are exposed to multiple phthalates and mixtures of phthalates that have cumulative effects in rats, and
- Effects have been reported in humans in several epidemiology studies including one which reported an association between higher levels of maternal phthalates and reduced anogenital distance (AGD) in male infants (Swan et al., 2005). Shortened AGD is considered an index of demasculinization in rats.

## **Bisphenol A (BPA)**

BPA is a high-production-volume chemical used in the synthesis of polycarbonate plastics and found in many consumer products including baby bottles and can liners. Studies show that most people are exposed to low levels of BPA <sup>26</sup>.

My comments about Bisphenol A are based on my participation on the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction Expert Panel (Final Report, Nov 2007<sup>c</sup>) where we evaluated several hundred papers on the reproductive toxicity of BPA. In addition, I have conducted research in my own laboratory on BPA<sup>16,27</sup> and other environmental estrogens <sup>16 28</sup>

<sup>c</sup> <http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPAFinalEPVF112607.pdf>

National Toxicology Program's Center for Evaluation of Risks to Human Reproduction Panel on BPA. (<http://cerhr.niehs.nih.gov/>)

In 2006, the National Toxicology Program's (NTP) Center for Evaluation of Risks to Human Reproduction (CERHR) formed the BPA Expert Panel with experts in the fields of statistics, epidemiology, reproductive and developmental toxicology and exposure. The Panel included several internationally known scientists, some of whom have worked on BPA. A search for citations on the National Library of Medicine Pub Med database on scientific publications reveals that this group has well over 700 scientific publications in the fields mentioned earlier.

The literature on BPA is quite unique in two respects. First, there is no lack of data for such a review. There were over 700 studies considered by our Expert Panel and more are published every day. Secondly, the results of the studies on the low dose effects of BPA are mixed. In

general, studies that have examined common endpoints after exposure to BPA during development have not produced consistent results.

The Panel independently developed criteria to rate the quality of the studies. We reviewed studies published in the scientific literature and reports, established levels of concern for potential adverse effects of low doses of BPA in humans, and wrote draft and final reports. Early on, a contractor who had routinely assimilated all of the scientific studies and prepared a draft summary for all the chemicals that had been reviewed by CERHR panels was dismissed from the process for reviewing BPA. However, neither the contractor nor the CERHR staff influenced our decisions. The Panel reviewed all constructive comments submitted to the NTP through their public comment period and adjusted our assessment as warranted.

At the first face-to-face meeting of the Panel, reproductive and developmental toxicologists as a group developed criteria for inclusion of papers in the final report. The criteria provided minimum standards for experimental design and statistical analysis. Many studies failed to meet these minimal criteria – these studies came from industry, government and academic laboratories. One of the most common deficiencies was failure to control for and statistically account for “litter effects,” an error that can result in random variation being identified as a low dose effect of BPA <sup>29,30</sup>. We also omitted studies from review that used a positive control group of animals that did not show any adverse effects, studies that injected BPA into the brain or spinal cord, and studies that did not have a concurrent control group of animals.

In our evaluations we never considered the sources of funding or where the investigators were employed. In our initial evaluation of study quality we also did not consider who the investigator was or if the study detected low-dose effects or not. We were evaluating only the

experimental designs and statistical methods to ensure that our report would be based only on high quality studies. Studies that did not meet these criteria were deemed “inadequate” for inclusion in the final report.

Unlike phthalates, which have also been reviewed by panels of independent experts convened by CERHR, the literature has not led to a scientific consensus on the reproductive effects of low doses of BPA in any rodent species. Also, in contrast to the phthalates, there currently is no evidence of high-level exposures to BPA *in utero* or to children. Most of the “low dose” studies that have been conducted in rodent models appear to be using BPA levels that are several orders of magnitude higher than human exposures.

### **Why is there so much controversy about the low dose effects of BPA?**

In my opinion, the controversy exists because:

- Many of the low dose effects of BPA in rodents are not robust and have not, or cannot be reproduced across multiple laboratories. Effects need to be robust and reproducible. .
- The low dose **effects** are frequently not **adverse** effects.
- None of the studies reporting effects at low doses have included a sufficient number of dosage levels to enable researchers to link the effects with adverse effects and many do not include any functional assessment of the reproductive system at all. These low dose effects must be causally linked to adverse effects to be useful in a risk assessment.
- If we assume that these low dose effects are “real,” then why aren’t there effects at high dosage levels in multigenerational studies? Every other EDC studied in this manner produces a continuum of effects across the dose-response curve, including all other estrogens, and although the effect at low doses can differ from that at high doses the high doses result in adverse changes in reproductive function.

Many “effects” in the “low dose” BPA studies such as cancer, reproductive tract malformations and infertility, have never been causally linked to BPA administration.

Currently, there is no proven biological mode of action for the low-dose effects reported for BPA. We do not know what pathway might be disrupted in rodents and whether it is conserved in humans or whether these “effects” are unique to rodents. For example, around the time of birth estrogens have a very important role in masculinizing the brain of the male rat whereas this pathway is generally assumed to be much less important in human males where the androgen signaling pathway predominates.

BPA is an estrogen mimic, displaying estrogenic activity *in vitro* and in short-term *in vivo* Estrogen Receptor (ER) alpha and beta-dependent assays. However, BPA is about 10,000 fold less potent than estradiol, an important human estrogen. The nuclear ER alpha receptor is the most important mode of action for estrogens in the reproductive tract. Based on the low levels of human exposure to BPA, this mode of action would not likely be activated at very low dose levels. Genomic studies in rodents do not detect activation of estrogen-dependent genes after exposure to low dose levels of BPA, indicating the ER signaling pathway is only induced at moderate to high dose levels in the rat uterus or fetal rat testis <sup>29,31</sup>.

To explain many of the low-dose effects, BPA would have to be as potent as the most potent estrogens such as estradiol 17 $\beta$ , ethinyl estradiol and diethylstilbestrol (DES). Note that all of these estrogens produce obvious adverse reproductive effects at higher dosage levels. Such a remarkable proposition requires remarkable proof, and the database does not provide this level of

proof. Hence the present controversy in the scientific community about the low dose effects of BPA.

The CERHR Expert Panel had different levels of concern for the low-dose effects of BPA on humans for different endpoints. These are presented in the attached appendix.

- Overall, the Panel's highest level of concern was "*Some Concern*" for neural and behavioral effects of BPA on humans. However, these studies did not reveal a clear pattern of behavioral or neural alterations or disruption of a single neural pathway. My opinion is that this indicates an obvious need for more research. All other effects were determined to be of either negligible or minimal concern.

## Summary

In summary, I have different levels of concern for these two classes of EDCs, with a higher level of concern for some phthalates than for BPA.

- **Phthalates**
  - *Concern*<sup>c</sup> for children and women of child-bearing age and
  - *Serious Concern*<sup>d</sup> for children and pregnant exposed to phthalates by medical interventions

<sup>c</sup> This level of concern is one level higher than that expressed in the 2006 NTP Monograph on DEHP<sup>10</sup>.

because I considered a) that people are exposed to multiple phthalates, not just DEHP, and b) that new data have shown that some people are exposed to very higher levels of phthalates than previously reported.

<sup>d</sup> This level of concern are the same as that expressed in the 2006 NTP Monograph on DEHP<sup>10</sup>.

- **BPA<sup>e</sup>**
  - *-Some Concern* for neural and behavioral effects and
  - *-Minimal to Negligible Concern* for other effects

<sup>e</sup> These levels of concern are compared to those expressed in the NTP Draft Brief in Table 1

The difference in levels of concern expressed here for some phthalates as opposed to BPA is based upon the fact that:

1. Several publications indicate that some women and children are exposed to high levels of phthalates, levels are only 5- and 24-fold lower than levels seen in rats displaying statistically significant incidences of adverse reproductive effects, thereby providing a small margin of exposure<sup>1,2,8-10,25</sup>, and
2. The consistency of the scientific literature on the phthalates showing adverse effects in offspring produced by disruption of a hormonal signaling pathway common to all mammals including humans.

Thank you, Chairman Rush and members of the Subcommittee for this opportunity to discuss EPA's work on phthalates and BPA. I look forward to answering any questions you may have.

*LE Gray Jr's comparison of CERHR BPA Expert Panel's (2007) levels of concern for the potential of "low doses" of BPA to produce adverse effects in humans with the levels of concern in the NTP draft Brief (2008)*

<b>Effect</b>	<b>Expert Panel Report Level of concern (Section 5)</b>	<b>NTP Draft Brief Level of concern</b>	<b>Difference</b>
<b>Neural and behavioral effects in fetuses, infants and children</b>	<b>Some</b>	<b>Agreed</b>	<b>None</b>
<b>Age at puberty in females</b>	<b>Minimal</b>	<b>Some</b>	<b>NTP higher</b>
<b>Prostate gland "lesions" – PIN</b>	<b>Minimal</b>	<b>Some</b>	<b>NTP higher</b>
<b>Tissue changes ("lesions") in mammary gland</b>	<b>Negligible</b>	<b>Some</b>	<b>NTP higher</b>
<b>Fetal or neonatal mortality</b>	<b>Negligible</b>	<b>Agreed</b>	<b>None</b>
<b>Birth weight or growth of offspring</b>	<b>Negligible</b>	<b>Agreed</b>	<b>None</b>
<b>Reproductive effects in non-occupationally exposed adults (including fertility, hormone levels and sperm numbers)</b>	<b>Negligible</b>	<b>Agreed</b>	<b>None</b>
<b>Reproductive effects in occupationally exposed adults</b>	<b>Minimal</b>	<b>Agreed</b>	<b>None</b>
<b>Malformation in offspring or fetuses</b>	<b>Negligible</b>	<b>Agreed</b>	<b>None</b>
<b>Effect</b>	<b>Expert Panel Report Level of concern (Section 3)</b>	<b>NTP Draft Brief Level of concern</b>	<b>Difference</b>
<b>Fertility in offspring</b>	<b>Negligible</b>	<b>Unclear</b>	<b>None</b>
<b>Hormone levels in offspring</b>	<b>Literature on low dose studies in inconsistent and insufficient to reach a conclusion</b>	<b>Same</b>	<b>None</b>
<b>Sperm numbers with developmental exposure in offspring</b>	<b>Literature on low dose studies in inconsistent and insufficient to reach a conclusion</b>	<b>Same</b>	<b>None</b>

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