September 9, 2014

Dr. Mary Ann Danello, Associate Executive Director
Directorate for Health Sciences
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Dear Dr. Danello:

I am writing on behalf of the High Phthalates Panel of the American Chemistry Council (ACC) in response to the final report of the Chronic Hazard Advisory Panel (CHAP) on phthalates and phthalate alternatives, which the Consumer Product Safety Commission (CPSC) released on July 18, 2014. Section 108 of the Consumer Product Safety Improvement Act (CPSIA) required CPSC to appoint a CHAP to conduct a *de novo* examination of the effects on children's health of all phthalates and phthalate alternatives used in children's toys and child care articles. ACC has urged CPSC to subject the resulting CHAP report to an open, public comment period in accordance with guidelines set forth in the Office of Management and Budget's (OMB) Information Quality Bulletin for Peer Review (2005) prior to the commencement of rulemaking under the CPSIA. The OMB guidelines for the peer review of "highly influential scientific assessments" were established to enhance the peer review of government science documents and to improve the quality and credibility of information upon which policy decisions are based.

ACC sponsored ToxStrategies, Inc. to manage and coordinate an independent peer review of the final CHAP report by highly-respected and internationally-recognized subject matter expert scientists with recognized expertise in the following key subject areas covered in the CHAP report: reproductive and developmental toxicity, endocrine activity, human relevance of animal studies, epidemiology, exposure, and cumulative risk methodology [See report, attached].

These reviews identified some serious areas of concern. As Dr. Douglas L. Weed, M.D., M.P.H., Ph.D. states: "[t]he CHAP report is not a systematic review of the available scientific evidence and, as such, is of questionable reliability and validity, lacking in the objectivity and transparency generally recognized as critical by the scientific community. The credibility of the recommendations in this report [is] therefore questionable, given that they are not 'evidence-based' as the co-chair of the committee, Dr. Hauser, recognized and mentioned in a separate review published in the peer-reviewed literature (Braun et al., 2013)."

The serious scientific questions identified by these independent subject matter experts call into question the validity, reliability and transparency of the CHAP report and underscore the need for a public comment period on that report before it is used as a basis for rulemaking under the CPSIA.

We urge your staff to review the science findings of these experts and consider the findings when preparing your recommendations to the Commissioners. The CHAP report cannot and should not serve as a basis for rulemaking.

Sincerely,

Eileen Conneely

Eileen Conneely, M.P.H., J.D.
Manager, High Phthalates Panel
American Chemistry Council

cc: DeWane Ray, Acting Executive Director
Dr. Michael Babich
(Robert) Jay Howell, Deputy Executive Director, Safety Operations

Independent Expert Peer Review of the Final CHAP Report on Phthalates and Phthalate Alternatives

SEPTEMBER 7, 2014

ToxStrategies

Innovative solutions
Sound science

Independent Expert Peer Review of the Final CHAP Report on Phthalates and Phthalate Alternatives

SEPTEMBER 7, 2014

PREPARED FOR:
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Table of Contents

1.0 Overview

The U.S. Consumer Product Safety Commission (CPSC) convened a Chronic Hazard Advisory Panel (CHAP) to study the potential effects on children's health of phthalates and phthalate alternatives as used in children's toys and childcare articles. The CHAP Phthalates Panel has been engaged in this effort since the spring of 2010. CPSC released the final CHAP report on July 18, 2014. ToxStrategies, Inc. (ToxStrategies) was retained by the American Chemistry Council (ACC) High Phthalates Panel to manage and coordinate an independent peer review of the final CHAP report by a team of highly respected and internationally-recognized subject matter experts. This effort was undertaken to ensure that a scientifically robust review of the report was performed by independent scientists with recognized expertise in the key subject areas covered in the CHAP report. All aspects of the peer review process were managed by ToxStrategies, including selection of the experts, contracting with the experts, communication with the experts, evaluation of potential conflicts of interest, development of general guidelines for preparation of comments (in lieu of charge questions), distribution of the CHAP report and CPSC-funded peer review of the report, collection of each expert's written comments, and compilation of all comments into the current single report. Neither ACC nor members of the ACC High Phthalates Panel had any contact or communication with the subject matter experts engaged to perform the independent peer review of the CHAP report. The opinions expressed by each peer reviewer are solely their own and do not represent the opinions of their employers or other affiliations, ToxStrategies, or the ACC.

2.0 Expert Peer Review

2.1 Initial Identification of Potential Peer Reviewers

Potential subject matter experts were initially identified and considered by ToxStrategies staff based on their expertise in subject area(s) anticipated to be pertinent to the CHAP report and prior experience with phthalates. A preliminary teleconference was held between ToxStrategies and each potential expert to discuss their specific expertise in the subject matter of interest, as well as to ascertain their interest and availability to participate upon release of the final CHAP report at some future date. As part of this exercise, a conflict of interest check was performed for all parties involved (ToxStrategies, ACC, and the experts).

Following this preliminary conference call, ToxStrategies selected experts to review each of the potential subject areas anticipated to be included in the CHAP report. ToxStrategies periodically communicated via E-mail with each expert during the time between the initial contact and the release of the final CHAP report, in order to ensure continued interest and availability.

2.2 Selected Peer Reviewers

ToxStrategies reviewed the final CHAP report in detail immediately following its release to the public. Based on this review, the key subject areas for independent peer review were identified and determined by ToxStrategies to be: 1) Reproductive and Developmental Toxicity/Endocrine/Human Relevance, 2) Epidemiology, 3) Exposure, and 4) Cumulative Risk. The experts previously identified for these subject areas were subsequently contacted to confirm both their interest and availability to participate in the independent peer of the CHAP report.

The specific experts ultimately selected to perform the independent peer review of each of the subject areas of interest are identified in Table 1. As noted above, the peer reviewers are highly respected and internationally recognized experts in the designated subject areas. The curriculum vitae for each peer reviewer demonstrate their unique qualifications in their particular subject matter and are provided in Appendix C.

Table 1. List of Expert Peer Reviewers and Subject Area

Expert	Affiliation	Subject Area
Christopher J. Borgert, Ph.D.	Applied Pharmacology and Toxicology, Inc.	Cumulative Risk
Kathryn Clark, Ph.D., P.Eng.	BEC Technologies, Inc.	Exposure
Warren G. Foster, Ph.D.	Department of Obstetrics & Gynecology McMaster University	Reproductive and Developmental Toxicity/Endocrine/ Human Relevance
Bette Meek, Ph.D.	McLaughlin Centre for Population Health Risk Assessment University of Ottawa	Cumulative Risk
Douglas L. Weed, M.D., M.P.H., Ph.D.	DLW Consulting Services, LLC	Epidemiology
Raphael J. Witorsch, Ph.D.	School of Medicine, Medical College of Virginia Virginia Commonwealth University	Reproductive and Developmental Toxicity/Endocrine/ Human Relevance

2.3 Peer Review Process

General guidelines for performing the technical peer review were drafted by ToxStrategies and shared with each of the subject matter experts prior to their beginning their independent peer review. General guidelines were used in lieu of specific charge questions so as not to limit the scope or viewpoints of the peer reviewers. Further, the guidelines were purposefully general in nature in order to allow the experts to perform a wholly independent and comprehensive review of the CHAP report relevant to their subject area. In brief, peer reviewers were charged with conducting a thorough technical review based on all pertinent information (including all data evaluated by the CHAP) and using the weight-of-evidence to develop relevant comments on the designated subject area(s). The guidelines for review as provided to each expert are included in Appendix A (Guidance for Conducting Independent Expert Review of CHAP Final Report on Phthalates and Phthalate Alternatives).

In addition to providing each subject matter expert with the general guidelines for performing the peer review, each peer reviewer was also provided with the following prior to initiating work: 1) Subcontractor consulting and confidentiality agreement with ToxStrategies, Inc., 2) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel On Phthalates and Phthalate Alternatives[1], and 3) Peer Review of the CHAP Draft Report on Phthalates and Phthalate Substances, submitted to the CPSC by Toxicology Excellence for Risk Assessment[2].

ToxStrategies subsequently contracted directly with each peer reviewer (listed in Section 2.2). Depending on the date of execution of the contract, each peer reviewer was given approximately 2-3 weeks to perform the review and provide written comments to ToxStrategies. Each reviewer was tasked with following the guidelines in Appendix A as provided. However, due to existing time constraints, Drs. Borgert and Meek followed the guidelines to the extent possible with the focus of their reviews being limited to the methodological aspects of the approach used and, as such, their review did not necessarily encompass a full technical review of all data evaluated by the CHAP.

Each expert submitted his or her comments electronically to ToxStrategies in PDF format. The independent comments submitted by each subject matter expert are provided in their entirety in Appendix B as originally authored by each peer reviewer without modification. In addition, key findings/conclusions noted by each subject matter expert are summarized in Section 3.0 below.

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[1] Accessed from: https://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/\

[2] *Ibid.*

3.0 Key Findings of Independent Peer Review

Each subject matter expert was asked to highlight his or her key findings as an outcome of their independent technical review of the CHAP report; the key findings/conclusions identified by the six experts are quoted below organized by subject area. As noted above, the independent comments submitted by each subject matter expert are provided in their entirety in Appendix B.

3.1 Reproductive and Developmental Toxicity/Endocrine/ Human Relevance

Reviewer: Warren Foster, Ph.D.
Key Findings:
Although the authors have done a very good job of managing a very rich data set and preparing a very well written document, several weaknesses with the report need attention. From this review three main points are as follows:

- *The epidemiological evidence linking phthalate exposure to decreased circulating testosterone concentrations, even in young boys, and developmental abnormalities of the male reproductive tract are thought to be weak.*

- *While the animal literature provides a plethora of studies documenting the characteristics of the rat phthalate syndrome, the relevance of these findings to human health remain questionable. Specifically, differences in cross species sensitivity to the effects of phthalates, the high concentrations of phthalates needed to induce effects in rats, potential confounding from xenoestrogens in the diet, data gaps in understanding of the relevant mechanisms of phthalate action, and the relatively low concentrations of phthalate metabolites measured in human urine.*

- *The assumption of additive effects appears to have weighed heavily in the authors consideration of risk. However, as discussed by others, there is concern about the potential for phthalates to act in an additive manner when present [in] concentrations well below those used in animal studies to demonstrate an additive effect. Moreover, potential for additive effects when divergent mechanism or modes of action are operable raises concerns about the soundness of using the potential for an additive effect in risk assessment and generating the conclusions presented in the CHAP report.*

Taken together, human exposures to phthalates remains low with MOEs that are many times above the concentrations needed to induce adverse effects in rats. Hence, there should be confidence in existing regulatory decisions and the recommendations presented in the CHAP report are viewed as overly cautious.

Reviewer: Raphael J. Witorsch, Ph.D.
Key Findings:
While the CHAP is commended for a very scholarly and in depth review of the literature pertaining to the adverse effects [of] prenatal pththalate exposure on the development male reproductive system, this reviewer noted three issues that deserved further discussion.

- *First of all, this reviewer seems more optimistic than the CHAP about the utility of the rat as a model for risk assessment of exposure to phthalates both individually and as mixtures.*

- *Secondly, the weight of evidence indicates that the rat is more sensitive to the effects of phthalate than the mouse and possibly than primates, as well.*

- *Finally, in contrast to the opinion expressed by CHAP, the epidemiologic data associating maternal phthalate levels in body fluids with decreased AGD in human male offspring are inconclusive.*

3.2 Epidemiology

Reviewer: Douglas L. Weed, M.D., M.P.H., Ph.D.
Key Findings:
The following represent key findings of my review of the CHAP report to the U.S. Consumer Product Safety Commission on phthalates. These findings are made with particular emphasis on epidemiology and, more broadly, an emphasis on the methodological approach taken by the CHAP committee.

- *The CHAP report is not a systematic review of the available scientific evidence and, as such, is of questionable reliability and validity, lacking in the objectivity and transparency generally recognized as critical by the scientific community. The credibility of the recommendations in this report are therefore questionable, given that they are not "evidence-based" as the co-chair of the committee, Dr. Hauser, recognized and mentioned in a separate review published in the peer-reviewed literature (Braun et al., 2013).*

  Indeed, the CHAP committee specifically rejected the need for a systematic review (see CHAP Report, p. 12). This unfortunate decision on the part of the CHAP committee puts the credibility of their entire project at risk. Their argument—that interpreting different streams of evidence is not amenable to the systematic review methodology—is at best an indication that they are unaware of the well established need for a systematic approach, and at worst, scientific nonsense. The systematic review methodology is clearly the best approach to be used in the situation in which there is evidence from different disciplines.

- *The CHAP report misrepresents the results of some (but not all) of the available epidemiological evidence, ignoring or downplaying negative results and emphasizing*

positive (i.e. apparently harmful) results. Theirs is not a critical and balanced review of the epidemiological evidence. That evidence, which I have examined in detail, is inconsistent and, in some instances, shows that exposure to phthalates may be good for children. I am not advocating that exposure to phthalates be encouraged. I am pointing out that the CHAP report is biased with respect to the findings of the epidemiological evidence.

- *The CHAP report fails to justify their recommendations to reduce exposure to phthalates. It cannot be justified by the available epidemiological evidence. The CHAP committee fails to point out that there are no studies documenting a reduction in developmental outcomes or neurodevelopmental outcomes in children after a reduction in exposure to phthalates. No effort is made on the part of the CHAP Committee to grade the strength of the evidence or the recommendations made, despite the fact that the Committee reviewed literature that provides a process for grading the quality of evidence and the quality of recommendations.*

- *The CHAP report fails to mention much less discuss a relatively large number of published reviews and several epidemiological studies on the topic of phthalates and human health including children's health. The missed epidemiological studies provide evidence of null ("no association") results. In addition, the fact that many of these reviews disagree with the CHAP report's assessment of the epidemiology (and of the use of animal models to represent adverse health events in humans) is important and should have been addressed in the CHAP Report.*

3.3 Exposure

Reviewer: Kathryn Clark, Ph.D., P.Eng.
Key Findings:

- *In general, the approach employed was sound and included comparisons of human exposure to phthalate esters from biomonitoring data with exposures estimated from a range of sources including consumer products, diet, and environmental media.*

- *My concerns with the report are in how the results of the exposure assessment are used to respond to the questions posed to the CHAP, deficiencies in the methodology and available data for estimation of exposure to children's toys and child care articles, and also in some assumptions used in the calculations and inconsistencies in those assumptions, including receptor characterization and statistical measures.*

- *The CHAP report states that "phthalates cause a wide range of toxicities in experimental animals but the one considered of greatest concern for purposes of this report is a syndrome indicative of androgen insufficiency in fetal life, what is referred to in rats as the phthalate syndrome, caused by exposure of pregnant dams to certain phthalates". Review of the toxicity evaluation is beyond the scope of my review; however, from a high level review point, it is unclear how recommendations can be made with respect to children's toys and child care articles when the toxicity*

endpoint is for non-users of those products (i.e., pregnant women, fetuses, and neonates).

- *The CHAP report (Table E1-20) indicates that there is no exposure of pregnant women to phthalates contained in child care articles and that the highest potential exposure from dermal contact with toys is for DNOP (comprising 4.7% of total exposure to DNOP), followed by 0.5% for DEHP, and 0.1% for DINP. These estimated exposures are based on a scenario-based assessment described in the CHAP report as "highly uncertain" (p.E1-46) and are "hypothetical because these PEs currently are not allowed in toys" (p.E1-35).*

- *The CHAP report recommends that the interim ban on the use of diisononyl phthalate (DINP) in children's toys and child care articles at levels greater than 0.1% be made permanent. The basis for this recommendation is not clear; according to the CHAP report (Table E1-20), exposure to toys and child care articles represents only 0.1% of total exposure to DINP for pregnant women so a ban would not be expected to alter exposure of pregnant women. For infants (Table E1-21) exposure to toys and child care articles represents 30% of total exposure to DINP; however, this percentage was calculated in the scenario-based assessment, which over-estimates total exposure to DINP by a factor of six (Table 2.14) and, therefore, it is highly uncertain what effect a ban on DINP in toys and child care articles would have.*

3.4 Cumulative Risk Methodology

Reviewer: Christopher J. Borgert, Ph.D.
Key Findings:
The Report to the U.S. Consumer Product Safety Commission by the CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES, dated July 2014, suffers a number of scientific deficiencies that limit its utility for evaluating the safety of consumer products. These deficiencies, and potential remedies for them, are summarized below and detailed in the review and cited literature that follows.

- *The CHAP report failed to test logical extensions of its cumulative risk theory, methodology and conclusions, and thus failed to recognize obvious inconsistencies with human experience and clinical evidence.*

- *The CHAP report failed to account for model uncertainties in extrapolating chemical mixture effects observed at high doses in animal studies to the lower doses potentially received by humans; consequently, the CHAP overstates the accuracy of its cumulative risk methods and conclusions.*

- *The CHAP report failed to compare human versus rodent sensitivity to antiandrogenic effects of chemicals, and as a consequence, appears to have grossly overestimated chemical potencies in assessing potential risks to humans from*

cumulative exposures to phthalates, phthalate alternatives, and other potential antiandrogens.

- *The CHAP report failed to consider published literature at odds with its selected cumulative risk theory and methodology, thereby undermining the scientific credibility and reliability of its cumulative risk predictions and recommendations based on them.*

- *Deficiencies in the CHAP report could be remedied by adopting reasonable limitations of potency and dose in applying its cumulative risk assumptions and methods, and reforming its recommendations accordingly.*

Reviewer: Bette Meek, Ph.D
Key Findings:
Focus of this review was on methodology for the cumulative assessment, which with few exceptions represents state of the art methodology drawing maximally on multiple sources of relevant data. Principal comments relate to the defensibility of the use of Hazard Indices based on Reference Doses rather than Points of Departure, since this limits transparency and consideration of important aspects of uncertainty and variability not currently addressed in traditionally applied uncertainty factors. It also complicates comparison with the individual exposure data since reference doses are designed to protect populations.

- *Consideration of uncertainty and variability in the assessment is uneven, being fairly robust for the biomonitoring data but extremely limited for the scenario based exposure and potency estimates.*

- *Sensitivity, though mentioned, is seemingly not analyzed as a basis for weighting of various approaches and/or identification of critical datagaps.*

- *Weight of evidence analysis including consideration of broader biological knowledge as a basis for more robust discussion of potential species differences for bounding of the PODs is not evident and weight of evidence considerations across the available database (beyond those that are study specific) are also not specified.*

Appendix A

Guidance Provided to Expert Peer Reviewers

Guidance for Conducting Independent Expert Review of CHAP Final Report on Phthalates and Phthalate Alternatives

1. Objective and overview of the review process

The overall aim of the technical review is to assess the work carried out, including methodology and conclusions, as reported in the CHAP Final Report on Phthalates and Phthalate Alternatives. The final product of this review will be a written report that consists of a brief executive summary based on the key findings of each reviewer (to be drafted by ToxStrategies, Inc.) with the comments as received from each independent reviewer attached.

Each reviewer's task is to perform an independent expert review of a specified section(s) corresponding to their subject matter area(s) of expertise (other sections should not be reviewed unless necessary to review the assigned section and related conclusions). It is expected that the expert will conduct a thorough technical review based on all pertinent information (including all data evaluated by the CHAP) and use the weight-of-evidence to provide conclusions on the designated subject area(s). Upon execution of a subcontractor agreement with ToxStrategies, Inc., the reviewer should prepare and provide written comments to ToxStrategies, Inc. no later than August 31, 2014. These comments will remain unaltered and will be attached directly to an overall executive summary as described above. For any logistical issues during the review process, each reviewer is expected to follow the terms of their respective contract with ToxStrategies, Inc. (as a subcontract to ACC).

2. Preparation of written comments

The reviewer is asked follow these general guidelines when drafting written comments:

- Review all sections of the CHAP Final Report and the Peer Review of the Draft Report specific to your topic area(s) as specified in the Scope section of the Consulting Agreement with ToxStrategies, Inc.
- Provide an independent discussion and opinion of your assessment of:
    - the evaluation of available data for your topic area(s), and
    - whether or not the data for your topic area(s) support the risk assessment, overall conclusions and recommendations of the CHAP Report (if applicable).
- Include discussion on both positive and negative aspects of the analyses related to your topic area(s) in the CHAP Report, as well as recommendations on how to improve the evaluation of your topic(s), if warranted.
- Summarize the conclusions of your assessment, and in doing so, highlight 2-3 key findings.
- Include citations and a reference list as support for your assessment where relevant.
- Use the standard terminology/abbreviations/acronyms listed in the CHAP Final Report.

Submission of written comments

The reviewer will provide their written comments electronically as PDF document to ToxStrategies, Inc. by the designated deadline at the contact information provided below:

Rayetta G. Henderson, Ph.D.
Phone: (919) 797-9938
Email: rhenderson@toxstrategies.com

Appendix B

Expert Peer Reviewer Comments

APPLIED PHARMACOLOGY AND TOXICOLOGY, INC.

Consulting & Research Services

Independent Technical Review of Cumulative Risk Approach, Methods, and Recommendations In:

July, 2014 Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives

Submitted September 3, 2014, by

Christopher J. Borgert, PhD
Applied Pharmacology and Toxicology, Inc.
2250 NW 24th Avenue
Gainesville, Florida 32605

Christopher J. Borgert, Ph.D.
President & Principal Scientist

Coordinated by ToxStrategies, Inc., Raleigh, NC
Sponsored and Funded by American Chemistry Council, Washington DC

Summary

The Report to the U.S. Consumer Product Safety Commission by the CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES, dated July 2014, suffers a number of scientific deficiencies that limit its utility for evaluating the safety of consumer products. These deficiencies, and potential remedies for them, are summarized below and detailed in the review and cited literature that follows. In summary:

The CHAP report failed to test logical extensions of its cumulative risk theory, methodology and conclusions, and thus failed to recognize obvious inconsistencies with human experience and clinical evidence.

The CHAP report failed to account for model uncertainties in extrapolating chemical mixture effects observed at high doses in animal studies to the lower doses potentially received by humans; consequently, the CHAP overstates the accuracy of its cumulative risk methods and conclusions.

The CHAP report failed to compare human versus rodent sensitivity to antiandrogenic effects of chemicals, and as a consequence, appears to have grossly overestimated chemical potencies in assessing potential risks to humans from cumulative exposures to phthalates, phthalate alternatives, and other potential antiandrogens.

The CHAP report failed to consider published literature at odds with its selected cumulative risk theory and methodology, thereby undermining the scientific credibility and reliability of its cumulative risk predictions and recommendations based on them.

Deficiencies in the CHAP report could be remedied by adopting reasonable limitations of potency and dose in applying its cumulative risk assumptions and methods, and reforming its recommendations accordingly.

Introduction

In order to focus this review of cumulative risk methods and conclusions on issues of greatest importance in the CHAP report, it first documents that the CHAP's recommendations explicitly rely on the assumption of cumulative risks (Section 1). It then tests whether logical extensions of the cumulative risk theory, approach, and methods used in the CHAP report produce predictions that are consistent with human clinical observations and experience (Section 2). Consistency implies that the theory may be correct, whereas inconsistency implies that the theory is either fundamentally unsound or requires revision. To understand why the CHAP's theory and methods are inconsistent with observations that it should explain, an evaluation of the CHAP's assessment theory, methodology, and underlying assumptions is then outlined (Section 3), and a potential remedy is suggested (Section 4).

1. Cumulative Risks Are Cited as Rationale for Several of the CHAP's Recommendations

5.3.2.5 Recommendation to CPSC regarding children's toys and child care articles

The CHAP recommends that the interim ban on the use of DINP in children's toys and child care articles at levels greater than 0.1% be made permanent. This recommendation is made because DINP does induce antiandrogenic effects in animals, although at levels below that for other active phthalates, and therefore can contribute to the cumulative risk from other antiandrogenic phthalates. [emphasis added]

5.4.3.5 Recommendation to CPSC regarding children's toys and child care articles

Current exposures to DIBP alone do not indicate a high level of concern. DIBP is not widely used in toys and child care articles. However, CPSC has recently detected DIBP in some children's toys. Furthermore, the toxicological profile of DIBP is very similar to that of DBP, and DIBP exposure contributes to the cumulative risk from other antiandrogenic phthalates. The CHAP recommends that DIBP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 %. [emphasis added]

5.3.4.5 Recommendation to CPSC regarding children's toys and child care articles

The CHAP recommends that DPENP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1%. The toxicological profile of DPENP is very similar to that of the other antiandrogenic phthalates, and DPENP exposure contributes to the cumulative risk. [emphasis added]

5.3.5.5 Recommendation to CPSC regarding children's toys and child care articles

The CHAP recommends that DHEXP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1%. The toxicological profile of DHEXP is very similar to that of the other antiandrogenic phthalates, and DHEXP exposure contributes to the cumulative risk. [emphasis added]

5.3.6.5 Recommendation to CPSC regarding children's toys and child care articles

The CHAP recommends that DCHP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1%. The toxicological profile of DCHP is very similar to that of the other antiandrogenic phthalates, and DCHP exposure contributes to the cumulative risk. [emphasis added]

2. Testing the CHAP's Cumulative Risk Theory

The CHAP's cumulative risk approach and theory is based on two premises: 1) antiandrogenic phthalates produce effects in humans (the so-called "testicular dysgenesis syndrome" (TDS)), purported to be similar to what has been labeled "phthalate syndrome" in rats, and 2) each antiandrogenic chemical to which humans are exposed contributes to the syndrome in proportion to its antiandrogenic potency and dose. Using a Hazard Index (HI) approach to sum effects of exposure to multiple chemicals and No Observable Adverse Effect Levels (NOAELs) based on rat studies, the CHAP concluded that 10% of pregnant women and 5% of mothers and infants have phthalate levels that exceed an acceptable HI, i.e., have HIs greater than unity (CHAP Report, Executive Summary). The implication of this conclusion is that the offspring of these women are at risk for TDS, and therefore, that exposures to these phthalates should be prevented or reduced, consistent with the CHAP's recommendations.

The CHAP further contends that the risks posed by cumulative antiandrogen exposure are not limited to antiandrogenic phthalates, and that the HI is increased when exposure to other antiandrogens is considered:

> *The CPSIA requires the CHAP to consider the health risks from phthalates both in isolation and combination. To characterize the cumulative risks (risk in combination), the CHAP applied a hazard index approach for the antiandrogenic phthalates only: DBP, DIBP, BBP, DEHP, and DINP (Section 2.7). However, the CHAP also points out, that other antiandrogens can be added to the hazard index approach, increasing the HI (Appendix D).* [CHAP Report, Section 3.0, page 69]

2.1. Logical Extension of the CHAP's Cumulative Risk Theory and Assumptions

2.1.1. Risks from Thousands of Antiandrogens

Using a linear extrapolation of data from Kortenkamp and Faust (2010), the CHAP estimated that up to 21% of pregnant women have hazard indices that exceed the acceptable level (unity) based on an assessment of just 15 antiandrogenic chemicals. Hence, according to the CHAP's estimate, the addition of only a few antiandrogenic chemicals to the assessment increases, by approximately 10%, the proportion of pregnant women whose infants are exposed to unacceptable levels of antiandrogens and thus suffer risks of TDS. By logical extension of the CHAP's cumulative risk theory, the true proportion of infants at risk for TDS could only be estimated by a cumulative assessment of all antiandrogens to which humans are exposed. Not only would such an estimate provide a more complete perspective on infant risks of TDS according to the CHAP's methodology, it would also provide a check on the reasonableness of the CHAP's theory and methodology for assessing cumulative risks. Although the CHAP neglected to conduct such an assessment, the information necessary to do so is conveniently found in the same publication cited by the CHAP for the cumulative assessment of 15 antiandrogens:

> *More than 100 chemicals have been identified as antiandrogens, including certain phthalates, widely used as plasticizers, pesticides and various other chemicals found in food and consumer products. With estimates that 8% of all known chemicals show antiandrogenicity (Vinggaard et al., 2008), the number of chemicals on*

the EU market alone, that may fall into this category, runs into several thousands.
[Kortenkamp and Faust, 2010; emphasis added]

Using the quoted figures and a few extremely conservative assumptions based on the cited information, the reasonableness of the CHAPs cumulative risk theory and conclusions can be tested. Assuming that even an additional 1500 chemicals on the market in the EU are actually antiandrogenic, and assuming that each of those chemicals produces a hazard quotient of only 0.001 (1 E-03), which is the lowest mean value for the chemicals shown in Figure D-9 of the Appendix D (CHAP Report), then the true HI for every pregnant woman in the EU would exceed unity. If the number of antiandrogens to which humans are exposed is actually several thousands, as stated by Kortenkamp and Faust (2010), then a significant proportion of infants would be exposed to hundreds of times or more the acceptable level (HI >>> 1.0). This logical extension of the CHAP's cumulative risk theory suggests that every male child born suffers an unacceptable but unquantified risk of TDS.

2.1.2. Risks from Widely Used Medications

The ramifications of the CHAP's cumulative risk theory and approach is even more dramatic when exposure to potentially antiandrogenic medications is considered. Non-steroidal anti-inflammatory drugs (NSAIDs) are available over-the-counter and by prescription, are taken by more than half of pregnant women worldwide, and are present in the environment secondary to human consumption. These drugs are reported to be antiandrogenic and to reduce testosterone levels in both rat and human fetal testes (Albert et al. 2013; Kristensen et al. 2012) and are associated with increases in male reproductive tract disorders in humans (Kristensen et al. 2011). These reported effects, widespread exposures, and potentially high doses were apparently not considered by the CHAP, but if one accepts the CHAP's cumulative risk theory and methodology, which produces unacceptable exposures for up to 20% of women based on only a fraction of one percent of the total number of antiandrogens alleged to be in commercial use, and which did not consider NSAIDs, it is surprising that a single human male has been born in the last decade without reproductive tract anomalies. Yet, the incidence of hypospadias and cryptorchidism are below 10% and 1% respectively (Toppari et al. 2010), and the etiology so uncertain and confounders so extensive that the veracity of TDS itself has been questioned (Thorup et al. 2010):

> *It has been hypothesized that poor semen quality, testis cancer, undescended testis, and hypospadias are symptoms of one underlying entity - the so-called TDS - leading to increasing male fertility impairment. ... These data point to the complexity of the pathogenic and epidemiologic features of each component and the difficulties in ascribing them to a single unifying process, such as TDS, particularly when so little is known of the actual mechanisms of the disease.*

Clearly, logical extensions of the CHAP's cumulative risk theory and methodology cannot account for, and in fact, seem to contradict human data and clinical experience. Fortunately, the reasons for this disparity are evident and easily resolved, as explained in Sections 3 and 4.

3. Potential Reasons for Failure of the CHAP's Cumulative Risk Theory, Methods and Conclusions to Approximate Human Clinical Experience.

3.1. The CHAP Report Inappropriately Assumes Methodological Accuracy

First, it is necessary to understand that the CHAP report overstates the accuracy and general applicability of the dose addition model upon which the HI method is based.

> *"...mixture effects of these substances can be predicted quite accurately when the potency of individual phthalates in the mixture is known.* [CHAP Report, page 26, Section 2.3.4]

To be clear, the basis for such statements is constrained to rodent studies, as no test of phthalate mixtures has been conducted in humans. From rodent data, the CHAP Report and authors of a risk assessment for antiandrogenic phthalate mixtures concluded that the dose addition model of combined action provided a better fit to the data than the independent action model, and further justified the choice of dose addition based on conservatism (Kortenkamp and Faust, 2010). However, even within those rodent experiments, the dose-addition model, upon which the HI methods relies, produces measurable variance and model uncertainty. Isobolograms constructed from published figures for one of the underlying data sets on antiandrogenic effects of phthalates reveals at least two-fold variance within the dose-addition model (Figure 3 in Borgert et al. 2012, attached as Appendix 1). This finding of at least two-fold variance is a best-case estimate because the analysis assumes that the data perfectly fit the model applied by the researchers who conducted the rodent studies. The true variance would be unique to each study, but is likely to be greater than this best-case estimate of two-fold. A precise analysis of the underlying variance in mixture prediction models for antiandrogenic effects of phthalates would require reanalysis of the raw data from each of the underlying studies.[1]

The importance of variance in dose-additive predictions cannot be understood from reanalysis of the rodent data alone because the rodent experiments were conducted at doses that exceed human exposures by orders of magnitude. Even a two-fold variance in the dose-additive prediction would expand greatly when extrapolated from the high doses used in the mixture experiments to the much lower doses potentially received by humans. Predictions based on the independent action model would have a similar variance, and would also expand as predictions are extrapolated from high to low doses. Consequently, the ability to determine which model best fits the data is lost as predictions are extrapolated across large dose ranges. A graphic depiction of this concept is shown below in Figure 1. Other issues further confound the choice of models based on particular mixture studies with phthalates,[2] but the failure to account for the expansion of uncertainties in mixture model predictions across dose ranges applies generally to the CHAP's methodology.

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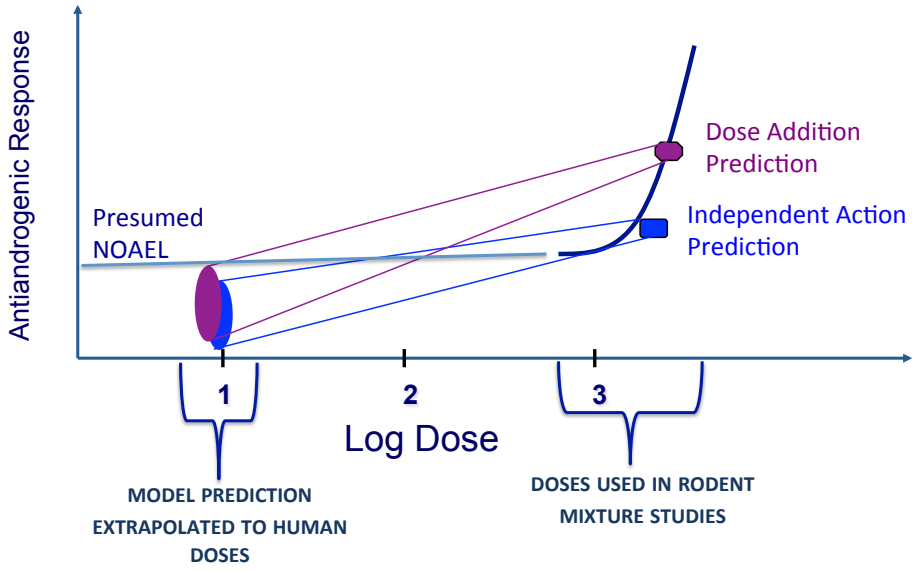
[1] Raw data for various published mixture experiments on phthalates were requested from A. Kortenkamp and from L.E. Gray prior to publication of Borgert et al. 2012, but no data have been provided.

[2] For example, Borgert et al. (2012) explain how the dichotomous categorization of mild fetal malformations into the "no malformation" category in some experiments skewed the analysis toward rejecting independent action.

Figure 1. Extrapolation of uncertainty in mixture model predictions



3.2. The CHAP Report Mischaracterizes Human Sensitivity to Antiandrogens

The HI methodology used by the CHAP relies on human Reference Doses (RfDs) for phthalates and other putative antiandrogens, which are considered to be acceptable human doses of these chemicals. The RfDs used in the CHAP report are derived by reducing No Observable Adverse Effect Levels (NOAELs) determined in rodent studies by factors of 100 to 500 to account for uncertainties regarding human versus rodent responses to a chemical arising from both pharmacokinetic and pharmacodynamic processes. In effect, the RfD values used by the CHAP assume humans may be hundreds of times more sensitive than rodents to antiandrogenic chemicals. The methodology is arguably justified when little is known about the relative sensitivity of humans versus rodents, but is not justified when human versus rodent sensitivity can be compared. Here, the CHAP failed to avail itself of compelling information indicating that the developing reproductive tract of human males is less sensitive, not more sensitive, to malformations and other anomalies produced via various antiandrogenic mechanisms.

A comparison of the doses at which human males versus rodents are affected by two chemicals with known antiandrogenic actions has been published (Borgert et al. 2012). One chemical, finasteride, is a human pharmaceutical and the other, diethylstilbestrol (DES), was used pharmaceutically in millions of pregnant women during the 1950s through 1970s. Finasteride inhibits 5α-reductase, an enzyme common to rodents and humans that converts testosterone to the more potent androgen dihydrotestosterone. DES interrupts the same pathways in Leydig cells thought to be responsible for the antiandrogenic effects of certain antiandrogenic phthalates (see Borgert et al. 2012 for a summary), produces effects similar to the phthalate syndrome in rats, and at very high doses, produces a pattern of malformations in the developing reproductive tract strikingly similar to the recently-proffered TDS. In fact, DES

has been called the prototype inducer of TDS. As shown in figures 2 and 3, excerpted from Borgert et al. (2012) (also attached as Appendix 1), humans are less sensitive than rats to the antiandrogenic actions of these well-known drugs.

Figure 2: DES potency comparison for male reproductive tract parameters. Human clinical data (ovals, circles); Rat experimental data (triangles). Asterisks denote no-effect doses. Plus (+) denotes in utero administration. [see full legend for Figure 4 in Borgert et al. 2012]

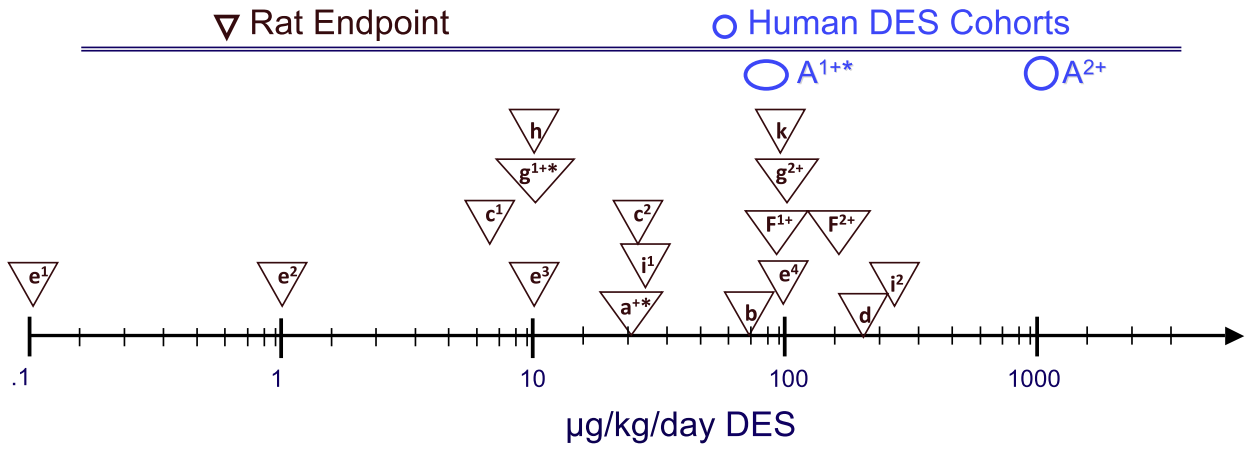
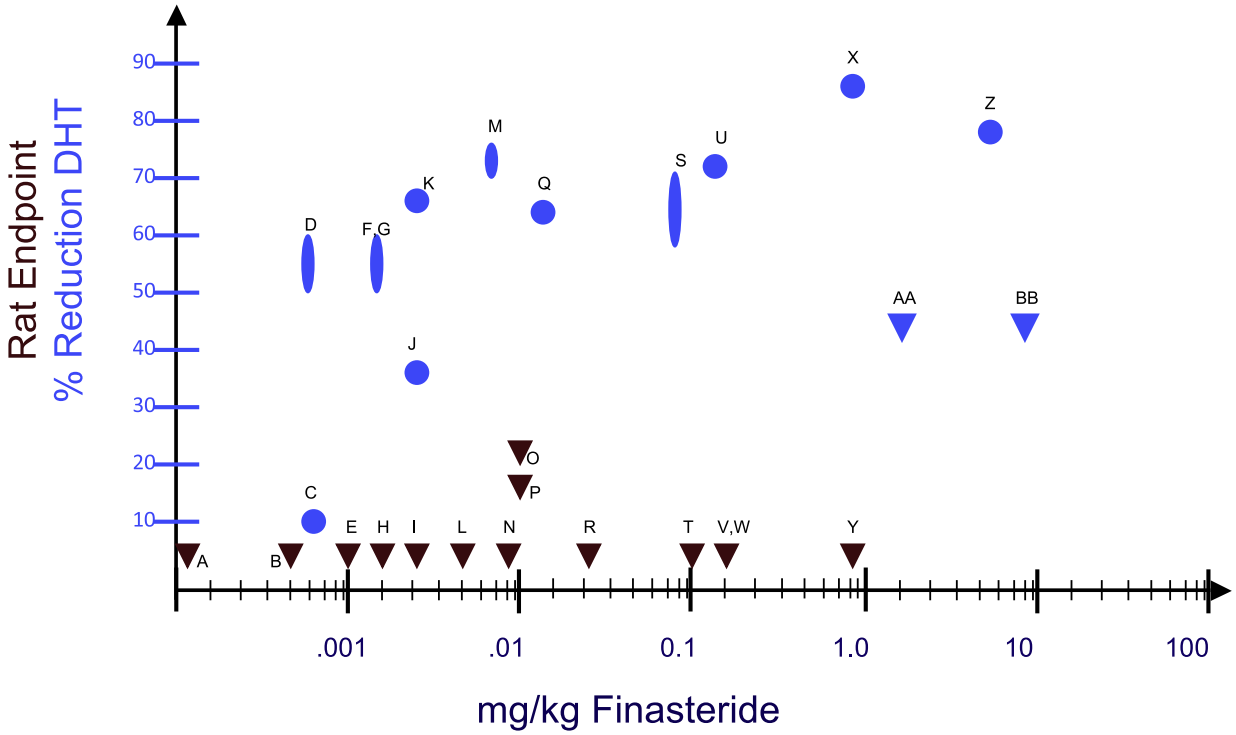


Figure 3: Finasteride potency comparison for human clinical suppression of DHT versus rat endpoints. Human clinical data (ovals, circles); Rat experimental data (triangles).



3.3. The CHAP Report Fails to Acknowledge Limitations of the HI Methodology

The HI methodology provides an algorithm for transforming points of departure from dose-response data for single chemicals administered in animal studies - whether NOAELs or benchmark doses - into estimates of safe levels for human exposure to multiple chemicals. Although the methodology has been widely used, it is not "tried and tested," because its' predictive value for human effects has never been evaluated. The HI methodology is mathematically simple and easy to apply, providing a means of ensuring safe levels of exposure at hazardous waste sites and in occupational environments where risk considerations are narrowly constrained. However, the HI methodology is not routinely used in more complex areas such as in medical pharmacology. This is not surprising because its simplicity imparts a number of inherent inaccuracies that would skew an analysis of risk versus therapeutic value toward artifactual risks.

Perhaps the most excessive simplification inherent in the HI methodology is its implicit assumption that any dose of a chemical - no matter how low the potency of the chemical and no matter how small the dose - will contribute to the manifestation of an effect in proportion to the chemical's dose and potency. In essence, this assumption eliminates any possibility of a threshold below which a chemical exposure is considered inconsequential because according to the HI methodology, every chemical's fractional potential is added to that of every other chemical capable of producing the same or similar effect, even if the effect can only be produced with high doses. Although simple and useful as a crude screening method for hazard waste sites and occupational environments involving small numbers of chemicals, and accepting of excessive conservatism, the assumptions inherent in the HI method nonetheless violate basic tenets of endocrine pharmacology and physiology developed over decades of thorough laboratory and clinical research. The certainty of a potency threshold, below which chemicals are incapable of contributing to a biological effect - whether alone or in combination with other chemicals - is axiomatic to methods that are, in fact, "tried and tested" in the field of drug development for humans. Such potency thresholds exist for all effects that arise from molecularly-specific activity, including interactions with receptors, enzymes, transporters, transcription factors, etc. An explanation of these principles is beyond the scope of this review, but has been succinctly explained in a publication released a little more than a year prior to release of the CHAP report (Borgert et al. 2013; attached as Appendix 2).[3] Together with the aforementioned deficiencies, the failure of the CHAP report to acknowledge a limitation on potency and dose below which cumulative effects would not occur accounts for failure of the CHAP's cumulative risk theory and methods to explain human clinical data and experience.

3.4. The CHAP Report Failed to Cite, and Apparently Failed to Consider, Pertinent Literature Contradictory to its Methods and Assumptions.

The CHAP report conspicuously avoids citing peer-reviewed scientific articles that contradict or call into question its methods, underlying assumptions, and conclusions. Although a comprehensive evaluation of the omitted literature is beyond the scope of this review, it is noteworthy that none of the arti-

[3] The title of the paper and its keywords render it eminently discoverable by literature searches for articles on endocrine effects of chemicals, including phthalates.

cles cited in this review were cited by the CHAP, even though they are pertinent to the scope of the CHAPs charge. These omissions occurred despite the fact that at least one of the articles cited in this review (Borgert et al. 2012) was brought to the attention of the CHAP in early 2012, and a few months later was recognized by the Society of Toxicology's Risk Assessment Specialty Section as ranking among the top publications of 2012 demonstrating an application of risk assessment.[4] Failure to cite pertinent literature, particularly literature that contravenes its underlying premises and resulting conclusions, undermines the scientific integrity and credibility of the CHAP's report.

4. Resolution of Deficiencies in the CHAP Report

The various failures outlined in sections 2 and 3 of this review render the CHAP's recommendations of little value for rationally considering use of consumer products in the context of other risks. The arbitrary distortion of risks, as occurs when methods such as the HI methodology are applied indiscriminately, obscures objective comparisons and thus makes impossible any scientifically justifiable choice regarding the market acceptability of consumer products. Nonetheless, the deficiencies in the CHAP's methodology and report are easily remedied without a whole-sale reassessment. Application of the CHAP's HI and cumulative risk methodology, and recommendations based on it, could be limited to conditions consistent with human clinical data and experience. In practical terms, this would require setting a potency threshold below which the HI approach should not be applied. Such a constraint would take into account the tremendous uncertainty implicit in the derivations of RfD's for antiandrogenic effects, given that malformations of the human male reproductive tract require larger, not smaller, doses of antiandrogenic pharmaceuticals than in rodents. Furthermore, limiting application of the CHAP's cumulative risk methodology in this fashion would acknowledge that conclusions about which model of combined action best fits the data cannot be reliably extrapolated over large dose ranges, and that indiscriminate use of the dose addition model leads to predictions inconsistent with human clinical data and experience. A limitation that would apply the CHAP's cumulative assessment theory and methodology only to chemicals with antiandrogenic potency 0.1 times or greater than that of DES, or for less potent chemicals to doses greater than 0.2 times the respective rat NOAEL, would resolve the problems explained in this review, yet would seem sufficiently conservative to assure safety. These appropriate and necessary limitations preclude fully accepting several of the CHAP's recommendations to restrict certain phthalates in consumer products based on cumulative risk assumptions, but are necessary to reconcile the CHAP report and recommendations with established pharmacological theory, data, and clinical experience.

[4] https://www.toxicology.org/isot/ss/riskassess/pastwinners.asp

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APPENDIX 1

Borgert, C.J., Sargent, E.V., Casella, G., Dietrich, D.R., McCarty, L.S., and Golden, R.J. (2012). The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. Regul Toxicol Pharmacol 62, 313-328.

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The human relevant potency threshold: Reducing uncertainty by human calibration of cumulative risk assessments

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ABSTRACT

The 2008 National Research Council report "Phthalates and Cumulative Risk Assessment: Tasks Ahead," rejected the underlying premises of TEQ-like approaches – e.g., chemicals are true congeners; are metabolized and detoxified similarly; produce the same biological effects by the same mode of action; exhibit parallel dose response curves – instead asserting that cumulative risk assessment should apply dose addition (DA) to all chemicals that produce "common adverse outcomes" (CAOS). Published mixtures data and a human health risk assessment for phthalates and anti-androgens were evaluated to determine how firmly the DA–CAOS concept is supported and with what level of statistical certainty the results may be extrapolated to lower doses in humans. Underlying assumptions of the DA–CAOS concept were tested for accuracy and consistency against data for two human pharmaceuticals and its logical predictions were compared to human clinical and epidemiological experience. Those analyses revealed that DA–CAOS is scientifically untenable. Therefore, an alternative approach was developed – the Human-Relevant Potency-Threshold (HRPT) – that appears to fit the data better and avoids the contradictions inherent in the DA–CAOS concept. The proposed approach recommends application of independent action for phthalates and other chemicals with potential anti-androgenic properties at current human exposure levels.

1. Background and introduction

The USEPA (EPA)[1] has established the use of relative potency approaches, i.e., toxic equivalent (TEQ)-like approaches, for mixtures risk assessment. TEQ-like approaches assume that if the following four key pharmacological or toxicological premises are met, (1) chemicals are true congeners, (2) are metabolized and detoxified by the same biological processes, (3) produce the same spectrum of biological effects by the same mode of action, and (4) exhibit parallel dose response curves for the biological effect being modeled (Safe, 1990), then one may assume that in mixtures, those chemicals will behave according to dose addition (DA) for specific toxic effects. The DA assumption treats chemicals as if they all behave as dilutions of a single prototype chemical scaled according to their potencies relative to the prototype. Thus, risks of exposure to mixtures of such chemicals are assumed to be equivalent to the risk of exposure to the total equivalent dose of the prototype chemical. Risk assessment practices at EPA and other agencies have traditionally assumed independent action (IA) for mixtures of chemicals thought to exert effects by dissimilar modes of action (ATSDR, 2001a,2001b; USEPA, 1986, 1989, 1999, 2000).

The difference between DA and IA has important practical implications for cumulative risk assessment that can be illustrated by a simple example. Consider a mixture of three nephrotoxic chemicals, each present at one-half its threshold concentration for producing tubular acidosis: IA would predict a sub-threshold effect for the mixture (i.e., 0 + 0 + 0 = 0) whereas DA would predict measurable tubular acidosis (0.5 + 0.5 + 0.5 = 1.5) (Borgert et al., 2005). Thus, IA would predict that doses of chemicals far below the observable response range would not increase the effect of other chemicals present at concentrations near or within the

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[1] *Abbreviations:* CAOS, common adverse outcomes; DA, dose addition; DES, diethylstilbestrol; DHT, dihydrotestosterone; EPA, Environmental Protection Agency; IA, independent action; TEQ, toxic equivalence; TDS, testicular dysgenesis syndrome.

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observable response range, whereas DA would predict an increased response.

The main obstacle to applying DA broadly for diverse groups of chemicals has been the required demonstration that the underlying TEQ premises are met (Safe, 1998). The latter has prompted argumentation that the TEQ concept is too restrictive for cumulative risk assessment. Indeed, the definition of DA does not include TEQ requirements, as DA is a purely quantitative model of combined action that does not require specific chemical, toxicological or pharmacological properties and requires only that the underlying dose response relationship is quantified according to a common biological metric. However, TEQ premises (Table 1) have been included explicitly to increase the reliability of extrapolating the DA model to dose ranges, chemical ratios, and species that have not been tested empirically (Safe, 1998). Hence, requiring similarity of mode of action and biological effects serves to reduce the potential for differences in the molecular, cellular and physiological response characteristics of different mixtures components from producing non-dose-additive combined action. Consequently, inclusion criteria (Table 1) reduce the potential for pharmacokinetic differences to alter DA combined action expected at molecular, cellular and physiologic levels based on similar modes of action and toxic effects, and increase confidence in treating a mixture of chemicals as if it were the total equivalent dose of the prototype chemical alone. In contrast, chemicals with non-parallel dose response curves have different relative potencies at different doses and thus, cannot reliably be treated as simple dilutions of a prototype chemical across all doses and ratios (Fig. 1).

One prominent example of how rejecting TEQ premises may lead to misinterpretation of data and over-interpretation of risk is the report "Phthalates and Cumulative Risk Assessment: Tasks Ahead" by the National Research Council (NRC, 2008). The report asserts that based on the available data for phthalates and other chemicals that result in androgen deficiency by different modes of action (anti-androgens), cumulative risk assessment should be conducted by applying DA to all chemicals that produce "common adverse outcomes" (CAOS) rather than only to chemicals satisfying TEQ criteria. Further, the report recommends DA to the exclusion of other models of combined action, such as IA, irrespective of whether chemicals exhibit parallel dose response curves for CAOS, and places no other restrictions on the application of DA to CAOS (DA–CAOS), including potency, exposure level, or mechanistic assumptions regarding the anti-androgenic effects.

Some phthalates and other chemicals with potential anti-androgenic properties have been found to produce malformations of the developing male reproductive tract in rats, an observation to which some researchers have attached the collective name "phthalate syndrome" (Foster, 2005). The mode of action for these

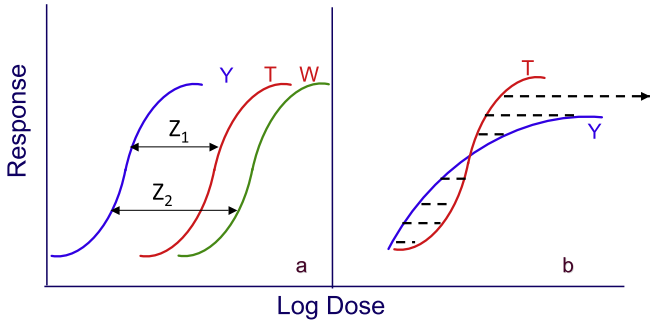

Fig. 1. Extrapolating DA requires parallel dose–response curves. In panel a, dose response curves for chemicals Y, W and T are parallel and there is a constant proportionality between the curves, illustrated by the arrows, reflecting the fact that the potency differences are constant at every response level. (Y–T; Y–W) thus give relative potency factors Z_1 and Z_2 for those chemicals, which enable prediction of the dose-additive response for untested dose combinations by transforming any dose of T or W to its equivalent dose of Y. DA Response [Y,T,W] = Response [Y + (T-Z_1) + (W-Z_2)]. These relationships hold for any number of chemicals with parallel dose response curves. In panel b, dose response curves for chemicals Y and T are not parallel, resulting in a different proportionality between the curves at every response level (dashed lines), reflecting a different relative potency Y-T at every response level. Thus, there is no uniform function that will accurately transform T into an equivalent dose of Y, and so predicting DA Response [Y,T] becomes highly uncertain for doses not tested empirically. Uncertainties expand with increasing numbers of chemicals with non-parallel dose response character.

effects is believed to involve an impairment of fetal Leydig and Sertoli cell function, leading to androgen deficiency in the developing reproductive tract of male rats (David, 2006). Similar malformations have been reported in other species, however species differences in response to phthalates are apparent (Gaido et al., 2007; Johnson et al., 2011; Lambrot et al., 2009; Hallmark et al., 2007). Based on certain similarities between these malformations in rodents and a so-called testicular dysgenesis syndrome (TDS) in humans (Skakkebaek et al., 2001), some have speculated that TDS may be caused by exposure to anti-androgenic chemicals (Skakkebaek et al., 2001; Foster, 2005).

Mixtures studies (Table 2) conducted by two research groups, one based at universities in Europe (Christiansen et al., 2008, 2009; Hass et al., 2007; Metzdorff et al., 2007) and the other at EPA (Hotchkiss et al., 2004; Howdeshell et al., 2007, 2008b; Rider et al., 2008) have reported DA combined effects on the developing male reproductive tract of rats for anti-androgens that differ in molecular structure as well as in their mechanism of action and pattern of anti-androgenic effects. Based on those findings, it has been reasoned that limiting the application of DA only to chemicals that fit TEQ criteria may be insufficiently inclusive and thus,

Table 1
Chemical similarity criteria for applying DA in cumulative (mixtures) risk assessments.

	ATSDR mixture risk assessment[a]	ILSI cumulative risk criteria[b]	EPA mixture risk assessment[c]	EPA TEQ approach[d]	DA–CAOS (NRC)[e]
Organ system (CAOS)					X
Target organ	X	X	X	X	
Molecular target	X	X	X	X	
Cellular target			X	X	
Toxic intermediates		X		X	
Pharmacokinetics				X	
Detoxification pathways				X	
Parallel dose–response curves			X	X	
Chemical structure				X	

[a] USDHHS (2001).
[b] Mileson et al. (1998) and USEPA (1999).
[c] USEPA (2000).
[d] Safe (1998).
[e] NRC (2008).

Table 2
Mixture studies of anti-androgens in rats.

Study	Chemicals	Mixture design	Model type consistent with mixture data
Hass et al. (2007)[a]	Vinclozolin Flutamide Procymidone	1 ratio 5 doses	DA fit most data; did not test IA
Metzdorff et al. (2007)[a]	Vinclozolin Flutamide Procymidone	1 ratio 5 doses	DA fit the data; did not test IA
Christiansen et al. (2008)[a]	Vinclozolin Flutamide Procymidone	1 ratio 2 doses	Did not formally test a model; concluded that results exceed IA
Christiansen et al. (2009)[a]	Diethylhexyl phthalate Vinclozolin Prochloraz Finasteride	1 ratio 3 doses	DA and IA equally fit most data; synergism observed for external malformations
Hotchkiss et al. (2004)[b]	Benzylbutyl phthalate Linuron	1 ratio 1 dose	Did not formally test a model
Howdeshell et al. (2007)[b]	Di(*n*)butyl phthalate Diethylhexyl phthalate	1 ratio 1 dose	DA and IA fit some endpoints; DA fit better than IA for most endpoints
Howdeshell et al. (2008b)[b]	Butyl benzyl phthalate Diethylhexyl phthalate Di(*n*)butyl phthalate Diisobutyl phthalate Dipentyl phthalate	1 ratio 7 doses	DA fit; Did not test IA
Rider et al. (2008)[b]	Vinclozolin Procymidone Prochloraz Linuron Butyl benzyl phthalate Diethylhexyl phthalate Di(*n*)butyl phthalate	1 ratio 4 doses	DA-based models fit data; IA did not fit data
Benson (2009)[b]	Butyl benzyl phthalate Diethylhexyl phthalate Di(*n*)butyl phthalate Diisobutyl phthalate Diisononyl phthalate Dipentyl phthalate	Risk Assessment based on common mode of action and adverse outcome	Assumed Hazard Index Approach, consistent with DA Estimated mean, upper 95% CI and maximum human exposures compared to RfDs 100-fold lower than observed mixture effects in rats (1000-fold lower for diisononyl phthalate) Concluded that exposures are within acceptable risk levels
Kortenkamp and Faust (2010)[a]	Butyl benzyl phthalate Diethylhexyl phthalate Di(*n*)butyl phthalate Diisobutyl phthalate Diisononyl phthalate Vinclozolin Prochloraz Procymidone Linuron Fenitrothion p,p′-DDE Brominated diphenyl ether 99 Bisphenol A Butyl paraben Propyl paraben	Risk Assessment based on DA–CAOS concept	Assumed Hazard Index Approach, consistent with DA Estimated mean and upper 95% CI of human exposures compared to RfDs 200–500-fold lower than observed mixture effects in rats Concluded that 95% UCI exceeds acceptable risk levels

[a] Studies conducted by the researchers at European universities.
[b] Studies conducted by the researchers at EPA.

produce insufficiently conservative human health risk assessments that fail to protect from TDS (NRC, 2008). Subsequently, two human health risk assessments have been conducted using NRC's assumptions, both of which employed a hazard index calculation to estimate risks (Table 2). One considered exposure to a mixture of six phthalate esters (Benson, 2009), while the other utilized the full DA–CAOS concept, considering exposure to a mixture of 15 potential anti-androgens spanning a range of chemical structures and modes of action including phthalate esters, pesticides, and industrial chemicals (Kortenkamp and Faust, 2010).

2. Analysis of mixtures studies, risk assessment of anti-androgens, and predictions of DA–CAOS

The DA–CAOS concept obviously contravenes well-established pharmacological principles for defining relative potency of adverse outcomes. In view of this, an in-depth analysis of the empirical and theoretical foundations of the DA–CAOS concept and the respective practical consequences of its use was carried out. As well, potency assumptions made in risk assessments based on the DA–CAOS concept were evaluated. The following analyses were conducted:

(i) An evaluation of the extent to which the study designs employed to test mixtures (Table 2) can support the extrapolation of DA versus IA to lower, untested doses and chemical ratios.
(ii) A statistical analysis of variability within the published data for one endpoint evaluated in the mixtures studies as an example to illustrate the uncertainty that might evolve from extrapolation of the DA–CAOS assumption to lower, untested doses and chemical ratios.
(iii) A consideration of whether the DA–CAOS concept can be reconciled with the pharmacological basis underlying relative potency approaches.
(iv) an evaluation of the logical extensions of the DA–CAOS concept and resulting risk assessment for consistency with human clinical and epidemiological observations, and;

(v) A comparison of humans versus rat sensitivity to chemicals with anti-androgenic properties to test the premise and key default assumption of the risk assessment based on DA–CAOS (Kortenkamp and Faust, 2010), that the developing male reproductive tract of humans responds to chemicals at doses two orders of magnitude lower than those required to affect rats.

As shown below, these five analyses demonstrated that the DA–CAOS concept and the risk assessments conducted per its premises are scientifically untenable. Consequently, an alternative approach – the Human-Relevant Potency-Threshold (HRPT) approach – was developed to better fit the data and to avoid the contradictions that arise in using the DA–CAOS concept.

2.1. Study designs

Five criteria for evaluating interaction studies used in risk assessment have been defined (Borgert et al., 2001) and were used to assess the mixtures studies listed in Table 2. Criterion 1 addresses the fact that the better defined the dose response parameters for the individual chemicals, the more reliably distinctions can be drawn between different combined effect models. Criterion 2 requires that non-interaction model(s) be explicitly defined since inferences of greater-than-additive (synergy) or less-than-additive (antagonism) are typically made on the basis of statistically significant departures from a defined non-interaction model.[2] Usually, DA and IA are the competing models of non-interaction tested. Criterion 3 requires testing an adequate number of combinations across a sufficient dose range to meet the goals of the study. The latter is important as combination effects can vary with the concentrations and with the ratios of mixture constituents. Criterion 4 requires formal statistical tests to distinguish the combined response from the response predicted by the non-interaction model. Prerequisite for a robust statistical analysis is to account for biological variation and experimental error. Finally, Criterion 5 requires the evaluation of interactions at a relevant level(s) of biological organization. Combination effects measured at molecular, cellular and higher-order physiological endpoints may be necessary to gain an unambiguous understanding of the biological response to a mixture.

2.1.1. Study designs: Dose ranges and ratios

Conducting experiments in whole animals or human subjects often prevents satisfying all five criteria (Price et al., 2002; Borgert et al., 2001) due to the difficulty of obtaining sufficient dose–response information. Those limitations affect the studies under consideration here (Table 2), as acknowledged by some of the authors (e.g., Hass et al., 2007). Nonetheless, greater conformity with the five criteria provides for more unequivocal data interpretation across the concentration ranges tested. In contrast, studies fulfilling fewer criteria or with less stringency must be interpreted with more caution, i.e., limiting the interpretation to the specific doses and ratios tested. Uncertainties are compounded when combination effects are extrapolated to doses and ratios not tested empirically.

The interpretations supportable from a mixture study are inherently dependent on the quality of dose–response data available for the individual mixture components, which should be tested across a concentration range and with a sufficient number and spacing of doses to reveal maxima, minima, points of inflection, and regions of linearity (Borgert et al., 2001). The mixtures studies (Table 2) used for the risk assessment of anti-androgens (Kortenkamp and Faust, 2010) varied widely in their characterization of dose response data for the individual chemicals. In some studies, as many as seven doses were tested while in other studies, dose response data from prior experiments and different rat strains were used as surrogates. In most instances, dose response models were used to curve-fit the data, and model parameters obtained from single chemical experiments were used to predict mixture effects.

All of the studies employed single ratios of chemicals to simulate mixture effects (Table 2). This design is often referred to as a fixed ray design (Cassee et al., 1998) and has advantages over experimental designs employing only a single concentration of the mixture components because it allows local interpretations beyond one data point. A fixed ray design may be the broadest study design achievable in live animals due to limitations on the manageable size and number of dose groups (Cassee et al., 1998; Price et al., 2002), but this feature should constrain the interpretations to the ratios tested and preclude extrapolation to untested ratios. Several of the studies chose individual constituent ratios predicted to yield an equal contribution from each component across the entire range tested, however, confidence in that prediction is unjustified unless all components have parallel dose response characteristics. It is highly questionable whether the slopes of the dose response data for male reproductive tract effects of the individual chemicals are sufficiently similar to support this assumption. Although DA assumptions and calculations can be made for chemicals with non-parallel dose response curves, the reliability of those calculations diminishes rapidly as they are extrapolated beyond the ratios and concentrations tested empirically (Fig. 1) (Cassee et al., 1998; Borgert et al., 2001; Price et al., 2002).

Although the mixtures studies (Table 2) all reported testing "low doses" of the mixture components administered to dams, this term must be understood in the context of the physiological system. The doses tested appear to be within an order of magnitude of the observable response range for physiologically relevant anti-androgenic effects. For example, Rider et al. (2008) reported that the mixture doses used in their study were below the observable response range for malformations of the developing male reproductive tract in rats, i.e., procymidone at a maternal dose of 7.5 mg/kg/day. Contrary to the latter no observable effect assumption, Metzdorff et al. (2007) reported that 5 mg/kg/day procymidone produced statistically significant changes in seminal vesicle weight, and 10 mg/kg/day produced changes in testis, ventral prostate, levator ani/bulbocavernosus muscle, and bulbourethral gland weights, thus suggesting that Rider et al. (2009) were testing mixtures containing doses of procymidone well within the observable effect range for anti-androgenic action. Further, although Rider et al. (2008) reported that vinclozolin was without statistically significant effects at 3.75 mg/kg/day, Metzdorff et al. (2007) reported that a slightly higher dose of 10 mg/kg/day vinclozolin produced statistically significant changes in epididymal, ventral prostate, and seminal vesicle weights. These examples demonstrate the substantial variability that exists in defining the observable response range, especially for endocrine-sensitive endpoints (Ashby, 2003). Because the comparison of no-interaction dose–response models for mixtures, i.e., DA versus IA, entirely depends on the precision of the no observable effect estimate, this latter precision must influence the confidence placed on the interpretations drawn from such data, as exemplified below.

Rider et al. (2008) also showed that individual phthalates (dibutyl phthalate and diethylhexyl phthalate) failed to increase the incidence of male reproductive tract malformations at maternal doses below 500 mg/kg/day,[3] but that in a mixture with the anti-

[2] Models that test directly for synergism have been devised (e.g., Barton et al., 1993; Laska et al., 1994) but have not gained wide acceptance.

[3] Ranges inferred from Fig. 1 of the cited paper.

androgenic pesticides vinclozolin, procymidone, prochloraz, and linuron, doses of 75 mg/kg/day of butyl benzyl phthalate, dibutyl phthalate and diethylhexyl phthalate contributed to an increased incidence of observable malformations.[4] This suggests that the combination of the three phthalates (75 mg/kg/day each, thus a total of 220 mg/kg/day) would provide for an effect greater than the no observable effect estimate demonstrated for 500 mg/kg/day of dibutyl phthalate or diethylhexyl phthalate. In a previous study by the same group, these three phthalates reduced fetal testosterone production at doses of 300 mg/kg/day individually and at doses of 60 mg/kg/day in combination with two other phthalates (Howdeshell et al., 2008b), suggesting that the three phthalates alone (butyl benzyl phthalate, dibutyl phthalate and diethylhexyl phthalate) would reduce fetal testosterone production when combined in a mixture at approximately 100 mg/kg/day each. Thus, although the doses of phthalates and other chemicals used in these mixtures were statistically below their individual no effect levels on male reproductive tract malformations in particular studies, they are nonetheless close to the dose range that produces a clear reduction in fetal testosterone individually and in mixtures. Slight differences in the experimental protocols, time of dosing, or rat strain could explain these differential responses. Regardless of the underlying reason, this comparison underscores how imprecise the distinctions might be regarding the no observable effect level for androgen sensitive tissues, and illustrates that the label "low dose" cannot be taken to mean a dose that is without a physiologically relevant anti-androgenic effect. To put the doses used in these rat studies into perspective with human-relevant exposures, the "high intake" level of vinclozolin and procymidone (9 μg/kg/day) and butyl benzyl phthalate (4 μg/kg/day), dibutyl phthalate (6 μg/kg/day), and diethylehexyl phthalate (3.6 μg/kg/day) estimated for the US population are roughly 3–4 orders of magnitude lower (Kortenkamp and Faust, 2010).

Despite limitations just described, the DA–CAOS concept was extended well below the dose range where DA was demonstrated (Kortenkamp and Faust, 2010; NRC, 2008). Fig. 2a illustrates the general study designs that have produced DA mixture effects from "no-effect" combinations of anti-androgenic chemicals with different modes of action. Fig. 2b illustrates how the DA–CAOS approach extrapolates the same studies depicted in Fig. 2a to far lower doses of the mixture components, which were not tested empirically. The conservatism introduced here goes well beyond extrapolating observed toxicity from high to low doses; that conservatism is compounded by the choice of DA over IA based on very limited study designs.

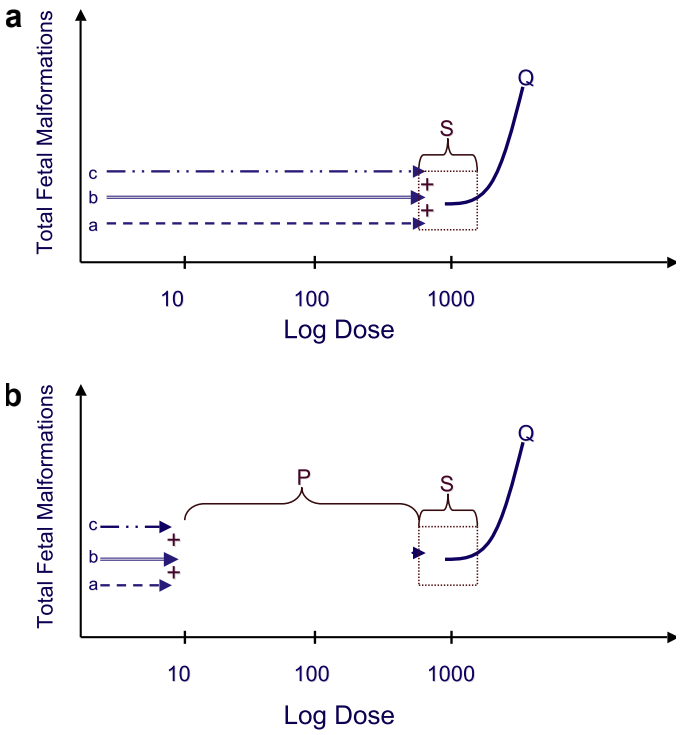

Fig. 2. Conceptual Model for DA–CAOS. Different line patterns a, b, and c represents chemicals with anti-androgenic potential that produce CAOS via different modes of action. (S) indicates the dose range where mixture experiments (Table 2) have been performed relative to the dose–response curves for observable effects (Q). Panel a: Generation of dose addition data. Available data suggest that sub-effective doses of a few such chemicals may produce a DA response when the dose of each is within S, i.e., near the observable response region Q. Panel b. Extrapolation of mixture data to DA–CAOS model. The DA–CAOS concept assumes that doses of such chemicals far below the observable response region (S) also operate by DA and may produce an observable response if sufficient numbers of chemicals are present. However, no data support this extrapolation (P).

2.1.2. Study design: Endpoints and dose response metrics

Mixtures studies on potential anti-androgenic chemicals consistently report conformity with the DA model of combined action, however, those studies report inconsistent results as to whether the data also conform to IA (Table 2). For example, one study reported that IA under-predicted combination effects and only DA–models adequately fit the data for all malformations combined (Rider et al., 2008), whereas another study (Christiansen et al., 2009) found that the data for most endpoints could be fit adequately by either model, with some greater-than-additive exceptions. The inconsistency of results obtained from the different approaches used by these two research groups could be due to any number of factors, including the animals used, the exact doses tested, the way endpoints were measured, or slight differences in the mathematical algorithms used for DA and IA.

Although the application of DA is not constrained to any particular type of effect, the use of scored endpoints, which are inherently subjective (Haschek et al., 2010), presents challenges for analyzing experimental variance not typically encountered when continuous variables are measured according to objective scales. Several of the mixtures studies listed in Table 2 assessed scored endpoints, but it is unclear how variance was assessed statistically for these endpoints, if it was addressed at all. Except for gubernacular underdevelopment (not categorized as a malformation above a certain length), all other male reproductive tract malformations were combined into a single group, further complicating the assessment of experimental variance; it is unclear if or how this was addressed in the statistical analysis (Howdeshell et al., 2007; Rider et al., 2008). Other studies categorized fetal malformations according to a four-point scale that included none observable, mild, moderate, or severe (Christiansen et al., 2008, 2009). To reduce those scores to a dichotomous variable suitable for statistical analysis used to test DA versus IA combined effect models, moderate and severe malformations were grouped together in the "malformations" category, while mild malformations were grouped together with no observable malformations in the "no-effect' category. Although this practice allows some statistical analysis of results, it introduces additional potential errors of interpretation.

IA predicts that no-effect doses of individual chemicals will also produce no effect when combined. Therefore, including mild malformations or gubernacular underdevelopment in the no-effect category for single chemical responses, as was done in some analyses (Christiansen et al., 2008, 2009) increases the chance that malformations will be observed when so-called "no-effect" doses of several chemicals are combined in the mixtures study. Because malformation severity also increases with dose, these methods of

[4] Inference from Fig. 3 of the cited paper.

scoring and grouping malformations may have ensured rejection of the IA model or biased the analysis toward synergism because a slight increase in "dose" from the combination of agents would raise certain mild malformations to the moderate/severe category. The uncertainty introduced by this procedure was not addressed, and methods for assessing its impact are lacking. The fact that small differences in experimental protocol or analysis alter the results of the mixture experiment raises concerns as to the degree of uncertainty inherent in interpreting the results for risk assessment. The risk assessment of anti-androgens chose DA over IA based on a stated preference for the more conservative model (Kortenkamp and Faust, 2010), however, the implications of inconsistent results for extrapolating to untested doses and mixture ratios appear to have been overlooked.

2.2. Statistical analysis of variability

In order to provide an objective estimate of the potential uncertainty contributed by the dose response information discussed above, data presented in one of the published mixture studies (Rider et al., 2008) was evaluated. Because the original raw data were unavailable, data points were inferred from published figures (Rider et al., 2008, Fig. 1). In order to be as consistent as possible with the published study, the dose response model used to fit the published data (Rider et al., 2008) was also used in the analysis presented here. Specifically, based on the data points inferred from the graphs published by Rider et al. (2008) and the dose response model they fit to their data, a dose–response curve was developed and then data points were generated from the theoretical curve. A number of different samples were obtained in this way. Such iterations of the dose–response experiment comprise a statistical bootstrap procedure (Efron and Tibshirani, 1993), and the results are presented in a series of isobolograms (Fig. 3). The variability in the bootstrap samples is representative of that in the original data, providing a clear picture of the range of doses consistent with any particular level of response.

Isobolograms are a simple means of graphically evaluating data on binary mixtures for conformity to DA. Doses of one of the mixture components are plotted along the abscissa and the other along the ordinate. The equation for DA describes a line connecting equally effective doses of these two chemicals on the ordinate and abscissa. All other equally effective doses, representing defined mixtures of both components, are DA if they fall on the line, less than DA if they fall above the line, and greater than DA if below the line. Since some degree of variability and experimental error are inherent to the measurement of any observation or biological endpoint, the lines of additivity representing DA combination doses in an isobologram must be enveloped by statistical

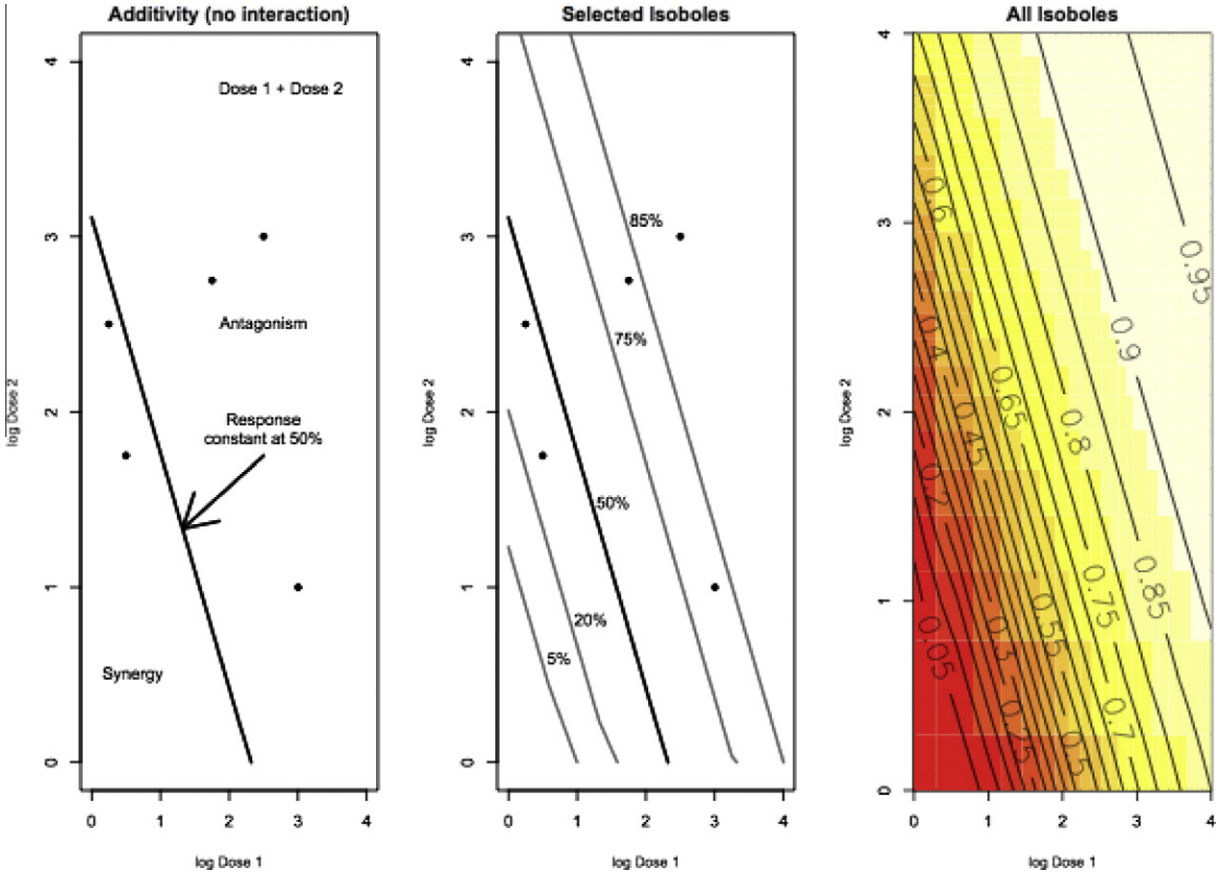

Fig. 3. Statistical analysis of uncertainty; isoboles created from Bootstrap procedure. 3–1: The left panel is an isobologram for two agents, Dose 1 and Dose 2, at 50% response. Dose addition (DA) defines a line connecting equally effective doses of Dose 1 and Dose 2 administered individually. Points above the line would demonstrate less-than-additive (antagonistic) dose combinations, below the line, greater-than-additive (synergistic). The dose is plotted on a log 2 scale, so a change from 2 to 4 on the log 2 scale would represent a doubling of the dose. The center panel shows a collection of isoboles at different response levels. Again, each line represents a constant response over the mixture of doses. The right panel shows the output from one analysis, and depicts all of the isobolograms, from 5% to 95% response. As this is the output from one sample, the isobolograms will vary from sample to sample. 3–2: This variation is illustrated for the data inferred from Fig. 1 of Rider et al. (2008). The estimated variance in equi-effective doses, and thus, the extent of uncertainty surrounding the DA prediction, is illustrated by comparing how the 95% effective dose for one mixture component changes across experiments as plotted on the abscissa. The lowest log (base-2) dose estimated to produce a 95% response is approximately 1.7 (panel e) whereas the highest dose estimated to produce the same level of response is approximately log dose 3.2 (panel c), indicating that the iso-effective dose of just one mixture component can vary nearly 2-fold even within the observed data. The parallel lines correspond to isoboles for equi-effective doses at lower response levels indicate that the variance at lower doses and response levels is proportional to the variance at higher doses and response levels, i.e., nearly twofold.

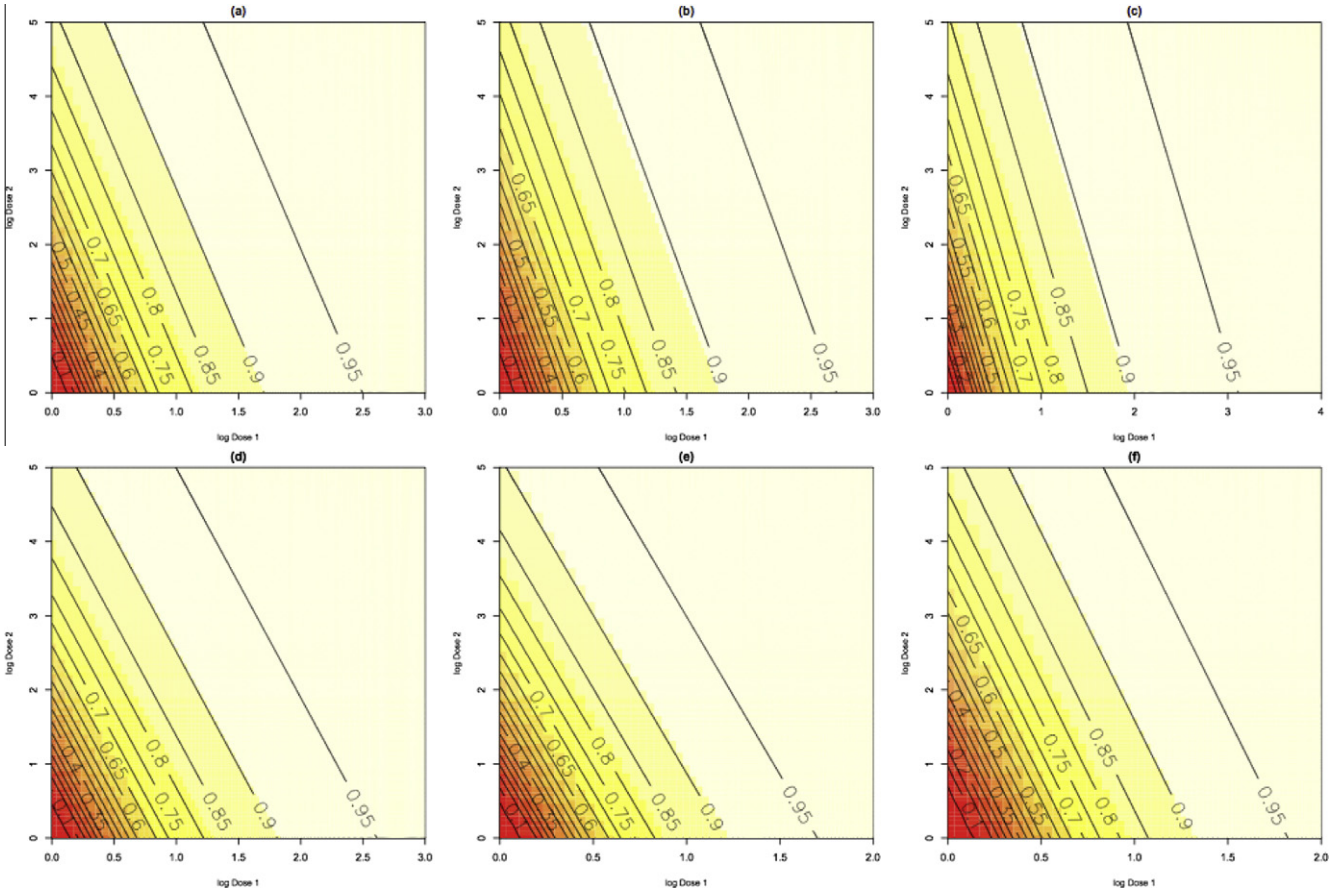

Fig. 3 (*continued*)

confidence intervals defined by this variance. Assays with higher variance and/or experimental error will produce larger confidence intervals than assays with lower variance and/or experimental error (Borgert et al., 2005).

The variability attending any DA prediction can be estimated by observing how the equi-effective dose of each mixture component varies from experiment to experiment. The isobolograms shown in Fig. 3(2), a–f indicate considerable variance within the published data, despite the fact that the bootstrap procedure used to generate the new "data" on which the isoboles in Fig. 3(2) were constructed employed the underlying dose–response model that Rider et al. (2008) concluded best fit their data. Even within these contrived, best-case experiments, nearly 2-fold variance is observed, indicating that this variability surrounds any DA conclusion, even within the range of doses tested empirically. It is thus surprising that Rider et al. (2008) unequivocally excluded IA for nearly all of the reported combination effects, since this requires an absence of overlap between IA and DA predictions after accounting for the experimental variance. It is unclear how this variance was handled in the analysis of combination effects (Rider et al., 2008). Similar to the analysis presented here, other studies employed a bootstrap procedure to assess variance, and on that basis, concluded that both IA and DA predicted most of the mixture responses (Metzdorff et al., 2007).

It is critical to appreciate that for assessing risk, the DA–CAOS theory extrapolates the DA model beyond the doses and ratios tested in mixtures studies (Kortenkamp and Faust, 2010). Since the apparent variance of the data within the range of doses tested in those studies (Table 2) raises questions as to whether a single model of combined action can be unequivocally declared the most accurate, even for all mixture ratios within that dose range, extrapolation to much lower doses and different mixture ratios would be quite tenuous. Little attention was given to the fact that the uncertainty of the predictions will expand in accordance with the variance in the data, other than to justify the choice of the model on a preference for conservatism.

The statistical analysis presented here has implications for the feasibility of selecting a 'best' model of combined action as well as for future mixtures studies aimed at supporting such a determination. Unless the observed variance were so small that no significant overlap of DA and IA model predictions could occur as the model is extrapolated across untested dose ranges, it would be futile to attempt to select a model of combined action based on a statistical analysis of mixtures data within the observed response region. Indeed, the research group from Europe found that DA and IA overlapped even within the dose regions tested (Table 2), substantiating this point.

2.3. Relative potency and pharmacokinetics: Pharmacological principles

In addition to the problems discussed above, the DA–CAOS theory contravenes fundamental pharmacological principles of receptor/enzyme affinity, intrinsic activity, and potency. Affinity is a term referring to the strength of attachment between two molecules and is applicable to interactions of a small ligand with a larger macromolecule such as an intracellular or membrane-bound receptor, an ion channel, an enzyme, or specific binding protein. For simplicity, all of these are referred to as 'receptors' with the understanding that the general principles apply to all such interactions with macromolecules. The affinity of a ligand for a specific receptor determines its residence time of association, a parameter

often quantified by the dissociation constant. Generally, higher affinity ligands have longer residence times. Intrinsic activity is the relative ability of a drug-receptor complex to produce a maximum functional response and is sometimes used interchangeably with efficacy. However, 'intrinsic activity' refers to a cellular response whereas 'efficacy' is more often used in the context of a clinical response. Assuming equivalent pharmacokinetic parameters and affinity, a drug with greater intrinsic activity would have greater efficacy. Potency is the intensity of effect produced per unit of drug, and is a function of intrinsic activity and affinity.

Because most receptor-based physiological responses can be triggered when only a small fraction of available receptors are activated by a strong agonist (a ligand with high affinity and intrinsic activity), receptor ligands with very low affinity and no intrinsic activity (weak antagonists) will fail to interfere with endogenous agonists unless their concentrations reach levels that obstruct access to the receptor by shear mass action. The same principle applies to competitive inhibitors of enzymes involved in steroidogenic pathways or to activators or blockers of ion channels in cellular membranes. Thus, because of vastly different residence times, ligands with very low affinity spend such little time in contact with a receptor that they produce no discernible interference with high-affinity ligands unless their concentrations reach a sufficient level that interference by mass action occurs. In other words, low affinity ligands cannot compete with high affinity ligands by their strength of attachment, but rather, only by shear numbers of molecules that impede access to the receptor. This is why low affinity ligands have no discernible effects at low concentrations. Even agonists with relatively similar affinity but different intrinsic activity are incapable of producing linear isoboles, commonly used to detect DA (see Section 2.2 above), because the physiological response reflects both affinity and intrinsic activity. Drugs or chemicals that differ in intrinsic activity will necessarily compete at a molecular site of action and will not produce a linear DA combined response, as demonstrated mathematically and empirically by Tallarida (2006, 2007).

In contradiction of these principles, DA–CAOS posits, for example, that any dose of a weak androgen receptor antagonist will diminish the physiological activity of dihydrotestosterone by some finite degree, irrespective of whether its affinity approaches that of a natural ligand. This demonstrably faulty premise provides the underlying basis for the DA–CAOS supposition that chemicals capable of reducing androgen levels at high doses will add to the effect of weak receptor antagonists even at very low doses. In fact, however, multiple chemicals given at doses incapable of affecting physiological processes individually, by separate mechanisms, would not be expected to produce a physiological effect in combination. A combined physiological effect would not be expected unless doses of those chemicals were on the cusp of producing overt effects individually. In other words, fundamental pharmacological principles dictate that a weak androgen receptor antagonist would not produce a combination effect with an androgen synthesis inhibitor or Leydig cell toxicant unless the doses were sufficient to reduce both the concentration of endogenous androgen and the numbers of available receptors to levels near the critical minima necessary for supporting normal physiology. The DA–CAOS theory fails to recognize that the presence of myriad weak hormone receptor agonists and antagonists in the environment would fail to be DA in combination or to achieve physiological significance, in part because their weak properties cancel one another and in part because their low affinities and intrinsic activities preclude it (Safe, 1998; Tallarida, 2006).

Furthermore, the role of pharmacokinetics and how these phenomena may change with dose and ratio of mixture constituents is often under-appreciated in discussions of the joint toxicity of chemicals. This is important because pharmacokinetic alterations underlie the majority of documented interactions between chemicals (Krishnan and Brodeur, 1994) and the dose-dependence of many toxicity mechanisms, even for single chemicals (Slikker et al., 2004). Obviously, the potential for concomitant administration to affect the absorption, distribution, metabolism and excretion of chemicals in mixtures increases with dose and the number of chemical constituents as the underlying processes that control each reach the limits of their capacity. Such influences would be of greatest consequence for highly potent compounds. Without understanding how pharmacokinetic processes change with dose and ratio of constituents, it is impossible to reliably extrapolate combination models across different dose ranges and chemical ratios. Neither the mixture studies of potential anti-androgens (Table 2) nor the NRC report (NRC, 2008) considered these issues.

2.4. Testing predictions of the DA–CAOS concept

Despite the uncertainties inherent in the published mixtures studies and the unnecessary conservatism introduced into the risk assessment by assuming DA at all chemical concentrations, it is important to consider whether the logical extensions of the DA–CAOS theory are nonetheless concordant with human clinical and epidemiological experience. To test this concordance, an attempt was made to reconcile the incidence of TDS in humans with application of the DA–CAOS concept to the full suite of chemicals alleged to have anti-androgenic potential. As well, the DES dose–response for male reproductive tract malformations was considered according to the DA–CAOS concept in light of extant information regarding other environmental exposures during the period when DES was administered to pregnant women.

2.4.1. Incidence of TDS and cumulative exposure to anti-androgens

The published risk assessment based on the DA–CAOS concept (Kortenkamp and Faust, 2010) concludes that "*...the cumulative risks from anti-androgen exposures exceed acceptable levels for people on the upper end of exposure levels*," i.e., the upper 95% confidence interval of human exposures to only 15 anti-androgenic chemicals. This conclusion implies that pregnant women and their fetuses are at an unacceptably high risk for anti-androgenic effects, and specifically, that approximately 5% of male fetuses are at risk for development of TDS. The authors also claim that 8% of all known chemicals are likely to possess anti-androgenic potential, including thousands of chemicals on the market in the European Union (Kortenkamp and Faust, 2010). Presumably, similar exposures occur in other industrialized nations. Logically extending the DA–CAOS theory would thus project that the percentage of human fetuses at risk for the development of TDS is actually much higher than 5% if exposure to all chemicals with anti-androgenic potential were included. Given the author's contention that thousands of chemicals marketed in Europe may have anti-androgenic potential, their published risk assessment on 15 anti-androgens considered only 1% or fewer of the relevant chemicals. If one further considers that in utero exposures to over-the-counter analgesics have also been linked to similar male reproductive tract disorders in rats and humans (Kristensen et al., 2011), the projected percentage of affected fetuses should approach 100%, depending on exposure levels for the various putative anti-androgens.

However, the actual incidence of TDS could not be nearly so high, as the incidence of hypospadias and cryptorchidism have been estimated at between 0.2–1% and 2–9% respectively (Toppari et al., 2010). Even without considering the DA–CAOS theory, some clinicians have questioned the etiologic role of industrial chemicals in TDS (Thorup et al., 2010), asserting that the epidemiological data do not support such a relationship. Their in-depth analysis of the incidence and biology of these male reproductive tract

abnormalities argues against the existence of a 'syndrome' of effects caused by a common etiologic agent(s), instead pointing to a complex array of clinical diagnostic, genetic, and other factors that may be individually involved in the apparent increased incidence of hypospadias, cryptorchidism, testicular cancer and other malformations (Thorup et al., 2010). For example, an analysis by Fisch et al. (2001) revealed that hypospadias was significantly associated with increasing maternal age as a consequence of more women who delay childbearing until their mid-30s. It is also worth noting that Sharpe (2003), who was initially one of the principle proponents of the TDS hypothesis as a consequence of in utero/neonatal exposure to a variety of weakly estrogenic compounds from the environment, offered the following reassessment: "What is reasonably clear is that all of the identified "environmental estrogens" possess weak or very weak intrinsic estrogenic activity when measured by conventional in vitro and in vivo assays for estrogenicity... By comparison with the potency of DES, for which there [are] both human and rodent data on incidence of male reproductive developmental disorders following in utero exposure (or neonatal exposure in rodents), it seems unlikely that any of the identified environmental compounds could induce either cryptorchidism, hypospadias or testis germ cell cancer and only a tiny possibility that such compounds could affect sperm counts/sperm production. ...Based on estrogenic potency, human exposure to the most potent environmental estrogens would need to be at least 1000-fold higher than this level for adverse effects relevant to the human male to be induced, and such levels of exposure are remote."

2.4.2. Cumulative exposure to anti-androgens and clinical threshold for DES

Because normal development of the male reproductive tract is dependent on the androgen/estrogen ratio, the DA–CAOS theory predicts that cumulative exposure to environmental estrogens, anti-androgens, and other chemicals that can produce TDS-like abnormalities will increase its incidence in a DA manner. Although great concern has been generated over current cumulative exposures to anti-androgenic chemicals, it is generally acknowledged that human exposures to a wide array of chemicals capable of affecting the developing male reproductive tract – both anti-androgenic and estrogenic – have decreased since the period during which diethylstilbestrol (DES) was administered to pregnant women and its eventual removal from the market, in part for its TDS-like effects induced in utero [see Section 2.5.1 for a detailed discussion]. Polychlorinated biphenyls (PCBs) (Andric et al., 2000a,b; Gray et al., 1999) chlorinated pesticides (Fernandez et al., 2007; Kelce et al., 1995), and 2,3,7,8-tetrachloro-p-dioxin (TCDD) (Gray et al., 1995, 1997) are but a few prominent examples of chemicals with anti-androgenic potential to which human exposures have been declining since the DES episode (Adeshina and Todd, 1991; Axmon et al., 2008; Hays and Aylward, 2001; Hovinga et al., 1992; Petreas et al., 2001; CDC, 2005; USEPA, 2006). Given that use of high-dose over-the-counter analgesics, which have also been associated with male reproductive tract malformations (Kristensen et al., 2011), was also common during the era when DES was given, it seems highly probable that exposures to chemicals capable of producing TDS-like effects were substantial during the DES episode, and most certainly higher than today.

If, as the DA–CAOS risk assessment predicts, a significant proportion of male fetuses experience anti-androgenic effects today, at least as high a proportion would likely have experienced such effects during the era of DES use in pregnancy. Assuming the DA–CAOS theory, it would follow that any dose of DES should have produced an observable increase in the incidence of TDS-like effects above the predicted observable background of chemical-induced male reproductive tract malformations. In contrast, no clear increase was observed in the incidence of TDS-like effects with the lower-dose regimens of DES (Dietrich, 2010; Golden et al., 1998).

2.5. Human versus rat sensitivity

One reason the hazard index-based DA–CAOS risk assessment (Kortenkamp and Faust, 2010) is irreconcilable with human clinical and epidemiological evidence is it employed reference doses (RfDs) that were developed without considering relevant data and physiological knowledge concerning species-specific sensitivity for chemical effects on the male reproductive tract (Cook et al., 1999; Hallmark et al., 2007; Scott et al., 2009). The derived RfDs incorporate uncertainty factors of 200–500 (Kortenkamp and Faust, 2010), consistent with an assumption that adverse effects on the developing male reproductive tract may be observed in humans at doses 200–500-fold lower than doses required to elicit such effects in rats. In the absence of relevant human data, such procedures are considered appropriate for extrapolating rodent toxicity data to humans. However, direct human data are available for many human pharmaceuticals, including drugs with anti-androgenic and/or TDS-like effects. The assumptions made in the risk assessment were thus tested against such human data. Data were evaluated by comparing human versus rat data from (a) in utero exposures to DES, a chemical that produces TDS-like malformations of rodent and human reproductive tracts by inducing androgen deficiency secondary to functional disruption of Leydig and Sertoli cells, and (b) human versus rat administration of finasteride, an anti-androgen that produces androgen deficiency by inhibiting conversion of testosterone to its active form, dihydrotestosterone.

2.5.1. Human versus rat – DES

To test the premise that chemicals affect the developing male reproductive tract of humans at doses 200–500 lower than in rats, human clinical data on gestational exposure to DES were compared with data from concordant exposures in the rat. Although DES is a potent estrogen agonist that interferes with Sertoli and Leydig cell function in rodents, some of its adverse effects on the male reproductive tract are complex, e.g., may involve both estrogen (Couse and Korach, 2004) and androgen pathways (Goyal et al., 2009; Rivas et al., 2003), and exhibit both similarities and differences compared to pure estrogens such as estradiol 17β (Adachi et al., 2004; Khan et al., 1998; Lassurguere et al., 2003; Warita et al., 2010). In addition to reducing activity of the steroidogenic acute regulatory protein (StAR) and other effects similar to those produced by some phthalates in rats (Guyot et al., 2004; Howdeshell et al., 2008a; Ikeda et al., 2008), treatment of neonatal rats with testosterone or dihydrotestosterone prevents most effects of DES on the developing male reproductive tract (Rivas et al., 2003; Goyal et al., 2009), providing evidence that androgen deficiency or alteration of the androgen-estrogen balance is involved in DES action. Loss of Leydig cell function, also proposed for phthalate esters (David, 2006; Howdeshell et al., 2007), is one of many anti-androgenic modes of action that can result in androgen deficiency and is encompassed by the DA–CAOS concept. Thus, the action of phthalate esters on fetal Leydig and Sertoli cells appears to be more similar to DES than to the other anti-androgens assessed in the mixtures studies analyzed here (Table 2).

Beginning in the 1940s, DES was widely prescribed to some 5 million pregnant women under the mistaken assumption that it prevented miscarriage. The discovery that gestational exposure to DES induced a low incidence of clear cell vaginal adenocarinoma in daughters and a low incidence of male reproductive abnormalities in sons led to its removal from the market in 1972. Its effects on sons exposed in utero, including epididymal cysts,

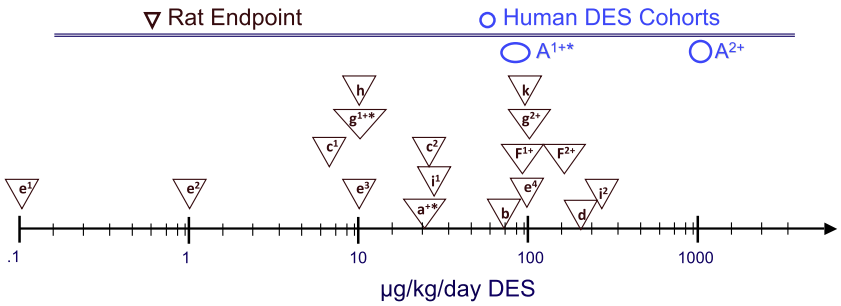

Fig. 4. DES potency comparison for male reproductive tract parameters. Human clinical data (ovals) Rat experimental data (triangles). Asterisks (∗) denote no-effect doses. Plus (+) denotes in utero administration. Pregnant women were assumed to weigh 70 kg. Where doses to rats were not reported per body weight, body weight data from Klinger et al. (1996) or Pullen (1976) were used to calculate approximate administered doses. (a) Adamsson et al. (2008). In utero exposure to Sprague–Dawley dams. +*No effect on fetal testicular T, Prog, StAR protein (steroidogenic acute regulatory protein), AR protein expression. (b) Filipiak et al. (2009). Administration on postnatal days 5–15 to Wistar pups. Reduced testes relative weight, seminiferous tubule diameter and length at puberty. (c) Goyal et al. (2001). Administration to 70–80 day old adult Sprague–Dawely males for 12 days. (1) Markedly reduced plasma testosterone levels; (2) reduced size and number of Leydig cells and plasma testosterone barely detectable. (d) Goyal et al. (2004). Administration every other day from postnatal days 2–12 to Sprague–Dawley pups: reduced penis weight, size and altered morphology; plasma testosterone levels undetectable. (e) Goyal et al. (2005). Administration every other day from pnd 2–12 to Sprague–Dawley pups; dose calculated based on 10 g rat pup average, and not averaged over days, i.e., plotted doses are overestimates. (1) Reduced weight of caudal epididymal fat pad (2) Reduced weights of caudal epididymal fat pad and seminal vesicles. (3) Reduced weights of caudal epididymal fat pad, seminal vesicles, testis, and reduced penis diameter. (4) Reduced weights of caudal epididymal fat pad, seminal vesicles, testis, and reduced penis diameter, weight and length. (f) Haavisto et al. (2001). In utero administration on embryonic days 13.5, 15.5 and 17.5 to Sprague–Dawley dams. +(1) 50% reduction in fetal plasma and testicular testosterone levels. +(2) Reduced hCG-stimulated testosterone surge. (g) Haavisto et al. (2003). In utero administration on embryonic days 13.5, 15.5 and 17.5 to Sprague–Dawley dams. +*(1) No-effects on fetal testicular and plasma testosterone. +(2) Reduced fetal testicular and plasma testosterone. (h) Mathews et al. (2009). Administration on postnatal days 1–6 to male Sprague–Dawley pups. Reduced testes weight and altered epididymal morphology, reduced androgen receptor expression and Leydig cell volume. (i) McKinnell et al., 2001. Administration to male Wistar rat pups every other day on postnatal days 2–12. (1) 38% reduction testes weight. (2) Reduced testes weight and altered epididymal morphology, reduced androgen receptor expression and 91% reduction in Leydig cell volume. (k) Mikkilä et al. (2006). Subcutaneous doses administered on postnatal days 0–4 to male Sprague–Dawley pups. Reduced plasma testosterone, testis weight, seminiferous cord diameter and steroidogenic acute regulatory protein expression. (A) Golden et al. (1998) and Dietrich (2010). Administration to pregnant women during weeks 7–35 of pregnancy. +*(1) No adverse effects observed +(2) cryptorchidism, decreased penis size and sperm counts.

microphallus, cryptorchidism, testicular hypoplasia, reduced sperm counts, and increased incidence of abnormal sperm (Dietrich, 2010; Golden et al., 1998) have made DES the prototype for chemical-induced TDS in humans, showing nearly identical effects in rats and humans (Toppari et al., 2010). Because no clinical trial had been conducted with DES to verify efficacy and optimize dosage, the total DES dose administered varied among clinics by more than an order of magnitude. Male reproductive tract abnormalities were significantly increased only among offspring of mothers enrolled in clinics that employed the higher dose regimens, i.e., administration of 12–18 g DES during pregnancy (Dietrich, 2010; Golden et al., 1998), or approximately 844–1266 µg/kg/day, assuming a body weight of 70 kg per pregnant woman. In contrast, no clear increase in incidence of male reproductive tract effects has been observed in offspring of mothers given lower dose regimens of DES, i.e., administration of 1.4 g DES during pregnancy (Dietrich, 2010; Golden et al., 1998; Leary et al., 1984), equivalent to 71 µg/kg/day for the first two weeks and 99 µg/kg/day during the entire pregnancy. Plotting these doses against data from studies conducted in rats (Fig. 4) demonstrates that effects on the developing male reproductive tract are observable in rats at DES doses approximately 1–2 orders of magnitude lower than those required to produce similar effects in humans. The data also indicate that the male rat reproductive tract is similarly sensitive across fetal, neonatal and adult life stages.

In a detailed analysis of species differences with respect to in utero DES-induced male reproductive tract anomalies, Hogan et al. (1987) compared the relative potency ratios for these effects in the mouse (the prototypical animal model for DES-induced reproductive tract effects) and humans. Depending on various assumptions, effects in humans occurred at doses from 1–2 orders of magnitude greater, to approximately equal those at which effects occurred in mice. Thus, both rat and mouse data challenge the seemingly arbitrary assumption that male reproductive tract malformations occur in humans at DES doses 200–500-fold less than required to produce effects in rodents (Kortenkamp and Faust, 2010). Although there could be speculation on mechanistic grounds as to why humans might be less sensitive than rodents to effects of DES but not to effects of other chemicals with potential anti-androgenic properties, such speculation would presumably be irrelevant within the context of the DA–CAOS concept wherein mechanistic similarity is not a criterion for predicting combination effects. Consequently, the comparison of human versus rat sensitivity to the effects of DES on the developing male reproductive tract appears to be relevant for the risk assessment of anti-androgens within the DA–CAOS concept, especially for phthalate esters. This comparison would seem to be an obligate exercise for using rat data to conduct a human health risk assessment, especially when the data are publicly available.

2.5.2. Human versus rat – finasteride

To further test the assumption that anti-androgenic chemicals affect the human male reproductive tract at doses lower than in the rat, data were compared for effects of finasteride, a human pharmaceutical prescribed for its anti-androgenic effects in the treatment of benign prostatic hypertrophy (Gormley et al., 1990). Finasteride was among the mixture of anti-androgens reported to synergistically induce reproductive tract abnormalities in male rats following in utero administration (Christiansen et al., 2009). Finasteride is a specific inhibitor of 5α reductase, the enzyme responsible for conversion of testosterone to dihydrotestosterone, the active androgen receptor ligand and agonist in humans and rodents. The inhibition of 5α reductase by finasteride is not mediated through DHT binding to the androgen receptor, thus mimicking hereditary 5α reductase deficiency where individuals with this deficiency present with poor prostatic growth (Gormley, 1992; Gormley et al., 1990). Finasteride has been shown to significantly reduce prostate size in humans and in several animal models. Both testosterone and dihydrotestosterone (DHT) are critical for normal male reproductive development. DHT is required for normal development of the external genitalia and prostate (Bowman et al., 2003).

Significant variability attends establishing a threshold for percent reduction in DHT in humans, as seen in Fig. 5. The lowest dose

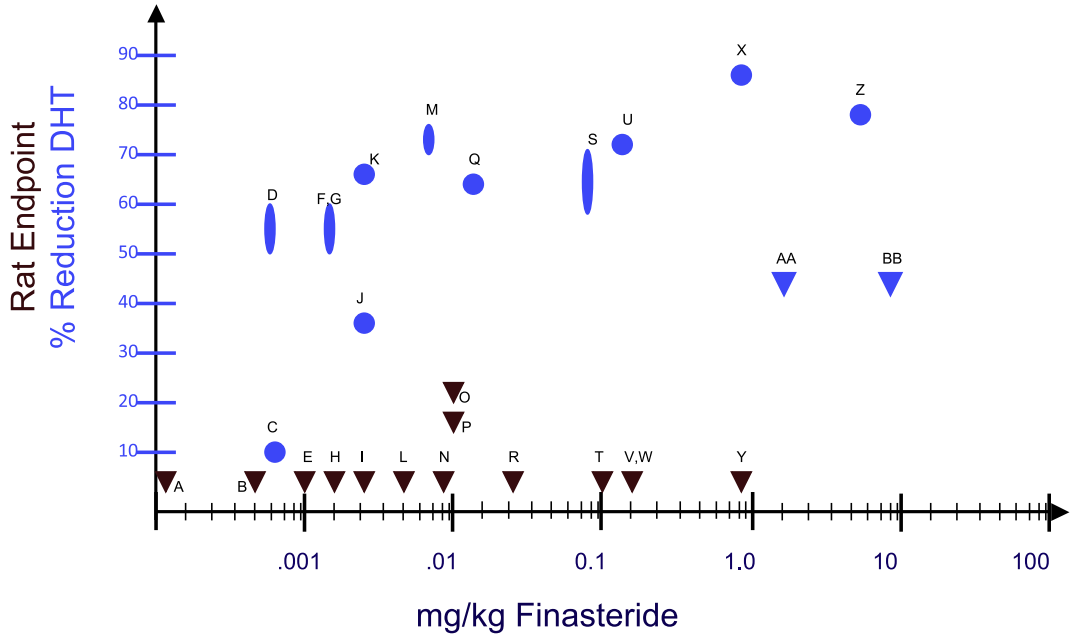

Fig. 5. Finasteride potency comparison for human clinical suppression of DHT versus rat endpoints (see Table 3).

at which a reduction of DHT was seen in men was 0.0006 mg/kg and ranged from 10% after one-day exposure to 50–60% after 14-day exposure (Gormley et al., 1990). In this study, a statistically significant percent reduction (approximately 40%) in DHT occurred in the baseline values for two treatment groups, further indicating the significant variability if this effect. The maximum suppression of DHT in serum is approximately 70% and occurs at doses > 0.007 mg/kg (Steiner, 1996). The plateau in suppression of serum DHT is shown out to 1 mg/kg in Fig. 5. Maximum suppression of DHT in the prostate is 85–90%. Finasteride has much greater affinity for the type 2 5α reductase isozyme than for the type 1, hence, the remaining DHT in the serum and prostate gland is likely to be the result of type 1 5α reductase (Bartsch et al., 2002).

Very little data were found to establish a threshold for the reduction of serum DHT in the rat. A threshold for the effect of DHT on the prostate has been demonstrated in rats, however the threshold is only apparent when the animals have been castrated, resulting in very low intra-prostatic testosterone and DHT levels (Bartsch et al., 2002). Thresholds for effects on male reproductive development in the rat using both standard developmental toxicity studies and the Hershberger assay are also shown in Fig. 5. Finasteride causes a decrease in anogenital distance in male offspring. The threshold for reversible decreased anogenital distance is 0.003 mg/kg (Clark et al., 1990) but is somewhat higher for irreversible decreased anogenital distance as determined by its presence at post-natal day 90 (Bowman et al., 2003).

Fig. 5 shows that the threshold for a clinically effective decrease (Fig. 5J) in circulating dihydrotestosterone in men occurs at approximately the same finasteride dose as produces a reduction in rat anogenital distance in the Hershberger assay (Fig. 5I). Thresholds for other effects in rats are observed at significantly higher doses, but still lower than the recommended clinical dose for treatment of benign prostatic hypertrophy in men (Fig. 5S). Taken together, the above data strongly suggest that irrespective of the high variability in both human and rat data, effects of a potent anti-androgen, finasteride, occur in human males at doses no lower than, and most likely considerably higher than are required to produce effects in the rat.

3. The Human-Relevant Potency-Threshold (HRPT)

As a conservative screening level assessment, the DA–CAOS concept may have some utility since it is reasonably simple to perform, requires only rudimentary dose–response information and demands virtually no understanding of mode of action, pharmacokinetics, or structure activity relationships. However, as demonstrated above, the DA–CAOS theory suffers an inordinate degree of uncertainty as evidenced by limitations in the studies on which it is based, contradicts fundamental tenets of pharmacology, and would predict outcomes incongruous with human clinical and epidemiological observations. The published risk assessment based on DA–CAOS magnifies those uncertainties with unnecessary conservatism regarding doses at which effects occur in humans versus rats. Thus, for any group of chemicals that warrant further analysis – for which concern might remain after conducting a DA–CAOS screening assessment – a better approach is needed that is well grounded in fundamental pharmacological principles, can be reconciled with human clinical data, and is consistent with clinical epidemiological experience.

Consequently, an improved risk assessment and prediction strategy is proposed that melds those features of the DA–CAOS concept that are tenable with requirements of the TEQ concept that are necessary to conform with fundamental pharmacological principles and to be compatible with the observed clinical and epidemiological data. The proposed approach, referred to as the Human Relevant Potency Threshold (HRPT) approach, proposes that DA be assumed for chemicals that can affect a common adverse outcome, but only at doses close to the lower limit of the observable effect range. It also proposes that DA be applied to chemicals that meet the TEQ requirements for receptor- or enzyme-mediated adverse effects and whose potency approaches that of an endogenous ligand or human pharmaceutical. In both cases, the observable effect dose or the potency of a natural ligand or human pharmaceutical should be based on human data whenever available. Below these ‘thresholds’ in either dose or potency (affinity/intrinsic activity), IA would be used for cumulative risk assessment of chemicals to which humans are exposed; i.e.,

Table 3
Human clinical data (ovals) rat experimental data (triangles). Blue points indicate % reduction in DHT.

Dose (mg/kg)	Human endpoint	Rat endpoint	Reference	
0.0001		Neg Hershberger assay	Ashby et al. (2004)	A
0.0005		Neg Hershberger assay	Ashby et al. (2004)	B
0.0006 (1 day)	10% ↓ serum DHT		Gormley et al. (1990)	C
0.0006 (14 days)	50–60% ↓ serum DHT		Gormley et al. (1990)	D
0.001		Neg Hershberger assay	Ashby et al. (2004)	E
0.0018 (1 day)	50–60% ↓ serum DHT		Gormley et al. (1990)	F
0.0018 (14 days)	50–60% ↓ serum DHT		Gormley et al. (1990)	G
0.002		Neg Hershberger assay	Ashby et al. (2004)	H
0.003		Threshold for ↓ AGD at PND 1	Clark et al. (1990)	I
0.0031 (1 day)	35% ↓ serum DHT		Gormley et al. (1990)	J
0.0031 (14 days)	65% ↓ serum DHT		Gormley et al. (1990)	K
0.005		Neg Hershberger assay	Ashby et al. (2004)	L
0.007	Reported threshold for maximal clinical suppression of DHT		Steiner (1996)	M
0.008		Threshold in Hershberger assay based on ↓ prostate and glans penis weight	Ashby et al. (2004)	N
0.01		Threshold for ↓ AGD at PND 90	Bowman et al. (2003)	O
0.01		Threshold for reversible male nipple retention	Bowman et al. (2003)	P
0.015	64% ↓ serum DHT, Suboptimal ↓ prostate volume in 6–12 mos, Suboptimal ↑ urinary flow in 6–12 mos		McConnell (1992) Gormley (1992) Gormley (1992)	Q
0.03		Threshold for permanent male nipple retention	Bowman et al. (2003)	R
0.077	Recommended clinical dose (5 mg), 59–71% ↓ serum DHT, Max ↓ prostate volume in 6–12 mos (19–26% ↓), Optimal ↑ urinary flow in 6–12 mos		Bartsch et al., 2002 Gormley (1992)	S
0.1		Threshold for hypospadias	Clark et al. (1990)	T
0.15	71% ↓ serum DHT		McConnell (1992)	U
0.2		+Hershberger assay (seminal vesicle wgt only)	Kennel et al. (2004)	V
0.2		Reported Hershberger LOELs (multiple tissues)	Owens et al. (2007)	W
0.77	85% ↓ serum DHT		McConnell (1992)	X
0.77		Lowest BMD for Hershberger assays	Owens et al. (2007)	Y
1.54	78% ↓ serum DHT, Maximum clinical dose		McConnell (1992)	Z
20		<45% ↓ serum DHT[a], 30% ↑ serum T, ↓ epididymal, prostate, SV wgt, No effect on testis wgt	Marty et al. (2001)	AA
80		45% ↓ serum DHT[a], 30% ↑ serum T, ↓ epididymal, prostate, SV wgt	Marty et al. (2001)	BB

[a] Not statistically significant.

individual RfDs would be appropriate benchmarks for risk estimation rather than hazard indices.

The HRPT approach accommodates both the DA–CAOS concept, where tenable, and the well-established TEQ concept, but improves upon each by providing a means for calibrating the assumption of DA with human data. The approach is broadly applicable whenever human data are available to support estimation of human-relevant thresholds. A conceptual diagram of the HRPT approach is presented in Fig. 6, which can be clearly contrasted with the DA–CAOS concept as depicted in Fig. 2b. Although the HRPT approach will not be possible for all chemicals due to lack of human data, the HRPT approach will be feasible in many cases, including any adverse outcome or intermediate step in the production of an adverse outcome that can be produced by a human pharmaceutical agent. For the pharmaceutical agents considered in this manuscript, DES and finasteride, clinical and rodent data were readily available in the published literature.

The steps necessary for applying the HRPT approach in cumulative (combined exposures) risk assessment include:

1. Defining the common adverse outcome or target organ effect upon which the cumulative effect from a group of chemicals is to be based. In most instances, this will be defined based on animal toxicology studies, but care should be taken to avoid effects that are arguably species specific and of questionable relevance to humans. It is important that the effect is defined specifically and that constellations of effects be avoided unless clearly and definitively related by physiological and mechanistic understanding.

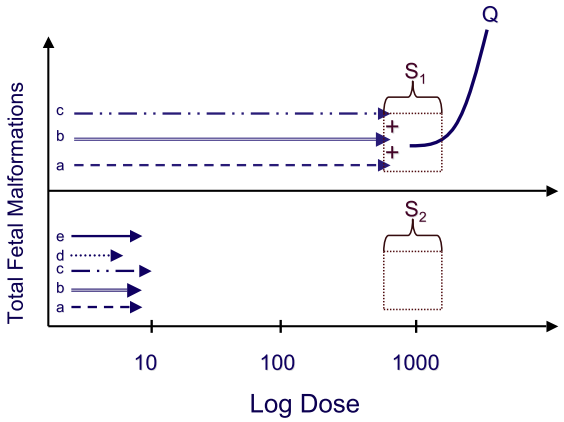

Fig. 6. HRPT conceptual model. Different line patterns a–e represent chemicals with anti-androgenic potential that produce CAOS via different modes of action. (S) indicates the dose range where mixture experiments (Table 2) have been performed relative to the dose–response curves for observable effects (Q). The HRPT approach proposes that DA be assumed for chemicals that can affect a common adverse outcome, but only at doses (S_1) that approach the lower limit of the observable effect range (Q), as depicted in the top panel. For cumulative risk assessments, IA would be used to combine chemicals to which humans are exposed that fall below these 'thresholds' (S_2, bottom panel) in either dose or potency.

2. Identifying the chemicals known to produce the common adverse outcome in the test species and determining whether data indicate DA combined effects of those chemicals. If demonstrable, identify the lowest concentrations in mixtures at which DA occurs.
3. Defining, if possible, the modes of action that can lead to the adverse outcome in the test species.
4. Identifying chemicals, including drugs, known to produce the adverse outcome in humans, including among these, chemicals or drugs known to operate by relevant modes of action that can produce the adverse outcome.
5. Identifying chemicals for which the TEQ concept is justified based on satisfying TEQ requirements (see Table 1).
6. Gathering and comparing dose–response data for the chemicals and drugs of interest in humans and the test species, whether based on end-organ toxic effects or intermediate, obligate steps in the production of toxicity. An example of the former is the comparison of the DES doses at which male reproductive tract malformations occur in humans versus rats; the latter, the comparisons based on doses of finasteride. Fortunately, because data providing direct dose sensitivity comparisons for frank adverse effects are rare, such as those for DES, comparisons based on measures of pharmacological effects will often be required.
7. Based on the comparisons of human versus test species sensitivity, potency differences between chemicals, and concentrations at which DA adverse effects are demonstrable in test species, estimating the potency differential between species, and thus the potency threshold at which DA would be a conservative but tenable assumption for humans. Defining these potency thresholds is required for TEQ-compliant chemicals as well as for broader groups based only on common adverse outcome or intermediate steps in toxicity.

4. Application of the HRPT approach to potential anti-androgens

The first three steps for applying the HRPT approach as outlined above were assumed from the NRC report (NRC, 2008) and the mixtures studies conducted on chemicals with potential anti-androgenic properties (see Table 2). Step 4 involved identification of DES as a chemical known to produce the common adverse outcome in humans, and identification of finasteride, a chemical included in the one of the subject mixtures studies (Christiansen et al., 2009) which has a defined mode of action and clearly measurable clinical endpoint in humans. Chemicals that are potent inhibitors of 5-alpha reductase, androgen receptor antagonists, and phthalate esters that interrupt Leydig and Sertoli cell development may be candidates for three separate TEQ groupings (Step 5). Step 6 has been outlined previously in this paper and is summarized in Figs. 4 and 5. Step 7 is described below using phthalate esters and finasteride as examples to illustrate how the HRPT approach is applied based on dose level and potency respectively.

For the broad grouping of chemicals with potential anti-androgenic properties, an HRPT should be set on dose level rather than potency because these chemicals do not satisfy TEQ criteria for application of DA across untested dose ranges. Based on the analysis outlined in steps 1 through 6 and the analysis presented in Section 2.4.1 and Fig. 4, a proposed dose-based HRPT for the broad grouping of phthalate esters and other chemicals with potential anti-androgenic properties can be conservatively set at doses 5-fold below rat LOAELs/NOAELs for CAOS on the developing male reproductive tract. Thus, for example, the HRPT approach would apply DA to combined human phthalate exposures that are within a factor of 5-fold lower (i.e., 20%) than rat LOAELs/NOAELs for effects on the male reproductive tract, but would apply IA to lower exposure levels, i.e., for cumulative risk assessment at current levels of human exposure to phthalates. Since the DES dose required for human in utero effects is approximately 1–2 orders of magnitude greater than required for rats (Fig. 4), an HRTP above the rat LOAELs/NOAELs may be justifiable. Thus, the proposed dose-based HRPT of 5-fold below the rat LOAELs/NOAELs for assuming DA in a cumulative risk assessment is a conservative estimate for TDS-like effects on the developing male reproductive tract of humans, and likely provides at least an additional order of magnitude conservatism. Although the DA–CAOS concept does not require a mechanistic rationale for estimating combined effects, the fact that both phthalates and DES produce effects on the developing male reproductive tract secondary to inhibition of Leydig and Sertoli cell function provides relatively high confidence that a dose-based HRPT of 5-fold below the rat NOAEL is adequately protective of human health.

Over the past decade, a number of epidemiology studies have appeared in the scientific literature that compared urinary concentrations of phthalate metabolites and developmental effects in infants, including anti-androgenic effects (e.g., cryptorchidism, anogenital distance). Those studies have a number of features in common: a proposed hypothesis based on the results of animal studies, limited populations, limited number of biomarker samples during pregnancy, and limited concurrence with animal data. Although virtually all of the studies report one or more statistically significant associations, none offer a basis for testing the HRPT approach on the potential for anti-androgenic effects in infants exposed to individual or multiple phthalates. Causal interpretation of the epidemiological findings is problematic due to several limiting factors, which are often well described by the investigators. In addition, there is a considerable amount of inconsistency among the human studies and between the animal and human studies.

Human versus rat comparisons for the potency of finasteride suggest a conservative potency-based HRPT of 1 order of magnitude below the potency of finasteride for effects on the rat male reproductive tract from androgen deficiency via inhibition of 5-alpha-reductase. This potency-based HRPT would be applied to chemicals meeting TEQ criteria for similarity of mode of action and structure–activity parameters with finasteride, and provides approximately an order of magnitude conservatism based on data indicating that humans have similar sensitivity as rats to effects of finasteride, as explained above in Section 2.4.2 and illustrated in Fig. 5. This potency-based HRPT would trigger the assumption of DA for all chemicals meeting TEQ criteria whose potency for inhibition of 5-alpha reductase is within one order of magnitude that of finasteride. Chemicals with lower potency would be assessed by IA, or by DA using an HRPT set on dose, in this instance, at doses within 5-fold below their individual NOAELs/LOAELs for CAOS on the developing male reproductive tract. Although we have not derived potency-based HRPTs specifically for androgen receptor antagonists or for inhibitors of particular enzymes in the steroidogenic pathway, these would be derived as was done for finasteride if cumulative assessments are desired for exposure to groups of chemicals that act specifically by these modes of action.

Applying the HRPT approach to the risk assessment for 15 anti-androgens results in an estimate of risk for phthalates 2 or more orders of magnitude lower than concluded in the published assessment (Kortenkamp and Faust, 2010). This is due to the fact that a conservative HRPT of 5-fold below the rat NOAEL precludes application of DA to lower human exposures, whereas Kortenkamp and Faust (2010) assumed DA for all doses and ratios based on human RfDs 200–500-fold lower than rat NOAELs. In contrast, use of the more biologically plausible HRPT approach leads to a conclusion that under current exposure conditions, phthalates should not be assessed by DA, and that few, if any of the other chemicals included in the published risk assessment (Kortenkamp and Faust, 2010)

should be assessed by DA at current exposure levels. Instead, IA should be applied to those chemicals.

5. Conclusions

Limitations in the study designs for mixtures of rodent anti-androgens (Table2), albeit imposed by practical necessity for studies in live animals, impart an undefined level of uncertainty to the extrapolation of experimental results beyond the doses and ratios tested. Additional uncertainty is introduced by the use of scored endpoints and the way these scores were combined for some analyses. A statistical analysis of precision using published data from the mixtures studies in question indicates that the model predictions may vary as much as 2-fold for the dose ratio and concentrations of chemicals tested. This variance would expand with extrapolation to untested ratios and doses. Extrapolation to lower doses is totally dependent on the model employed and because no data exist to support the extrapolation, this could dramatically increase variability and lead to erroneous conclusions. These factors reduce the confidence that can be placed in the conclusion that mixtures of anti-androgens are DA, even within the dose ranges evaluated, but even moreso at untested concentrations and ratios. No objective information allows one to conclude that DA is more accurate than IA at relevant human exposure levels. Given the questions raised here (Section 2.2) and the fact that the Rider et al. (2008) and Metzdorff et al. (2007) data, taken together, indicate that DA as well as IA predict a variety of relevant responses in the developing male reproductive tract of rats, it is unclear if not unscientific to assume DA by default based on a preference for conservatism, as claimed (Kortenkamp and Faust, 2010). Since risk management decisions often involve choosing between various options, it is impossible to make those decisions in a precautionary mode without understanding the underlying accuracy of scientific assessments. Therefore, the preference of models used to scientifically assess human health risks would be best based on data rather than on presumptions about what constitutes a precautionary decision.

The DA–CAOS theory is inconsistent with established pharmacological principles that relate affinity, intrinsic activity, and efficacy to relative potency estimation, and overlooks potential dose-dependent changes in pharmacokinetic interactions. Logical predictions of the DA–CAOS concept are also inconsistent with available clinical and epidemiological information. The incidence of TDS in humans, considered by some to be consistent with phthalate syndrome in rats, is quite low, whereas applying the DA–CAOS theory to all potential anti-androgenic drugs and chemicals would predict an epidemic of the syndrome affecting nearly the entire human population. The strong suggestion of a clinical threshold for DES-induced male reproductive tract malformations is inconsistent with the assumption of DA–CAOS, given the fact that human exposure to many anti-androgenic drugs and chemicals was significant during the DES episode. If combined exposures to chemicals that can affect a CAOS truly operate by DA irrespective of their potencies and concentrations, it is difficult to imagine how living organisms could survive in a world composed of hundreds of thousands of chemicals, all of which produce overt toxicity at some level of exposure. Indeed, the DA–CAOS theory contravenes well-established principles of pharmacological and toxicological action evidenced by mechanistic and clinical data derived from human pharmaceutical experience.

Comparison of published data for human and rat male reproductive tract sensitivities to DES and finasteride reveals that relying on rat data while ignoring the relative sensitivity of the human fetus has introduced considerable but unnecessary uncertainty and conservatism to the published human health risk assessments for anti-androgens (Kortenkamp and Faust, 2010; Benson, 2009). The magnitude of this unnecessary conservatism is at least 2 orders of magnitude, and perhaps as much as 4 orders of magnitude. Taken together, the uncertainties and conservatism introduced by applying DA to all anti-androgens at all doses, irrespective of mechanism, and ignoring human versus rat sensitivity render scientific conclusions based on the mixture studies at issue tenuous and regulatory decisions based on the risk assessment utilizing such studies arbitrary.

The DA–CAOS recommendation and the risk assessment based upon it are radical departures from past EPA practice regarding similarity criteria for applying dose addition (Table 1)(Borgert et al., 2004). Furthermore, this approach appears to ignore the entire logic of the TEQ requirements, which were developed as inclusion criteria for applying DA in cumulative risk assessments, i.e., to increase the reliability of extrapolating the DA assumption beyond empirical data. Nonetheless, because sophisticated pharmacological and toxicological knowledge is not required for its application, the DA–CAOS concept could be rationally applied, but only as a coarse screening level assessment. This is consistent with the historical use of hazard-index based approaches, which are used in screening-level baseline risk assessments to project acceptable cleanup criteria for hazardous waste sites.

If a DA–CAOS-type assessment suggests that human exposure to some groups of chemicals may exceed its conservative parameters, a more biologically based method of assessing actual risk is warranted. We have proposed such a method – the HRPT approach – to fulfill this need. The HRPT approach builds upon tenable assumptions of the DA–CAOS approach and the more biologically based TEQ approach used for decades by EPA and other regulatory bodies, but offers a means of improving the accuracy and reliability of the risk assessment by incorporating human data into the potency and combined-effect analysis. The HRPT approach is widely applicable and is feasible for any type of effect that is produced by groups of chemicals for which direct human data are available. Given the wide array of pharmacological modalities by which human pharmaceuticals act, sufficient data are available for applying the HRPT approach broadly in toxicological risk assessment.

6. Conflict of interest statement

The authors have no conflicts of interest that affect their scientific analysis or conclusions. There are no contractual relations or proprietary considerations that restrict the authors' publication or dissemination of their findings. C.J. Borgert received financial support to undertake portions of this analysis from the American Chemistry Council. The analysis and views expressed here are those of the authors and do not necessarily reflect those of the American Chemistry Council or its members.

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APPENDIX 2

Borgert, C.J., Baker, S.P., and Matthews, J.C. (2013). Potency Matters: Thresholds Govern Endocrine Activity. Regul Toxicol Pharmacol 67, 83-88.

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Potency matters: Thresholds govern endocrine activity ☆

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ABSTRACT

Whether thresholds exist for endocrine active substances and for endocrine disrupting effects of exogenous chemicals has been posed as a question for regulatory policy by the European Union. This question arises from a concern that the endocrine system is too complex to allow estimations of safe levels of exposure to any chemical with potential endocrine activity, and a belief that any such chemical can augment, retard, or disrupt the normal background activity of endogenous hormones. However, vital signaling functions of the endocrine system require it to continuously discriminate the biological information conveyed by potent endogenous hormones from a more concentrated background of structurally similar, endogenous molecules with low hormonal potential. This obligatory ability to discriminate important hormonal signals from background noise can be used to define thresholds for induction of hormonal effects, without which normal physiological functions would be impossible. From such thresholds, safe levels of exposure can be estimated. This brief review highlights how the fundamental principles governing hormonal effects – affinity, efficacy, potency, and mass action – dictate the existence of thresholds and why these principles also define the potential that exogenous chemicals might have to interfere with normal endocrine functioning.

1. Introduction

The European Commission asked DG Environment to develop a definition of and criteria for identification of endocrine disrupting chemicals (EDCs) applicable to several legislative structures, e.g., the plant protection products regulation (Reg. (EC) No 1107/2009), the biocidal products regulation (Reg. (EC) No 528/2012), and REACH (Reg. (EC) 1907/2006. Besides definitions and criteria for EDCs, the Commission intends to answer whether EDC threshold levels can be determined. Stakeholders offer different opinions on this matter and several agencies have responded to these issues. The European Food Safety Authority (EFSA) recommended clarification of issues regarding biological thresholds and the criteria for adversity versus physiological modulation and homeostatic responses (EFSA, 2013). The Swedish Chemicals Agency concluded "…that the decision on whether or not to accept a non-threshold model for EDCs has to be based on considerations of mechanism of action. Thus, the assumption of no threshold may be as valid, or questionable, for EDCs as for genotoxic carcinogens." (KemI, 2013a). The UNEP and WHO (2013) report entitled "State of Science of Endocrine Disrupting Chemicals" concluded that endocrine disruptors produce non-linear dose responses (there referring to non-monotonic dose response curves) and no threshold can be assumed. Similarly, several publications cited in these reports question the existence of thresholds and suggest that no safe dose can be defined for EDCs.

Overall, six primary considerations have been offered to refute safe threshold levels for EDCs (KemI, 2013b): (1) the complexity of the endocrine system; (2) the presence of sensitive developmental stages; (3) long intervals between the exposure event and the appearance of the adverse effect; (4) no threshold of effect for an endocrine disrupting agent added to a hormone system that is already active, where theoretically, one molecule could activate a receptor when adding to background; (5) scientific difficulties that preclude establishing safe exposure levels, especially for human and other populations, and; (6) the scientific uncertainty in predicting endocrine effects and thereby assessing risks of EDCs.

Many of these considerations can be addressed through an understanding of how the normal functioning of the endocrine system relies on fundamental principles of receptor, enzyme, and transport kinetics, upon which the fields of endocrine physiology and pharmacology are built. The fundamental principles of endocrine action dictate the existence of thresholds that determine whether and to what degree any substance – endogenous or exogenous – may affect the endocrine system. Hence, this

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present review intends to address (1) why the endocrine system could not function if thresholds did not exist; (2) how principles of endocrine pharmacology – affinity, efficacy and potency based on mass action (for reviews of receptor, enzyme and transport kinetics, see Matthews, 1993; Kenakin, 2009) – dictate thresholds, and; (3) why all conceivable effects of chemicals acting through or interfering with aspects of endocrine mechanisms that rely on molecular specificity are governed by these basic rules. In short, as has been concluded for other modes of action (MOA), we assert that principles of endocrine pharmacology imply certain "....rate-limiting key events that, if not met, can lead to a threshold for the dose–response, irrespective of the MOA involved." (Boobis et al., 2009).

We attempt here to concisely describe the fundamental principles that make the case for the existence of thresholds in endocrine action, but we specifically do not represent this work as a critical treatment of all related issues or as a comprehensive review of endocrine action. Toward this end, we have cited general textbooks in several places, for two important reasons. First, some concepts would have required intricate explanations if pieced together from the primary literature that established them, thus reducing clarity and brevity. Second, we wish to emphasize that many principles discussed here are sufficiently well established in the field of endocrine pharmacology that they have been taught in standard textbooks for many years up to the present. Finally, although we make the case that thresholds are obligate for endocrine action, we do not attempt to define thresholds for adverse effects, which may be higher than the thresholds at which normal endocrine functioning can be affected due to ADME and other adaptive and protective mechanisms within animals.

2. Elementary review of endocrine pharmacology

The endocrine system provides major physiological controls in animals with critical roles in development, maturation, and maintenance of health through long-term homeostasis. These functions are accomplished through sophisticated chemical signals mediated by substances known as hormones, which are produced in and released from specific cells and transported, often via blood, to target organs or tissues where the hormonal response is produced (Chedrese, 2009). Many different types of hormonal signals are required for the complex functioning of higher mammals and more than five hundred different effector molecules have been identified in humans (Chedrese and Celuch, 2009). Hormones within related classes are usually derived from common precursors and share similar chemical structures, e.g., steroid hormones derived from cholesterol or catecholamine hormones derived from tyrosine (Chedrese, 2009). Structural similarities extend to many common endogenous molecules, including hormone precursors and metabolites and intermediates and end-products of various biochemical pathways (Chedrese and Celuch, 2009).

Typical extracellular concentrations of functionally active hormones are in the range of 10^{-11} to 10^{-9} molar whereas those of structurally similar, non-hormone molecules (e.g., sterols, amino acids, peptides) are in the range of 10^{-5} to 10^{-3} molar (Chedrese and Celuch, 2009; Grannar, 1993). Given this overwhelming presence of structurally similar molecules relative to hormones, the challenge to maintaining a functional and efficient hormone-based communication system is formidable. Normal endocrine functioning requires that target cells efficiently identify and differentiate the various hormones from other molecules that are present in the extracellular fluid at molar excesses of 10^{6}- to 10^{9}- times (Chedrese and Celuch, 2009; Grannar, 1993). Without the ability to clearly distinguish molecules that convey critical physiological information from structurally similar molecules in the body, the endocrine system would be unable to process specific, vital signals amidst a steady roar of biological noise.

The capacity to achieve these distinctions is based on conformational matching of hormones with receptor structures present in target tissues (Chedrese and Celuch, 2009). These matches are highly selective so that only tight structural pairings produce biological effects that convey important information (Chedrese, 2009; Chedrese and Celuch, 2009). Only certain hormones (called "ligands") fit a particular class of hormone receptors with sufficient complementarity to produce receptor-mediated effects (Chedrese and Celuch, 2009).

2.1. Affinity

Affinity is a primary molecular property enabling the endocrine system to communicate vital information to different tissues of the body and to distinguish this information from biological noise. In broad terms, affinity is the strength of the molecular interaction between a receptor and its ligand (Chedrese and Celuch, 2009; Matthews, 1993), conferring a tendency for the molecules to remain associated once contact has occurred. An endogenous hormone has high affinity for its conjugate receptor such that when contact occurs, a strong molecular interaction follows. Conversely, molecules with low affinity for a hormone receptor will not associate tightly and will more readily dissociate from it.

Affinity has two important consequences for hormone action. A high-affinity ligand fits the receptor well, such that any given contact event is likely to result in a conformationally correct association. This accomplishes the first step of hormone action at the target cell, called receptor binding. Second, for a given number of molecular contact events, a high affinity ligand has a much greater tendency to remain associated with its receptor than a low affinity ligand, a property typically quantified by a dissociation constant. The affinity of a ligand for its receptor determines the fraction of available receptors that will be occupied at any particular ligand concentration (Chedrese and Celuch, 2009; Matthews, 1993), usually referred to as "receptor occupancy." Thus, the greater the affinity, the lower the concentration of the ligand required to bind and occupy receptors.

The affinities of various hormone receptor-ligand combinations can vary depending on the needs of the particular hormonal pathway. Normally, affinities are finely matched with the concentration of hormones required to produce the desired response in target cells (Chedrese and Celuch, 2009). As well, the fraction of available receptors that must be activated to produce a cellular response varies with target cell and tissue type. Overall, affinity dictates whether the ligand has the opportunity to accomplish the second task of hormone action, receptor activation (Chedrese and Celuch, 2009; Matthews, 1993).

2.2. Efficacy

The degree of receptor binding and occupation achieved by low concentrations of high affinity endogenous hormone ligands could theoretically be augmented by a proportionately greater concentration of low affinity ligands, and thus, might lead to cellular responses. However, affinity is not the only determinant of how effectively a ligand activates a receptor. The ability of a bound ligand to efficiently activate a receptor and trigger a cellular response is called "efficacy." There are several theories on the molecular nature of efficacy, including receptor occupancy theory and conformational models, with contributions from post-receptor events (Clarke and Bond, 1998; Kenakin, 2004). Efficacy can range

from negative to positive values where a ligand with high (positive) efficacy is capable of eliciting the maximal cellular response.[1]

2.3. Potency

Together, affinity and efficacy determine the potency of a ligand to activate specific hormone receptors and to elicit specific cellular responses in target tissues. Because the manifestation of these properties involves a variety of molecular interactions, potency and efficacy may not be tightly coupled across dose–response ranges and among different tissues and hormone receptor types (Kenakin, 2009; Simons, 2008). However, both properties are essential for hormonal activity (Kenakin, 2009), and endogenous hormones tend to be very potent because they typically possess both high affinity and high efficacy. Pharmacologically, these are referred to as potent hormone receptor agonists. Molecules with high affinity but no efficacy are receptor antagonists, i.e., they block the action of endogenous hormones because they interact with and occupy the receptor, preventing its occupation by ligands with efficacy, but themselves produce no response.

Endogenous hormones have high potency and so produce a greater cellular response for a given concentration than lower potency ligands. For example, in a yeast reporter assay, the endogenous estrogen 17β-estradiol achieves one-third maximal activation of the native human estrogen receptor at a concentration of 10^{-10} molar and maximal activation at 10^{-8} molar. In contrast, testosterone produces no measurable activation of that receptor at concentrations less than 10^{-6} molar, and its highest achievable activation requires 10^{-5} molar but is only one-third maximal. Progesterone is inactive at all concentrations in this system (Chen et al., 2004). On the basis of this assay, testosterone exhibits a relative potency of about 1×10^{-5} (one one-hundred thousandth) that of 17β-estradiol.

A chemical with low affinity can produce a cellular response if it has efficacy and if a sufficient concentration can be achieved at the receptor site. However, at relatively low concentrations, such chemicals would lack detectable endocrine activity against the background of endogenous hormones already occupying receptors. For instance, even in the treatment of hormone-deficiency disorders, where the background concentrations of natural hormone are low, only potent molecules have been found to be effective therapeutically. Similarly, during a woman's lifetime, potency differences dictate which estrogenic hormone is dominant – 17β-estradiol > estrone > estriol – yet even these differences span less than two orders of magnitude (Chen et al., 2004; Kuiper et al., 1997). In contrast, putative environmental estrogens exhibit potencies three or more orders of magnitude below that of 17β-estradiol (Borgert et al., 2003; Wu et al., 2008), indicating a low potential for estrogenic activity. Since circulating endogenous estrogen concentrations are several hundred times greater in women compared to rodent test species, an inference of human risk from low-potency chemicals based on endocrine disruptive effects observed in those species would be speculative (Witorsch, 2002).

2.3.1. Thresholds

The differences in affinity and efficacy between hormones and structurally similar endogenous molecules that do not act as hormones imply potency thresholds in the activation of cellular responses (Borgert et al., 2012). Although such biological thresholds would vary for different types of hormone receptors and with the degree of receptor activation required to induce cellular responses, any detectable hormonal activity will require an appropriate concentration of ligand with sufficient potency. These sufficiency requirements amount to thresholds for activation. Target cells may have receptors for various hormones, each present in a finite number at any given time (Chedrese and Celuch, 2009). However, target cells do not respond to receptor activation on an individual basis, but read the status of receptor activation collectively. An example of this is the regulation of gene expression, where on average, at least 5 transactivators need to be activated simultaneously to induce gene expression for any gene. Many, if not most, of these transactivator activations are the result of activity in the endocrine system (Nelson and Cox, 2008). Thus, hormonal responses in target organs, tissues or groups of cells require coordinated changes in the status of receptor activation. This requirement for a coordinated change in receptor activation creates a second threshold mechanism by which the endocrine system distinguishes important signals from biological noise (Matthews, 1993).

Nonetheless, it would be fair to ask, can the thresholds of biological potency and for a coordinated change in receptor activation status in target tissues and organs could be overcome by a molar excess of molecules that have low affinity but high efficacy, particularly if the endogenous hormone concentration is augmented by continuous, long-term exposure to environmental chemicals with similar properties? Some assert that because the endocrine system is already stimulated by endogenous hormones, the threshold for activation is already exceeded and therefore, any potential hormonal activity that is introduced, no matter how slight, will increase (or decrease) this baseline activity. This is the foundational hypothesis of the endocrine disruptor theory – usually termed "additivity to background" – and asserts that because concentrations of endogenous hormones are low and fluctuate widely, small additions or subtractions of even a single molecule will result in altered hormonal responses (Hass et al., 2013). A few simple calculations, however, illustrate why one or a few molecules added to an existing level of molecules will not change receptor occupancy in any detectable way, and why the molar excess of low potency ligands would need to be substantial to alter hormonal responses.

If the endogenous hormone is present at 10 parts per quadrillion, and we assume it has a molecular weight of 100 mass units, its concentration is 1×10^{-13} molar, or 6×10^{10} molecules per liter. This is at the low end of the effective physiologic concentration range for even the most potent endogenous hormones. The diameter of typical eukaryotic cells ranges from 10 to 100 μm. Choosing a value near the center of this range gives a radius of 20 μm, and assuming the cell is roughly spherical gives a volume for a single cell of about 3×10^{-11} liters, which translates to about 2 molecules per cell. At 1×10^{-13} molar, a hormone with an affinity constant of 1×10^{-11} molar would produce only about 1% receptor occupancy. If the endogenous hormone is present at its K_D concentration (1×10^{-11} molar) receptor occupancy would be at 50%. Adding an equipotent ligand at a concentration of 1×10^{-13} molar would increase receptor occupancy to 50.25%. If we add a ligand with high efficacy but with an affinity 10^3 lower than the endogenous ligand, it would require 250 times more of that molecule (2.5×10^{-11} - molar) to increase receptor occupancy by the same amount. If instead we add a ligand with the same affinity as the endogenous hormone but with low efficacy at a concentration of 1×10^{-13} - molar, this molecule would behave as a competitive antagonist and it would decrease receptor occupancy by the endogenous hormone by 0.25%. Similarly, lower concentrations of added ligands would have proportionally smaller effects. Therefore, any added receptor ligand, endogenous or exogenous, highly potent or not, would need to approach at least the 1×10^{-13} molar level to have any measurable or detectable influence on receptor occupancy.

[1] Efficacy is technically considered a product of a ligand's ability to stimulate a receptor, termed "intrinsic activity," and the ability of the stimulated receptor to elicit the cellular response. The distinction is not essential for understanding hormone action and thresholds.

This molar concentration translates to approximately 2 trillion molecules in the body water compartment (about 33 liters) of an average sized woman (66 kg), and more in men, in whom body water is typically a higher percentage of the body weight. This disputes the no threshold effect level hypothesis, given that a receptor is necessary for the effect, and negates the notion that a single molecule could produce an effect, even theoretically. If this were not so, normal, small changes in the intra- or extracellular milieu – i.e., in the concentrations of hormone precursors, metabolites, metabolic intermediates, etc., many of which possess low affinity and low efficacy for hormone receptors – would be detected as hormonal signals and produce measurable tissue and organ disturbances.

An example of this phenomenon involves the demonstrated ability of essential fatty acids to stimulate proliferation (Rose and Connolly, 1989) and selectively modulate estrogenic responses (Menendez et al., 2004) in estrogen-sensitive human breast cancer cells in culture, and to bind estrogen receptors and induce certain estrogen responsive genes in other in vitro assays (Liu et al., 2004). Nonetheless in women administered flaxseed supplementation, a rich source of these essential fatty acids, no significant changes are seen in serum hormones or biochemical markers of bone metabolism, both of which would be expected from estrogenic action (Brooks et al., 2004). Flaxseed supplementation does not alter follicle stimulating hormone or estradiol levels or produce clinically important estrogenic effects on the vaginal epithelium or endometrium in women (Colli et al., 2012), or alter uterine responses to estradiol in rats (Sacco et al., 2012). Insufficient potency appears to underlie the inability of even high levels of essential fatty acids to exhibit hormonal effects, despite activity in vitro. Another recently published example of this principle shows that metabolites of dehydroepiandrosterone (DHEA) lack sufficient potency via androgen or estrogen receptors to account for their biological activities, even though their potencies are within roughly three orders of magnitude of the principal endogenous hormones (Shaak et al., 2013). Although neither example precludes all possible modes of endocrine action, they clearly illustrate the difficulty of reconciling the additivity to background hypothesis with the ability of hormones to convey meaningful biological information amidst the high background of endogenous biological noise due to structurally related endogenous molecules.

Based on the above considerations, in order for an exogenous chemical substance to be able to alter the normal physiological functioning of the endogenous endocrine system, it is necessary for that chemical to achieve a sufficient activity level. This activity level will depend upon the ability of the chemical substance to interact with and modify the activity of one or more components of the endogenous endocrine system, its affinity for such interactions, and its concentration. To be sure, the existence of thresholds for endocrine activity is demonstrable from theory based on established principles of hormone action, as we have argued. The quantitative magnitude of a particular threshold is both calculable from theory, as our earlier example indicates, and empirically estimable. The minimum level of endocrine activity capable of altering physiological functioning can be used to quantify a biological potency threshold, the range of which is estimable from empirical measurements relevant to any specific endocrine activity. Recognizing that no biological measurement is without technical limitations and some uncertainty, conservative thresholds could be estimated based on the life stage or condition at which the activity level of the primary endogenous ligand is lowest. Defining endocrine thresholds in this manner identifies the types of endpoints useful for interpreting biologically meaningful effects, i.e., those that allow measurement of relative potency for a specific hormonal effect. We have not attempted to define thresholds for adverse effects, which may be higher than the thresholds at which normal endocrine functioning may be affected, i.e., biological potency thresholds, due to ADME and other adaptive and protective mechanisms within animals.

2.4. Signal amplification, regulation of receptor number and sensitivity, cross-talk, and feedback

Admittedly, an adequate description of endocrine mechanisms and responses is more complex than the recognition of thresholds and laws of mass action (Falkenstein et al., 2000; Björnström and Sjöberg, 2005). Not only are hormonal signals filtered from background biological noise by potency differences, but hormonal signals are amplified, receptor numbers are up- and down-regulated, there is cross-talk between different hormonal receptors, and hormones themselves are controlled by negative feedback loops (Chedrese, 2009). All of these processes are governed by the kinetic principles explained above, and may be important in further differentiating hormonal signals from endogenous and exogenous biological noise. Hormonal signals are enhanced by modifying factors within cells, a feature that allows the endocrine system to efficiently convey nuanced biological information through a single receptor-ligand system (Simons, 2008; Gronemeyer et al., 2004). The variety and complexity of hormone signal enhancement is beyond the scope of this simple review, but its significance cannot be underestimated; signal modification further differentiates biological information from background noise, making the endocrine system even more resilient to spurious interruption, not more sensitive to it. To provide one brief example, the influence of modulatory factors, including coactivators, co-repressors, and other transcriptional modifiers may influence the shape of the dose–response curve for gene expression and may underlie apparent differences in agonist EC_{50} values for inducing different genes via a single hormone receptor. Interestingly, the same factors that decrease the EC_{50} values for agonists usually increase the amount of partial agonist activity for antagonists, and this inverse relationship suggests that the two behaviors are tightly coupled (Simons, 2006). Thus, the dynamic sensitivity of hormone receptors to ligand activation appears to be coordinated in such a way that potency differentials are maintained, and also therefore, protection against spurious perturbation. The ability of endocrine signaling to convey these distinctions is critical to survival.

3. Other arguments against thresholds

The sensitivity of developmental life stages to endocrine-mediated perturbations is one of the arguments used most often as proof against endocrine thresholds. While true that hormonal activity is critical and even vital during development, one must ask whether an increased sensitivity to the severity of a perturbation equates to a lower threshold for that perturbation. These would seem to be distinctly different phenomena that should be distinguished when considering thresholds for endocrine disrupting effects. Similarly, while there is little disagreement that thresholds for endocrine-mediated adverse effects will vary depending on many factors, there is little evidence suggesting that the fundamental rules governing endocrine function cease to apply or that endocrine thresholds disappear altogether during certain periods of life. Indeed, thresholds for reproductive toxicity are the norm (Piersma et al., 2011). Moreover, it has long been known that, although oral contraceptives are embryo lethal at one hundred times the human contraceptive dose, fetuses that survive the exposure are not adversely affected (Prahalada and Hendrickx, 1983).

Indeed, endocrine pharmacotherapy could not be as effective as it is, regardless of whether natural or synthetic remedies are used, if effective and safe doses could not be predicted. The rare

occurrence of adverse effects that become evident only after extensive post-marketing surveillance would contravene this maxim only if those adverse events were produced by the primary hormonal mechanism targeted by the medication. In contrast, whereas toxic effects of drugs are dose-related, mechanistically predictable exaggerations of the desired therapeutic effect, untoward side effects and rare adverse drug reactions occur by some other mechanism and may or may not be dose-related (Edwards and Aronson, 2000).

Finally, citing the example of hormone-dependent cancers of the breast and prostate, the argument is often advanced that since adverse effects already occur at endogenous hormone levels, any change, no matter how small, portends additional disease. This argument depends on the logic that because growth and spread of these cancers depends on hormonal stimulation, endogenous hormones are the determinative factor in causing the cancer. However, that logic runs counter to most common rules of causal argumentation, which require a counterfactual demonstration, and contravenes current theories of cancer progression.

Current theories regarding the role of hormones in carcinogenesis posit that cellular abnormalities in hormone-responsive tissues, caused irrespective of hormonal involvement, produce cells whose response to hormones becomes increasingly aberrant, and eventually, neoplastic (Li et al., 1993). For example, the cancer stem cell theory posits that malignant breast stem cells, present in early development before estrogen receptors are expressed, play a key role in breast cancer development (Eden, 2010). These theories explain several observations, including why many individuals with similar or greater hormonal exposure fail to develop cancer. The observed correlation between lifetime estrogen exposure and breast cancer is logical since aberrant cells dependent on estrogen would be expected to grow more rapidly in the presence of more estrogen, or to out-compete normal cells whose replication number is limited by estrogen exposure.

4. Conclusion

The manifestation of a detectable hormonal response at the tissue and physiologic level in humans or animals depends on whether: (a) a sufficient number of specific cellular receptors are occupied by ligand molecules of sufficient specificity and potency to induce individual cells to respond to a given hormonal signal and (b) a sufficient number of cells respond to a given hormonal solicitation, enough to manifest a detectable physiologic effect at the tissue or organism level. These fundamental principles are derived directly from established knowledge about hormonal mechanisms. Normal functioning of the endocrine system thus requires precise discernment of ligand potency and amount to enable transmission of vital signals amidst an endogenous background of spurious molecular interactions. This ability to discern defines the threshold. Potency differences, laws of mass action, and the basic design and physiological functions of the endocrine system require and ensure the presence of thresholds.

Without thresholds, there would be chaos in cellular and tissue responses under normal physiological conditions, even absent exogenous EDCs, and there could be no regulated progression of signals and functions compatible with reproduction, development, behavior, repair, immunity, and life itself. It thus seems intuitive that if chemicals are to have a chance to disrupt natural endocrine signals, their doses/concentrations and potencies ought to be similar to or stronger than the natural hormones (Dietrich, 2010; Golden et al., 1998; Marty et al., 2011). This strength of potency and amount defines a minimum requirement for influencing endocrine activity, which implies that defining either an endocrine hazard or a potential therapeutic effect requires an evaluation of potency and physiologically achievable concentrations. These principles have successfully guided endocrine pharmacology (Cleve et al., 2012), wherein it is recognized that natural hormones and their specific modifiers are already present at concentrations that occupy the available cellular receptors and are well controlled to support normal physiological functioning. A reasoned assessment of the mechanisms of hormone signaling and processing shows that safe levels of exposure can be set for endocrine active substances based on biological and pharmaceutical principles, the empirical data on the doses at which adverse effects can be observed, and an appropriate degree of conservatism (Borgert et al., 2012; Caldwell et al., 2012).

Conflict of interest

The authors have no conflicts of interest that affect their scientific analysis or conclusions. There are no contractual relations or proprietary considerations that restrict the authors' publication or dissemination of their findings. C.J. Borgert received financial support to undertake portions of this analysis from BASF SE Corporation. The analysis and views expressed here are those of the authors and do not necessarily reflect those of BASF SE Corporation.

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August 28, 2014

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Attention: Rayetta G. Henderson, Ph.D., Senior Scientist

Dear Dr. Henderson:

RE: Independent Expert Review of CHAP Final Report on Phthalates and Phthalate Alternatives

Review of exposure-related sections of the "Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives" dated July 2014 has been completed and comments are attached. The review was conducted in accordance with the guidance you provided and focused on evaluation of Section 2.5 (Human Biomonitoring), Section 2.6 (Scenario-Based Exposure Assessment), and Appendices E-1 to E-3.

Please contact the undersigned should you require any clarification or additional information.

Respectfully submitted,
BEC Technologies Inc.

Kathryn Clark, Ph.D., P.Eng.

Comments on "Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives", July 2014

Summary

This review was focused on evaluation of exposure-related sections in the above referenced report (referred to herein as the "CHAP Report"), primarily Section 2.5 (Human Biomonitoring), Section 2.6 (Scenario-Based Exposure Assessment), and Appendices E-1 to E-3. In general, the approach employed was sound and included comparisons of human exposure to phthalate esters from biomonitoring data with exposures estimated from a range of sources including consumer products, diet, and environmental media. My concerns with the report are in how the results of the exposure assessment are used to respond to the questions posed to the CHAP, deficiencies in the methodology and available data for estimation of exposure to children's toys and child care articles, and also in some assumptions used in the calculations and inconsistencies in those assumptions, including receptor characterization and statistical measures.

The CHAP report states that "phthalates cause a wide range of toxicities in experimental animals but the one considered of greatest concern for purposes of this report is a syndrome indicative of androgen insufficiency in fetal life, what is referred to in rats as the phthalate syndrome, caused by exposure of pregnant dams to certain phthalates". Review of the toxicity evaluation is beyond the scope of my review; however, from a high level review point, it is unclear how recommendations can be made with respect to children's toys and child care articles when the toxicity endpoint is for non-users of those products (i.e., pregnant women, fetuses, and neonates). The CHAP report (Table E1-20) indicates that there is no exposure of pregnant women to phthalates contained in child care articles and that the highest potential exposure from dermal contact with toys is for DNOP (comprising 4.7% of total exposure to DNOP), followed by 0.5% for DEHP, and 0.1% for DINP. These estimated exposures are based on a scenario-based assessment described in the CHAP report as "highly uncertain" (p.E1-46) and are "hypothetical because these PEs currently are not allowed in toys" (p.E1-35).

The CHAP report recommends that the interim ban on the use of diisononyl phthalate (DINP) in children's toys and child care articles at levels greater than 0.1% be made permanent. The basis for this recommendation is not clear; according to the CHAP report (Table E1-20), exposure to toys and child care articles represents only 0.1% of total exposure to DINP for pregnant women so a ban would not be expected to alter exposure of pregnant women. For infants (Table E1-21) exposure to toys and child care articles represents 30% of total exposure to DINP; however, this percentage was calculated in the scenario-based assessment, which over-estimates total exposure to DINP by a factor of six (Table 2.14) and, therefore, it is highly uncertain what effect a ban on DINP in toys and child care articles would have.

Specific comments, listed by report section, are as follows:

Section 2.5 "Human Biomonitoring"

1. The CHAP report used human biomonitoring (HBM) data from the National Health and Nutrition Examination Surveys (NHANES; 2005–2006 data) for pregnant women and women of reproductive age and data from the Study for Future Families (SFF) for children from 2 to 36 months old, as well as prenatal and postnatal measurements of their mothers. The SFF data for children, age 2 to 36 months, are described in this section and elsewhere in the CHAP report as "infants". Infants (typically defined as 0 up to 12 months) differ greatly from toddlers (typically defined as 12 to 36 months) in their physical and behavioural characteristics and in their potential exposure to phthalate esters. Section 2.6 of the CHAP report (scenario-based exposure assessment) evaluates infants (0 up to 12 months) and toddlers (12 to 36 months), but compares the scenario-based infant exposure to HBM data for infants and toddlers. The HBM data for children, from the SFF, should be presented separately for infants and children, to examine if there are differences between the two groups and to enable comparison with the correct age group in the scenario-based assessment.

2. The NHANES data are "a national, statistically representative sample of the U.S. population"; however, it is not clear how representative the SFF data are of the population, especially given the small sample size (total sample size of 258 children of which approximately 25% were infants under 12 months of age). The CHAP report states that, for comparison to the NHANES and SFF data, a full literature review was conducted to compile worldwide data on phthalate exposure, in particular to pregnant women and infants; however, the list of references is not comprehensive. Examples of additional studies evaluating these receptor groups include Yan et al. (2009) for pregnant women in the USA; Lin et al. (2011) for pregnant women, toddlers, and children in Taiwan; and Koch et al. (2011) for children in Germany. Also, Tables 2.5 and 2.6 include data from studies of men (e.g. Duty et al. 2005a and 2005b; Jonsson et al. 2005) and studies where the data from both men and women are presented, but the original papers included data separated by gender (e.g. Guo et al. 2011; Koch et al. 2003b; Fromme et al. 2007b). The report would be improved if the women-only data were extracted from the original references and extraneous data were removed.

3. I am in agreement with the methodology used to calculate exposure from the HBM data. Section 2.5.3 states that the HBM data from NHANES was used to back-calculate exposure to nine parent phthalates: DMP, DEP, DIBP, DBP, BBP, DEHP, DINP, DIDP/DPHP, and DNOP and the SFF data were used to determine exposure to 8 parent phthalates: DMP, DEP, DIBP, DBP, BBP, DEHP, DINP, and DIDP/DPHP; however, Table 2.7 shows daily intake calculations for only six phthalates: DEP, DIBP, DBP, BBP, DEHP, and DINP. I was unable to locate the estimates for DMP, DIDP/DPHP, and DNOP.

Section 2.6 "Scenario-Based Exposure Assessment"

4. The scenario-based exposure assessment evaluates exposure to phthalate esters for four sub-populations, women of reproductive age (15 to 44 y), infants (0 to <1 y), toddlers (1 to <3 y), and children (3 to 12 y). Given the CHAP mandate, to evaluate exposure to products used by children, the sub-populations selected are appropriate, but it is not apparent how the results for toddlers

and children are used in the evaluation (i.e., the results of the exposure assessment do not seem to have been used in the risk assessment).

5. As discussed above, the SFF biomonitoring data for "infants" represent data for infants and children; Table 2.14 should be modified to show a comparison of estimated exposure of infants with biomonitoring data for infants only (not toddlers).

6. The scenario-based exposure assessment includes evaluation of all potential sources of phthalate esters, including environmental sources, consumer products, household media, and food products via inhalation, ingestion, and dermal contact. The objective was "to determine the significance of exposure to phthalates in toys as a major part of our risk assessment and for comparison to biomonitoring data. In addition, to meet part of the CHAP's charge, we estimated exposure to toddlers and infants for all soft plastic articles except pacifiers". Although some phthalate esters have been banned, the exposure assessment evaluated hypothetical exposures by assuming that the phthalate esters were present. This represents an important uncertainty in the analysis. Also, the HBM data were obtained from 1999 to 2005 (SFF data) and 2005 to 2006 (NHANES) when phthalate ester use patterns may have differed, even if not subject to a ban.

7. The scenario-based exposure assessment results in estimates of mean and 95th percentile estimates of exposure. I agree with use of 95th percentile estimates rather than maxima, but it would be preferable if median estimates could be provided as the HBM data are medians and 95th percentiles. For data that are positively skewed, as are the exposure data, the mean and median are very different.

Appendix E-1 "Modeling Consumer Exposure to Phthalate Esters"

8. This appendix presents a comprehensive analysis of exposure to phthalate esters by multiple pathways and provides the details to support the information presented in Section 2.6 of the main CHAP report.

9. Table E1-16 – the units for concentration in food should be ug/kg not ug/g; however, it appears that the correct values were used in the calculations.

10. Tables E1-20 to E1-23 note the categories of exposure that include products under CPSC jurisdiction. It would be helpful if these tables and the text also noted the subset of these products that are the subject of the CHAP report.

11. Section 4.1 of Appendix E-1 provides a good discussion of the uncertainties inherent in the scenario-based analysis. As mentioned on page E1-42, exposure to personal care products and air fresheners is likely double-counted as these exposures are calculated both directly and indirectly

through inhalation of indoor air. On page E1-46, the report concludes that the scenario of dermal contact with PVC products "provides highly uncertain exposure estimates". This is a very important uncertainty given the need to obtain reliable estimates of exposure from toys and child care articles. The CHAP report notes that "methods used here, for example, dermal contact with PVC articles, have not been validated, by comparison with more direct exposure measures. Additional data on percutaneous absorption are needed to estimate dermal exposure accurately". The report goes on to conclude that the results of the scenario-based exposure estimates compare favourably with the HBM estimates, "However, the appearance of concordance could also be due to compensating overestimates and underestimates in the present study".

Appendix E-2 "Children's Oral Exposure to Phthalate Alternatives from Mouthing Soft Plastic Children's Articles"

12. This appendix presents the estimation of exposure to phthalate alternatives due to mouthing of soft plastics. Three age groups were evaluated: 3 to 12 months, 12 to 24 months, and 24 to 36 months as "mouthing duration depends on the child's age and the type of object mouthed". This is appropriate; however, it is not consistent with the CHAP report evaluation of the biomonitoring data (refer to comment #1 above).

Appendix E-3 "Phthalate Dietary Exposure"

13. The purpose of this appendix is not clear as the methods, assumptions, and results of the evaluation of dietary exposure were adequately explained in Appendix E-1. Appendix E-3 presents a lengthy comparison of two sources of food data and three methods for grouping these data. However, Appendix E-1 justifiably argued that the measured concentrations in food in Page and Lacroix (1995) were too old as they were obtained in 1986 to 1989 and, instead, used the more recent data from the UK (Bradley, 2011). Therefore, it is not clear why the analysis in Appendix E-3 using the Page and Lacroix data was conducted. Also, Appendix E-3 includes receptors that are not part of the CHAP review (e.g. males and teens), further adding to the confusion.

References (cited above and not included in CHAP report)

Koch, H.M., M. Wittassek, T. Brüning, J. Angerer, and U. Heudorf. 2011. "Exposure to phthalates in 5–6 years old primary school starters in Germany—A human biomonitoring study and accumulative risk assessment. *Int. J. Hyg. Environ. Health*, 214(3):188-95.

Lin, S., H.-Y. Ku, P.-H. Su, J.-W. Chen, P.-C. Huang, J. Angerer, and S.-L. Wang. 2011. "Phthalate exposure in pregnant women and their children in central Taiwan". *Chemosphere*, 82(7):947-55.

Yan, X., A. Calafat, S. Lashley, J. Smulian, C. Ananth, D. Barr, M. Silva, T. Ledoux, P. Hore, and M.G. Robson. 2009. "Phthalates biomarker identification and exposure estimates in a population of pregnant women". *Hum. Ecol. Risk Assess*. 15:565–78.

REVIEW OF THE

REPORT TO THE U.S. CONSUMER PRODUCT SAFETY COMMISSION BY THE

CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES

JULY 2014

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Table of Contents

Background

This report of the Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate alternatives, prepared for the U.S. Consumer Product Safety Commission, describes a systematic approach to the review of the relationship between exposure to phthalates and phthalate replacement chemicals on reproductive, developmental, and systemic toxicology. The approach is broadly organized into an overview of the approach taken and methods for assessing the literature followed by a summary of the assessment for each individual phthalate and phthalate replacement chemical. Individual phthalates and phthalate substitute are discussed according to the relevant reproductive, developmental and systemic toxicology literature reviewed, human exposure, concluding with CHAP recommendation and answer to the charge of whether the recommended change would result in reduced exposure of children. In general the report is very well written and provides a comprehensive logical assessment of the literature. The authors are to be commended for their thorough assessment of the voluminous phthalate literature. A transparent and clear rational are provided for inclusion vs. exclusion of studies. Overall, this report addresses a very challenging subject and was a pleasure to read.

My review the CHAP assessment and recommendations on phthalates focuses on the relevance of animal data for human risk assessment. To accomplish this task, I have reviewed the epidemiological and animal sections of the report to identify critical evidence and endpoints used to establish report recommendations. I will provide a brief summary of what I see as the highlights of the report followed by detailed comments and suggestions for the author's consideration to strengthen the report as well as the resulting conclusions and recommendations.

Epidemiological evidence – Prior epidemiological studies reporting a decline in human semen quality, increasing rates of cryptorchidism and hypospadias, and increased prevalence of testicular cancer in young men have been linked with environmental contaminant exposures and are key elements in the testicular dysgenesis syndrome (TDS; (Skakkebaek *et al.*, 2001). The phthalate literature discussed in this report was reviewed in the context of the TDS. Phthalate exposure has been linked with developmental abnormalities of the male reproductive tract including cryptorchidism, hypospadias, and reduced anogenital distance (AGD) and anogenital index (AGI) in boys (Swan *et al.*, 2005; Swan, 2008; Huang *et al.*, 2009; Suzuki *et al.*, 2012) and decreased circulating testosterone concentrations in humans and experimental animals. Decreased AGD and AGI (Swan *et al.*, 2005; Swan, 2008) were considered to be the most sensitive outcome measure identified.

The rat phthalate syndrome - The authors take note of the rat phthalate syndrome which is characterized by reduced AGD, AGI, nipple retention, cryptorchidism, hypospadias, and attenuated circulating concentrations of testosterone (T). The authors provide a very nice rational for studies that form the basis for their conclusions vs. those that are excluded owing to inadequate sample size, lack of multiple dose groups necessary to characterize a dose response, routes of administration, and studies designed to provide mechanistic insight.

Proposed mode of action – Reduced AGD and cryptorchidism in human males and nipple retention, decreased AGD, cryptorchidism are all androgen dependent and thus the mode of phthalate action is thought to be the result of decreased circulating

concentrations of T. Also considered is the potential for phthalates to act as peroxisome proliferating receptor alpha (PPARα) agonists. However, the role of PPARα activation in the development of male reproductive tract abnormalities is unclear and thus this pathway was given less weight in the present assessment.

Mechanistic studies have demonstrated phthalate treatment induced decreased T concentrations and decreased expression of anti-müllerian hormone (AMH) and insulin like growth factor 3 (Insl3), genes encoding proteins central to development of the male reproductive tract. In addition, a small group of studies have relied upon animal and *in vitro* experiments to show that phthalates can decrease gene expression for cholesterol transport proteins including: peripheral benzodiazepine receptor, steroidogenic acute regulatory protein (StAR), and scavenger receptor class B1 (SRB1). Decreased expression for steroidogenic enzymes including: cytochrome P450 side chain cleavage (P450Scc), cytochrome P450c17 (P450c17), and 3-β hyrdoxy steroid dehydrogenase (3-βHSD). Although, the molecular mechanisms remain unclear and their relevance to developmental abnormalities in human males with developmental exposure to phthalates has yet to be determined, the underlying theme of this report is that the accumulated evidence suggests that phthalate exposure induces a hypoandrogenic state that culminates in decreased AGD and increased risk for cryptorchidism and hypospadias. In summary, the report does a nice job of summarizing the available literature and highlighting documented cellular and molecular targets underlying effects on the development of the male reproductive tract.

Order of endocrine disrupting potency - The author's put forward an order of potency of phthalates based on their reproductive and developmental toxicity as follows:

DPENP > BBP ~ DBP ~ DIBP ~ DHEXP ~ DEHP ~ DCHP > DINP

Cumulative action - The report brought forward several studies that illustrate potential additive effects of phthalates (Hotchkiss et al., 2004; Howdeshell et al., 2008; Rider et al., 2010; Hannas et al., 2012;). These data are used to suggest additivity of effects and support the conservative approach to the risk assessment based on anti-androgenic effects. This is most notable in the assessment and conclusions reached for DIBP and to a lesser degree for DPENP, DCHP, and DIOP.

Exposure estimates – The authors noted that exposures are higher for different age groups and in women, the highest phthalate exposures were reported for DEP, DINP, DIDP, and DEHP whereas in infants the highest phthalate exposures were DINP, DEHP, DIDP, DEP, DNOP, DEP, and BBP. In toddlers the highest phthalate exposures were DINP, DIDP, and DEHP whereas in older children the highest phthalate exposures included DINP, BBP, and DIDP.

Summary – From the report, the authors determined that the most sensitive adverse effect was decreased AGD and AGI in young boys based on two studies (Swan *et al.*, 2005; Swan, 2008). The most sensitive developmental stage was determined to be *in utero* development. Developmental effects representative of anti-androgenic effects were considered to be the most sensitive adverse outcomes documented in animal studies and adverse effects on testosterone production was considered the most relevant mechanism. Moreover, results from biomonitoring studies reveal widespread human exposure and several cited studies suggest that anti-androgenic phthalates can

act in an additive manner as stated above. Based on these considerations the interim ban on DNOP and DIDP are recommended to be dropped whereas the interim ban for DINP is recommended to be made permanent (**Table I**). The authors of the report also recommend that the phthalates BIBP, DPENP, DHEXP, and DCHP be changed to a permanent ban and DIOP be placed on an interim ban. Recommended changes to existing regulations, the endpoints used to reach these conclusions, no observable adverse effect level (NOAEL), exposure, and margins of exposure (MOE) are summarized in the table below.

Recommendations arising from the report

Table I. Phthalates and phthalate alternatives that are permanently banned, subject to an interim ban, or not banned, critical endpoints identified, estimated exposure from biomonitoring studies, margin of exposure and recommendations arising from the CHAP analysis.

	Name	Endpoint	NOAEL (mg/kg/day)	Exposure (µg/Kg/day)	MOE	Recommendations
Permanently Banned	Dibutyl Phthalate (DBP)	NR, AGD	50	0.6 – 4.0	8,000 - 83,000 1,300 - 13,000	NC
	Butylbenzyl phthalatae (BBP)	NR, AGD	50	0.3 – 1.3	6,800 - 147,000 770 - 10,000	NC
	Di(2-ethylhexyl) phthalate (DEHP)	RTM, DVO, DSP	5	3.5 - 181	116 - 191	NC
Interim banned	Di-n-octyl phthalate (DNOP)	NA	NA	4.5 - 16.0	2,300 - 8,200	Not banned
	Diisononyl phthalate (DINP)	NR	50	1.0 – 11.1	640 - 42,000	Permanent
	Diisodecyl phthalate (DIDP)	NAE	≥ 600	10 – 26.4	2,500 - 10,000 586 – 3,300	Not banned
Phthalates not banned	Dimethyl phthalate (DMP)	NAE	≥ 750	0.05 – 0.55	IC	NC
	Diethyl Phthalate (DEP)	NAE	≥ 750	3.4 - 75	NS	NC
	Diisobutyl phthalate (DIBP)	AGD	125	0.17 – 1.0	5,000 – 125,000 3,600 – 89,000	Permanent
	Di-n-pentyl phthalate (DPENP)	T PROD	11	NS	NS	Permanent
	Di-n-hexyl phthalate (DHEXP)	AGD	≤ 50	NS	NS	Permanent
	Dicyclohexyl phthalate (DCHP)	AGD	16	NS	NS	Permanent
	Diisooctyl phthalate (DIOP)	NA	NA	NS	NS	Interim ban

	Name	Endpoint	NOAEL (mg/kg/day)	Exposure (µg/Kg/day)	MOE	Recommendations
	Di(2-propylheptyl) phthalate (DPHP)	NA	NA	NS	NS	Inadequate data
	Phthalate substitutes					
	2,2,4-trimethyl-1,3 pentanediol disobutyrate (TPIB)	NAE	≥ 1,125	0.92 – 5.8	5,200 – 33,000	NC
	Di (2-ehtylhexyl) adipate (DEHA)	NAE	≥ 800	0.7 - 259	770 – 290,000	NC
	Di 2-ethylhexyl) terephthalate (DEHT)	NAE	≥ 750	0.69 – 2.8	56,000 – 230,000	NC
	Acetyl tri-n-butyl citrate (ATBC)	NAE	≥ 1,000	2.3 – 7.2	14,000 – 43,000	NC
	Cyclohexanedicarboxylic acid, dinonyl ester (DINX)	NAE	≥ 1,000	1.4 – 5.4	7,400 – 29,000	NC
	Trioctyltrimellitate (TOTM)	DSP	100	NS	NS	NC

AGD = Anogenital distance; DVO = Delayed vaginal opening; NA = Not available; NAE = No anti-androgenic effects observed; DSP = Decreased spermatocytes and spermatids; NC = No change; NS = Not stated; NR = Nipple retention; T PROD = testosterone production.

Comments for the authors

The CHAP report provides a thorough overview of a very rich data set and a logical progression is followed throughout the report. However, there are several issues and concerns that require the attention of the authors which are detailed below.

1. The CHAP report relies heavily on the purported relationship between phthalate exposure and reduced AGD in young boys (Swan *et al.*, 2005; Swan, 2008). However, the report fails to critically assess the reported link between phthalate exposure and reductions in AGD. Specifically, only four epidemiological studies are available in the literature and previous reviews have acknowledged the limited consistency of results for individual phthalates. While the present report recognizes the lack of consistency in the findings, it fails to discuss the lack of agreement between the U.S. studies in which many of the same subjects were included in the second study (Swan *et al.*, 2005; Swan, 2008). Furthermore, there is no discussion of the potential for type I error inflation and detection of spurious associations arising from multiple independent comparisons. Consequently, the link between phthalate exposure and reduced AGD is less convincing that suggested by the authors of this report. Moreover, the same evidence has been considered to be only modest by others (Kay *et al.*, 2014). Thus, it is suggested that the authors consider a more developed discussion of the dependence on the use of AGD as the critical marker of adverse effect and the overall strength or weakness of the data should also be acknowledged in the report. It is further suggested that the uncertainty in the association should be reflected in the risk assessment and conclusions reached.

2. Further to the points raised above, it is noted that several reports have raised the issue that AGD and AGI are not linked with any adverse clinical health outcome and thus lack of clinical relevance has been considered by others (McEwen, Jr. and Renner, 2006; Weiss, 2006) to be a weakness with these outcomes. This point should be discussed in the report. Several authors have made the point that these markers are linked with diminished reproductive health in males (Eisenberg *et al.*, 2012b; Eisenberg *et al.*, 2012a; Eisenberg *et al.*, 2011; Mendiola *et al.*, 2011b) and the strengths and weaknesses of this data should be discussed given the weight AGD and AGI are given in this report.

3. Human biomonitoring studies provide evidence of human exposure; however, the report does not acknowledge potential differences in absorption, distribution, rate of metabolism and excretion between rats and humans. Although the report places weight on the additivity of phthalates using this information to justify a conservative approach in the risk assessment, there is no discussion of the issues such as the rapid metabolism and excretion of phthalates and their metabolites (Anderson *et al.*, 2001). Moreover, evidence of phthalate metabolites in the urine provides evidence of exposure but provides no insight into potential target tissue distribution. Indeed, a detailed discussion of the pharmacokinetics of phthalates was noticeably absent from the report. The report would be much stronger with a discussion of the pharmacokinetics.

4. The report relies heavily on reports of additive effects with high doses of individual phthalates. It is suggested that this issue be treated more cautiously than done in the present study for several reasons as follows: (1) While there is evidence for additive effects at the high doses used by Howdeshell and co-workers (2007) there is no evidence that the same will hold true at concentrations representative of human exposure documented in contemporary biomonitoring studies (Kamrin, 2009). Indeed, typical exposures for most phthalates considered may be too low to by many orders of magnitude to produce the adverse effects described in this report. (2) The authors assume a single mechanism of action for all phthalates when stating that additive effects must be considered. While it is agreed that additive effects must be considered, it makes no sense to consider additivity when diverse mechanisms are at play and the individual phthalates are of divergent potency when acting via the same mechanism. (3) While there is evidence of additive effects in rats at high concentration it is unclear how these results translate to humans with much lower exposures, more complex exposures, and with generally less sensitivity to the adverse effects under consideration. Based on these considerations it is suggested that the authors consider a more detailed discussion of the issues relating to additive effects. Furthermore, on the basis of these considerations it is suggested that the conclusions and recommendations in the report are overly conservative and inadequately justified as written.

5. The testicular dysgenesis syndrome (TDS) has been proposed (Skakkebaek *et al.*, 2001) tying together several adverse health outcomes with a single unifying mechanism. The evidence linking exposure to environmental contaminants to increased rates of cryptorchidism is not well established. Despite similar exposures rates in cryptorchidism are not consistent from one region to the next and changing rates can also be explained by changes in medical practice and reporting methods and thus is a poor clinical outcome to consider as an indicator of contaminant effects on health. Although the rates of testicular cancer in young men have increased, environmental causes are not well established. Finally, the reported decline in male semen quality continues to be debated and a link with exposure to environmental contaminants far from being firmly established. Consequently, the TDS remains a proposed syndrome that has not yet gained general acceptance within the clinical, regulatory, and biomedical communities. In view of the uncertainty that continues to exist in the literature, it is suggested that the authors of the report acknowledge the weakness in the literature and allow for the associated uncertainty in their assessment of risk.

6. The assumed relevant mechanism of action described in this report is attenuation of androgen signaling via decreased T production that is directly translatable to humans. Following the review of individual phthalates the authors state that the animal data are assumed to be relevant to humans without any discussion. Indeed, comparative endocrinology between experimental animal models and humans is not given adequate attention in the report with each assessment stating only that the animal data is assumed to be relevant for humans. A robust literature exists which suggests that rats are relevant for hazard identification but may not be the best model for humans which appear to be less sensitive to phthalates. A recent report has illustrated that the abnormal clustering of Leydig cells and decreased T production seen in rats with developmental exposure to phthalates does not occur in mice and humans (Veeramachaneni and Klinefelter, 2014). Hence, it is suggested that mice appear to be a more relevant model for adverse health effects of phthalates on

reproductive tract development in humans (Kay *et al.*, 2014). This issue requires discussion in a revision to the report and should also be used in re-evaluating conclusions and recommendations.

7. The author's concluded that developmental effects on the male reproductive tract are the most sensitive adverse outcome in the animal studies. However, data contained in a recent systematic review of the literature suggest that semen quality is more sensitive to the adverse effects of phthalate exposure than reproductive tract development (Kay *et al.*, 2014). Can the authors comment on the divergent conclusions.

8. The heavy weight placed on effects on developmental abnormalities of the male reproductive tract is not unreasonable; however, the recommendation of a permanent ban on BIBP, DPENP, DHEXP, and DCHP seems difficult to comprehend in view of the large MOE for BIBP and the relatively weak data set available for the other three phthalates. Moreover, the absence of exposure data and any calculation of a MOE leads to difficulty in understanding the rational for the recommendations. Can the authors provide a more thorough argument for the recommendations?

9. The report provides a thorough review of the epidemiological evidence, animal studies and, where available, studies of phthalate mechanisms. The authors provide insight into the mechanisms for critically appraising the evaluated studies; however, the reviewed studies provide only a superficial assessment of the study quality limited to number of animals used, number of dose groups, and route of administration. Did the authors consider other potentially important variables such as use of positive controls, concurrent exposure to xenoestrogens, distribution of test chemical to target tissues, quantification of test chemical in body compartments such as testis, epididymes, or seminal plasma? I could not see if or where these issues were evaluated. It may be that these details were absent from the literature reviewed, however, it would be reasonable to anticipate that if the relevant mechanism is indeed androgen suppression as proposed then feeding the animals a phytoestrogen rich diet may confound the results and bias towards a greater effect. Consequently, the wide MOE documented for phthalate should give confidence that the human population is already adequately protected. Potential limitations of the animal literature and the impact of these considerations on risk assessment should be better developed in a revised report.

10. The epidemiological literature describing the association between phthalate exposure and circulating T is inconsistent. While several studies have reported a decline in circulating T concentrations (Jurewicz *et al.*, 2013) the association is lost after adjustment for confounding variables (Mendiola *et al.*, 2012; Mendiola *et al.*, 2011a; Mieritz *et al.*, 2012). Furthermore, a decline in circulating T would be expected to induce a compensatory rise in circulating Luteinizing Hormone (LH). However, circulating LH was not measured in the two studies in which serum T concentrations were decreased after adjustment for confounders (Jurewicz *et al.*, 2013; Meeker *et al.*, 2009). Results of a very recent study (Meeker and Ferguson, 2014) revealed that circulating T concentrations were significantly (p=0.018) reduced only for the ∑DEHP in young boys aged 6-12 years but were not associated with any of the nine (9) phthalate metabolites measured in the urine. Although a very useful addition to the literature, this paper further illustrates that the link between phthalate exposure and decreased circulating T concentrations is far from firmly established. Since this is a

central element of the argument of the risk estimates in this current report it is recommended that this weakness in the discussion receive more careful attention with re-evaluation of the impact on the stated conclusions.

11. In animal studies, phthalate exposures during gestation or juvenile periods have been shown to induce a decrease in circulating T and intratesticular T concentrations. However, the concentrations needed to induce these changes are, in all cases, higher than the concentrations reported to induce nipple retention, reduce AGD, and decrease semen quality. Consequently, these results call into question the role of decreased T concentration as the central mechanism in developmental abnormalities of the male reproductive tract. Taken together these data suggest that an alternative mechanism is likely important in developmental effects of the male reproductive tract. Please discuss this issue and clarify the rational for the heavy reliance on this mechanism in the risk estimations for this report.

12. The author's state the order of potency based on suppression of testosterone and potential anti-androgenic effects as follows:

    DPENP > BBP ~ DBP ~ DIBP ~ DHEXP ~ DEHP ~ DCHP > DINP

    Yet in the report the data cited for DPENP indicates that human exposure is unknown or undocumented and determination of an adverse effect on T production is based on a single study. Moreover, there have been no multigeneration studies and the results of this single study have not been replicated by another group. Furthermore, DPENP is not used in children's toys and thus has not been widely found in the environment. Therefore, human exposure remains poorly defined and the risk posed by this compound must be evaluated to be very low. Although the NOAEL for DPENP was indeed low and nipple retention was detected along with reduction in steroidogenic enzymes, developmental abnormalities of the male reproductive tract were not documented. Therefore, based on lack of replication of the study results, absence of any multigeneration study, inconsistency of effects on male reproductive tract development, and limited exposure, it is proposed that an interim ban, in recognition of the reported potency from a single study, may be more appropriate pending further investigation.

13. Similarly the data sets for DHEXP and DCHP are incomplete and thus the data are inadequate to reach a conclusion regarding risk although existing data does reveal potential reproductive and developmental toxicity. It would seem that a recommendation of an interim ban would be more appropriate pending new data.

14. The recommendation of an interim ban on DIOP is overly cautious and while the authors of the present report considered the animal data to be relevant for human health it is noted that the route of exposure in this study was via intraperitoneal injection and thus the relevance to humans is questionable. Furthermore, the results of this study did not produce adverse effects via androgen suppression and thus the basis for the recommendation of interim ban is seen as overly cautious and unsupported by the data.

15. The recommendation of a permanent ban on DIBP seems overkill in view of the MOEs of 3,600 and 125,000 even if additivity of effects of different phthalates are accepted as a reasonable approach which as argued above is not thought to be

scientifically defensible. Thus this recommendation cannot be supported by the available literature, current exposures, and wide MOEs.

16. Page 13 of the main report the author's highlight the effect of phthalates on development of the male reproductive tract as the most robust data set and, consistent with the prior assessment by NRC 2008, considered this endpoint the most sensitive. It may be worthwhile to mention that as other endpoints receive attention alternative mechanisms and endpoints may prove to be more sensitive.

17. Pages 18 and 19 of the report discuss mechanisms but fail to discuss oxidative stress. Emerging evidence from epidemiological studies suggests that phthalates increase the expression of markers of inflammation and oxidative stress (Ferguson et al., 2014; Guo et al., 2014). While these are very recent studies and may only have appeared after the preparation of the present report they should be added if possible.

18. Page 109 of the report states that the epidemiological evidence suggests that harmful effects of DEP exposure have occurred at current exposure levels. It is important to acknowledge that this report shows only an association and does not establish causality. Moreover, this report did not correct for multiple comparisons and thus the association demonstrated could be a spurious finding which cannot be overlooked in a careful and objective assessment of the literature.

Conclusions

The CHAP report on Phthalates and Phthalate alternatives, prepared for the U.S. Consumer Product Safety Commission, describes a systematic approach to the review of the relationship between exposure to phthalates and phthalate replacement chemicals on reproductive and developmental toxicology. Based on a review of the epidemiological and animal literature the authors of the report recommend no changes to the regulations for DBP, BBP, DEHP, DMP, DEP, and all of the phthalate substitutes. It is recommended that the interim bans on DNOP and DIDP be lifted whereas an interim ban be placed on DIOP. Finally, the authors of the report recommended banning of DIBP, DPENP, DHEXP, and DCHP. Although the authors have done a very good job of managing and very rich data set and preparing a very well written document, several weaknesses with the report need attention. From this review three main points are as follows:

1. The epidemiological evidence linking phthalate exposure to decreased circulating testosterone concentrations, even in young boys, and developmental abnormalities of the male reproductive tract are thought to be weak.

2. While the animal literature provides a plethora of studies documenting the characteristics of the rat phthalate syndrome, the relevance of these findings to human health remain questionable. Specifically, differences in cross species sensitivity to the effects of phthalates, the high concentrations of phthalates needed to induce effects in rats, potential confounding from xenoestrogens in the diet, data gaps in understanding of the relevant mechanisms of phthalate action, and the relatively low concentrations of phthalate metabolites measured in human urine.

3. The assumption of additive effects appears to have weighed heavily in the authors consideration of risk. However, as discussed by others, there is concern about the potential for phthalates to act in an additive manner when present a concentrations well below those used in animal studies to demonstrate an additive effect. Moreover, potential for additive effects when divergent mechanism or modes of action are operable raises concerns about the soundness of using the potential for an additive effect in risk assessment and generating the conclusions presented in the CHAP report.

Taken together, human exposures to phthalates remains low with MOE that are many times above the concentrations needed to induce adverse effects in rats. Hence, there should be confidence in existing regulatory decisions and the recommendations presented in the CHAP report are viewed as overly cautious.

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Summary of Key Points:

Focus of this review was on methodology for the cumulative assessment which with few exceptions, represents state of the art methodology drawing maximally on multiple sources of relevant data. Principal comments relate to the defensibility of the use of Hazard Indices based on Reference Doses rather than Points of Departure, since this limits transparency and consideration of important aspects of uncertainty and variability not currently addressed in traditionally applied uncertainty factors. It also complicates comparison with the individual exposure data since reference doses are designed to protect populations. Consideration of uncertainty and variability in the assessment is uneven, being fairly robust for the biomonitoring data but extremely limited for the scenario based exposure and potency estimates. Sensitivity, though mentioned, is seemingly not analyzed as a basis for weighting of various approaches and/or identification of critical datagaps. Weight of evidence analysis including consideration of broader biological knowledge as a basis for more robust discussion of potential species differences for bounding of the PODs is not evident and weight of evidence considerations across the available database (beyond those that are study specific) are also not specified.

Background:

The focus of this review was the methodology for "cumulative risk" (combined exposures assessment). Given time constraints, focus was necessarily limited to the content of the report itself. The content of the Executive Summary was considered initially and subsequently supplemented by review of relevant sections of the main text of the document (in particular, those addressing aspects relevant to "cumulative" risk and supporting analyses) and perusal of the nature of the content of each of the Appendices, with greater attention to specific aspects therein which were unclear based on content of the full report. The focussed and concise organization of the critical information in the report, supplemented by detailed Appendices facilitated considerably consideration of the pertinent information.

The cumulative assessment represents an impressive effort with appropriate reliance on previous work by a qualified team of experts. Also, with few exceptions, the cumulative assessment represents state of the art methodology, drawing maximally on multiple sources of relevant data including, for example, two sources of population biomonitoring data to address different age groups in the population, population exposure scenarios (essential to interpreting relative importance of various sources of exposure) and three options for potency estimates. Also, with few exceptions, information from different data sources was used appropriately to bound or "groundtruth" estimates or to address datagaps (e.g., scenario based estimates for one of the relevant compounds for which biomonitoring data were unavailable.

Also, in general, with few exceptions, the rationales for approaches and decisions in the cumulative risk assessment were clearly delineated. The rationale for inclusion of the various compounds in the grouping for cumulative assessment seems appropriate as does focus on the critical effect of interest (antiandrogenicity) for exposure of the relevant populations (women of child bearing age and children).

Comments here relate principally to potential additional assimilation of the relevant information on combined exposures in the context of regulatory risk assessment and evolution internationally of approaches to combined exposure and consideration of mechanistic data.

1. Though it's appreciated that considerations for individual phthalates were based on the ratios of the Point of Departure to estimated exposure (i.e., the MOE or Margin of Exposure), the rationale for reliance on derived reference doses (RfDs) or Acceptable Daily Intakes (ADIs) for development of the potency estimates (PEAA) for the Hazard Quotients and Indices (HQs/HIs) is somewhat unconvincing. In my view, this approach detracts from transparency in the desired direct comparison for the critical endpoint (antiandrogenicity), though the relevant PODs are included in tables. Bounding of the uncertainty/variability for the POD for the individual phthalates based on considerations of study design etc. would have increased transparency as a basis for appropriately weighting them in the overall assessment (HI). It would also have permitted consideration of sources of uncertainty and variability other than those addressed in traditionally derived uncertainty factors. Consideration of population based values (i.e., RfDs, ADIs) in the HQs/HIs also complicates interpretation of the comparison with exposure data for individuals, since RfDs take into account human variability (see comment 2, below). The CHAP committee conclusion that the "PODI approach cannot provide the flexibility needed in dealing with differing data quality", is incorrect in my view. In fact, it provides greater flexibility and transparency.

2. The CHAP committee highlighted the novel approach to calculate the HI by considering it for each individual based on his or her urinary concentrations of mixtures of phthalates (in this case, for each pregnant woman and infant). This is in contrast to the standard HI approach of using population percentiles from exposure studies on a per chemical basis. Since RfDs/ADIs incorporate uncertainty factors for protection of populations (addressing e.g., intraspecies or human variability), it would be important, to highlight and clarify additionally how this was taken into account (I couldn't easily identify such text - 2.7.2.3 Calculating the Hazard Index which states only that "Using the individual daily intake estimates for each of the phthalates and relating these DI values to the respective PEAAs, the HQs and HI were calculated for each pregnant woman and infant in the NHANES and SFF (Sathyanarayana et al., 2008a; 2008b) data. Distributions of the HQs and HIs were generated for all three cases, with sampling weights used from the NHANES data to accommodate the prediction for pregnant women in the U.S. population".

3. The consideration of uncertainty and variability in the assessment is uneven. For application of the biomonitoring data, the discussion of uncertainty and variability is robust, with stepwise consideration of various contributing elements (much of which constitutes variability) and quantitation to the extent possible as a basis to "bound" the estimates. This is extremely informative in the interpretation of the biomonitoring based HIs. Though the scenario based exposure estimates are probabilistic, characterization of uncertainties in this context is limited

largely to reference to missing data. Similarly, consideration of uncertainties related to the potency estimates is largely qualitative in nature, or at best semi-quantitative based largely on default uncertainty factors. This complicates interpretation of the HQs/HIs.

4. Though there is an attempt to "ground-truth" estimates based on comparison of output from different approaches and data sources, there is limited (even qualitative) sensitivity analysis, though the relatively robust discussion of, uncertainty and variability in application of the biomonitoring data would lend itself easily to identification of those aspects which had greatest impact. This seems rather important from the perspective of impact on regulatory risk assessment and priorities for follow up. For example, in the scenario-based exposure estimates, which were the most important parameters influencing the output? How robust were the data sources for the most influential parameters? In relation to hazard, while there were 3 different sets of potency estimates, as a basis to determine "sensitivity" (namely a published cumulative risk assessment, relative potency comparisons in the same case study and de novo values based on a literature review conducted by CHAP), there is no discussion of potential relative weighting of the options based on consideration of the relative importance of different contributing factors.

5. The report addresses a number of mechanistic investigations on toxicokinetics and toxicodynamics relevant principally to antiandrogenicity of the phthalates. Limitations, particularly, of the individual studies are highlighted. While information on mode of action may be considered insufficient to conduct a full analysis, it would be helpful to include consideration of broader biological knowledge in a discussion of the potential species differences as a basis for bounding the POD or HQ/HI estimates.

6. In relation to additional "groundtruthing" or semi-quantitative bounding of the potency estimates, I wondered if any of the epidemiological data (though fully recognizing stated limitations) had been considered in this context. I wondered also whether there had been any consideration of directly comparing biomonitoring data in experimental animals and humans as a basis to obviate the need for interspecies tk adjustment or to inform interspecies adjustments.

7. I appreciate the CHAP committee delineating criteria for their recommendations in Section 5.1. However, what might have been additionally helpful is more explicit delineation of considerations for some of the more important aspects of these criteria, notably the nature of the analysis conducted to consider relevance of the findings in animal studies and the weight of evidence (This often involves more formal analysis taking into account for example, modified Bradford Hill considerations.) In fact, many of the considerations in criteria 3 on "weight of evidence" relate to aspects of individual studies, rather than broader considerations of, for example, concordance of dose-response etc.

8. Rationale for lack of reliance of the CHAP committee on benchmark doses in the cumulative assessment was not provided. Based on consideration of the selection criteria for critical studies selected for potency estimates as stated in the report and perusal of the nature of the information on dose-response presented for them in Appendix A, information appears to be sufficient as a basis to meaningfully model benchmark doses. While it's recognized that this is mitigated to some degree by one of the options for consideration of potency being based in part on lower confidence intervals for benchmark doses in several of the relevant studies and that this particular aspect is a less influential determinant of the potency estimates than a number of other factors, BMDs could contribute to better (quantitative) characterization of uncertainty and variability.

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Independent Review of the Chronic Hazard Advisory Panel (CHAP) Final Report on Phthalates and Phthalate Alternatives

Epidemiology

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TABLE OF CONTENTS

INTRODUCTION

I have been asked to perform an independent review of the epidemiology section of the CHAP Report, comprised of a thorough technical review based on all pertinent information (including all data evaluated by the CHAP). I have been asked to use the concept of "weight-of-evidence" to provide conclusions regarding both positive and negative aspects of the CHAP analyses related to epidemiology and recommendations on how to improve the evaluation. In addition, I have been asked to review all sections of the CHAP Final Report and the Peer Review of the Draft Report specific to my topic area (i.e. epidemiology).

Finally, I have been asked to summarize my conclusions and provide 2-3 key findings. I turn first to my key findings.

KEY FINDINGS

The following represent key findings of my review of the CHAP report to the U.S. Consumer Product Safety Commission on phthalates. These findings are made with particular emphasis on epidemiology and, more broadly, an emphasis on the methodological approach taken by the CHAP committee.

1. The CHAP report is not a systematic review of the available scientific evidence and, as such, is of questionable reliability and validity, lacking in the objectivity and transparency generally recognized as critical by the scientific community. The credibility of the recommendations in this report are therefore questionable, given that they are not "evidence-based" as the co-chair of the committee, Dr. Hauser, recognized and mentioned in a separate review published in the peer-reviewed literature (Braun et al., 2013).

   Indeed, the CHAP committee specifically rejected the need for a systematic review (see CHAP Report, p. 12). This unfortunate decision on the part of the CHAP committee puts the credibility of their entire project at risk. Their argument—that interpreting different streams of evidence is not amenable to the systematic review methodology—is at best an indication that they are unaware of the well-established need for a systematic approach, and at worst, scientific nonsense. The systematic review methodology is clearly the best approach to be used in the situation in which there is evidence from different disciplines.

2. The CHAP report misrepresents the results of some (but not all) of the available epidemiological evidence, ignoring or downplaying negative results and emphasizing positive (i.e. apparently harmful) results. Theirs is not a critical and balanced review of the epidemiological evidence. That evidence, which I have examined in detail, is inconsistent and, in some instances, shows that exposure to phthalates may be good for children. I am not advocating that exposure to phthalates be encouraged. I am pointing out that the CHAP report is biased with respect to the findings of the epidemiological evidence.

3. The CHAP report fails to justify their recommendations to reduce exposure to phthalates. It cannot be justified by the available epidemiological evidence. The CHAP

committee fails to point out that there are no studies documenting a reduction in developmental outcomes or neurodevelopmental outcomes in children after a reduction in exposure to phthalates. No effort is made on the part of the CHAP Committee to grade the strength of the evidence or the recommendations made, despite the fact that the Committee reviewed literature that provides a process for grading the quality of evidence and the quality of recommendations.

4. The CHAP report fails to mention much less discuss a relatively large number of published reviews and several epidemiological studies on the topic of phthalates and human health including children's health. The missed epidemiological studies provide evidence of null ("no association") results. In addition, the fact that many of these reviews disagree with the CHAP report's assessment of the epidemiology (and of the use of animal models to represent adverse health events in humans) is important and should have been addressed in the CHAP Report.

PURPOSE, APPROACH, AND AN EVALUATION OF THE METHODOLOGY OF THE CHAP REPORT

Purpose of the CHAP Report

The Consumer Product Safety Commission (CPSC) charged the Chronic Hazard Advisory Panel (CHAP) with the following (selected) tasks (CHAP Report, p. 11):

1. (to) "examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates;"

2. (to) "consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates; and"

3. (to) "review all relevant data, including the most recent, best-available, peer-reviewed, scientific studies of these phthalates and phthalate alternatives that employ objective data collection practices or employ other objective methods."

There were other tasks mentioned by the CPSC, involving estimates of exposure and recommendations for actions to be taken given a "reasonable certainty of no harm" for various susceptible populations, but for my purposes here I will focus primarily on the tasks involving the examination of potential health effects. Because the word "effects" is used, I will reasonably assume that the concern of the CPSC (and therefore CHAP) is causation, i.e. does exposure to phthalates (singly or in combination) *cause* harmful health effects?

I do not mean to suggest that causation need be firmly established in order to make a recommendation for limiting (or eliminating) exposure to a substance (e.g. a particular phthalate or a mix of phthalates). However, I am suggesting that the first (primary) task of the CHAP, according to the CPSC charge, was to evaluate the existence (or not) of harmful human health effects. In the normal course of events regarding potentially harmful agents (e.g. chemicals) evaluation of the putative health effects takes place prior to a discussion of what actions (if any) should be taken. It follows that my focus here will

begin with a discussion of the methods the CHAP used (or not) to evaluate the existence of harmful human health effects given exposure to phthalates.

There are two basic concerns regarding causation:

1. does the available scientific evidence warrant claims that phthalates (in general), any combination of phthalates, or any specific phthalate cause adverse human health effects?

2. does the available scientific evidence demonstrate that reduction in exposure to phthalates (in general), any combination of phthalates, or any specific phthalate result in improvements in reproductive tract or neurodevelopmental outcomes in humans?

Note also that the focus of the CHAP report is children and not humans of any age. My comments will, therefore, be limited to answering these two questions for children.

Approach to the Assessment of the CHAP Report

I have been asked to assess the work carried out by the CHAP, including methodology and conclusions. Regarding methodology, the following issues are particularly important:

1. Whether the CHAP relied primarily upon a method or methods or primarily upon their subjective judgment in their report

2. Whether a method for evaluating scientific evidence is described. By "evaluating" scientific evidence, I mean the collection, description, and interpretation of scientific evidence, to be discussed in more detail below

3. Whether the method described is one generally recognized in the scientific community and referenced there

4. Whether the CHAP's description of that method is accurate (i.e. whether it reasonably conforms to the descriptions of that method in the published literature or misrepresents, i.e. deviates prominently from, those same descriptions)

5. Whether that method is appropriate for the scientific question at hand

6. Whether the method selected by the CHAP was used appropriately to analyze data or to interpret results

The approach I take here is directly analogous to the process of peer review in scientific practice. There, a scientist's claims regarding the existence of a harmful health effect (and the evidence and methods used to make and support those claims) are subject to review and critique. The peer review process, as such, is familiar to and accepted by practicing scientists. It is an essential part of the practice of science, serving to increase the validity and reliability of the content—the results and interpretation of results—found in the scientific literature. A scientist's data, methods, and interpretations are subject to scrutiny by one's peers. Rejection of an author's claims (indeed, rejection of the manuscript as a whole) is not uncommon and occurs for many reasons, including when the methods are faulty (or nonexistent) and when the claims made are unjustified.

Indeed, failure to meet any or all of these methodological concerns (#1-#6 above) would be grounds for rejection of a manuscript submitted for publication.

What Method Should Have Been Used by CHAP to Assess the Possible Human Health Effects of Phthalates?

Before discussing the method (if any) used by CHAP in their report on the possible health effects of phthalates, it will be helpful to briefly describe the method generally accepted by the scientific community for assessing the existence (or not) of human health effects. That method is the systematic review. By "systematic review" I do not necessarily mean a meta-analysis, although that quantitative technique may, in some circumstances, be incorporated into the body of a systematic review. Rather, I am referring to the systematic narrative review, discussed and promoted in the scientific literature for the past 25 years.

The discussion in the scientific community on the need for a systematic approach to reviewing the scientific and medical literature began in the mid-1980's (Mulrow, 1987) and has continued unabated. For detailed discussions of the method and examples of its application including, but not limited to epidemiology, see: Breslow et al. (1998), Crowther et al. (2007), Greenhalgh (1997), Hutchison (1993), Moher et al. (2008), Moher et al. (2009), Montori et al. (2003), Mulrow (1994), Oxman et al. (1988), Oxman (1994), Oxman et al. (2006), Rochon et al. (2002), Shea et al. (2007), Weed (1997), and Weed et al. (2011). A brief description follows.

The systematic review is a central method that can be referred to with the term "weight of evidence." Indeed, I note that there are many definitions of the "weight of evidence" concept in the scientific literature (Weed, 2005; Krimsky, 2005). Therefore, I will define "weight of evidence" for the purposes of this independent review to mean the current methods used in the scientific community to collect, summarize, and interpret scientific studies (Weed, 2005), mainly in terms of the systematic narrative review. I will provide specific details regarding these methods as appropriate although the key methodology is the systematic narrative review, a methodology developed in the scientific community over the past 25 years.

Systematic Narrative Review, or "Evidence-based" Review

The systematic narrative review (also called an "evidence-based" review) is a critically important methodology in the practice of determining health effects (Weed, 1997; Weed, 2000b). Here, the relevant scientific evidence is systematically collected, summarized, and interpreted. Typically, medical library databases are searched with a description of the search techniques made sufficiently transparent that the search could be repeated by others with similar if not exactly the same results. In addition, it is common for authors of systematic reviews to supplement the searches with additional studies found in the reference lists of published papers or textbook chapters on the topic, government reports, and possibly, unpublished studies, the so-called "grey" literature. The purpose of the review, the conditions (or criteria) for including and excluding the studies to be summarized and interpreted, and the criteria (or other methods) to be used in making claims about health effects are important—indeed, essential—components of a systematic narrative review. The word "narrative" is often used to describe this methodology, because it is common for authors to describe each study before the results are summarized and finally interpreted in terms of the existence (or not) of harmful health effects.

The quality of any review—whether it claims to be systematic or not— is a key concern. A good example of a validated assessment tool—called "AMSTAR"— for assessing the quality of a review can be found in Shea et al. (2007). The AMSTAR quality considerations include the following:

1. a clear description of the purpose of the review
2. explicit search terms and databases
3. explicit inclusion and exclusion criteria (for the studies to be reviewed)
4. duplicate data abstraction and a process for resolving disputes between abstractors
5. explicit consideration of the so-called "grey" literature, i.e. unpublished reports, etc.
6. detailed descriptions (e.g. a table) of the characteristics of the included studies
7. formal quality assessments of the included studies
8. appropriate incorporation of the quality assessments in combining results
9. appropriate methods for combining results of the studies
10. explicit assessment of publication bias
11. an explicit discussion of potential conflicts of interest (e.g. funding sources).

An unsystematic review is one whose conclusions (e.g. claims about human health effects) emerge primarily from the subjective judgment of the author(s) rather than from the well-recognized methods of reviewing scientific evidence, whose key considerations are captured by the AMSTAR considerations. I will return to an assessment of the quality of the review found in the CHAP report later.

The CHAP "Methodology" for Assessing Human Health Effects in Epidemiology Studies

After a careful review of the CHAP Report, I can state with certainty that the CHAP committee used no established method for systematically reviewing epidemiological evidence or, for that matter, any other type of evidence included in their report. Indeed, they concluded that no such method was needed. They write:

> "because of the nature of the subject matter and the charge questions, which involve different streams of evidence and information," their "review was not amenable to the systematic review methodology." (See CHAP Report, p. 12).

The CHAP's argument on this methodological matter is scientifically unsound and therefore inconsistent with the current state-of-the-art regarding the assessment of scientific evidence. When faced with evidence from different disciplines, the systematic (narrative) review is precisely the approach that should be taken. Indeed, systematic reviews are the approach taken by the scientific community at large in these situations, as discussed in detail in the many publications cited above. Furthermore, when the issues involve human health effects, the systematic (narrative) review is, again, the approach that is recommended and used by the broad scientific community in a variety of disciplines, including but not limited to medicine, epidemiology, the nutritional sciences, and, most recently, toxicology.

The fact that CHAP failed to systematically review the scientific evidence makes their claims and recommendations suspect, dependent more on their personal subjective judgment than on established methods for collecting, summarizing, and interpreting evidence. Indeed, by not performing a systematic review, the CHAP committee could (and did) make decisions and recommendations that have no clear objective methodological foundation.

In response to the peer review imbedded within the CPSC process, the CHAP commented on the question of systematic review methodology, rejecting it on specious unscientific grounds. To be fair,

however, I will briefly comment on the three publications the CHAP mentioned in their discussion of review methodology: Guyatt et al. (2011), Higgins et al. (2011), and Woodruff and Sutton (2011). It is possible although unlikely that one or more of these publications recommended against the use of a systematic approach in situations such as the one faced by the CHAP. In fact, as I will show, one of these publications states that a systematic approach is precisely what is needed in situations such as those faced by CHAP.

Guyatt et al. (2011) is an introductory paper to the GRADE evidence profile process that provides guidance. The GRADE process requires users to formally rate the quality of the evidence and grade the strength of the recommendations made on the basis of that evidence. Given that the CHAP Report involves both assessing scientific evidence and making recommendations from that evidence, it would appear that the GRADE process is an appropriate technique. However, the CHAP committee rejected using it.

Higgins et al. (2011) is a methodological tool for evaluating risk of bias in randomized clinical trials. As such, it seems ill-suited for the purpose of the CHAP (given that there are no randomized clinical trials of the effects of phthalates on human health). However, these authors also mention that the purpose of systematic reviews (more broadly) is to collate and synthesize all relevant studies using methods that attempt to minimize bias (Higgins et al., 2011, p. 1 of 9). Such a purpose seems particularly well-suited to the aim of the CHAP faced with the task of "review(ing) all relevant data, including the most recent, best-available, peer-reviewed, scientific studies of these phthalates and phthalate alternatives that employ objective data collection practices or employ other objective methods," as described above. Certainly it can be said that Higgins et al. (2011) do not recommend against a systematic review approach to evaluating a body of evidence.

Woodruff and Sutton (2011) describe a methodology designed to help evaluate the quality of evidence and to support evidence-based decision making (by clinicians and patients) regarding environmental effects on reproductive health. This goal is precisely the same as that provided to the CHAP by the Consumer Product Safety Commission. Funding for the Woodruff and Sutton (2011) project was provided by foundations, endowments, trusts, the University of California at San Francisco, Planned Parenthood Federation of America (described on their website www.plannedparenthood.org as "a trusted health care provider, an informed educator, a passionate advocate, and a global partner helping similar organizations around the world") the National Institute of Environmental Health Sciences, and the U.S. Environmental Protection Agency.

In sum, Woodruff and Sutton (2011) is a peer-reviewed publication that provides a methodology particularly well-suited for the aim of the CHAP, a methodology that "vet(s) the science linking environmental exposure to chemicals to reproductive and developmental health in a systematic and transparent way" (Woodruff and Sutton, 2011, p. 935).

Indeed, Woodruff and Sutton (2011, p. 934) specifically state that their methodology incorporates human studies, studies on laboratory animals, and other nonhuman streams of evidence, exactly the situation faced by CHAP. The four basic steps of this methodology are:

1. Specify the study question
2. Select the evidence (by conducting and documenting a systematic search for published and unpublished evidence)
3. Systematically rate the quality of the individual studies and then the quality of the overall body of evidence based on clearly stated criteria, consistent with the GRADE method

4. Grade the strength of the recommendations

Certainly it can be said that Woodruff and Sutton (2011) did not recommend against a systematic approach. Indeed, they note that failure to systematically and transparently evaluate and synthesize scientific evidence makes it difficult for clinicians, patients, and policy makers to make use of the science (Woodruff and Sutton, 2011, p. 932). The Woodruff and Sutton (2011) method is a reasonable choice for the CHAP, which nevertheless chose to reject it.

Given this brief examination of articles cited in the CHAP report, the decision by CHAP not to systematically and transparently review the scientific evidence on the health effects of phthalates flies in the face of published recommendations to the contrary and is scientifically unsound.

CHAP's Approach to Avoiding Bias

The CHAP believes that they avoided bias by obtaining "new information and opinions about the availability of other information through public comment and presentations." This approach is contrary to the published literature on systematically reviewing the literature.

While public comment and presentations may be a reasonable way to obtain some forms of new information, such an approach is unlikely to protect against bias. Given that bias is typically defined as a challenge to the validity of scientific evidence and thus a challenge to scientific objectivity, a better approach to avoiding bias than inviting public comment would be to systematically review the available evidence in the objective and transparent manner described above. The CHAP, however, chose not to proceed in this manner.

Assessment of the Quality of the CHAP Review

As mentioned above, one approach to assessing the quality of a review is to determine the extent to which it satisfies the 11 key features of a high quality review as discussed by Shea et al. (2007) in their presentation of the AMSTAR tool. See the table below for an assessment of the quality of the CHAP review with regards to the epidemiological evidence.

AMSTAR FEATURE	MET by CHAP?
Clear description of the purpose of the review	✓
Explicit search terms and databases	No
Explicit inclusion and exclusion criteria	No
Duplicate data abstraction and a process for resolving disputes	No
Explicit consideration of the so-called "grey" literature	✓
Table of the characteristics of included studies	✓
Formal quality assessments of included studies	No
Incorporation of quality assessments in combining results	No
Appropriate methods for combining study results	No
Explicit assessment of publication bias	No
Explicit discussion of potential conflicts of interest	No

The CHAP review satisfies only 3 of the 11 features of a high quality review. It follows that the quality of the CHAP review is poor.

I conclude that the CHAP report is not a systematic review of the available scientific evidence and, as such, is of questionable reliability and validity, lacking in the objectivity and transparency generally recognized as critical by the scientific community. The credibility of the entire report and, in particular, the recommendations made by the CHAP committee are questionable.

A Contradictory Recommendation by the CHAP Committee Co-Chair, Dr. Russ Hauser

Relevant to this issue is the fact that Dr. Hauser (a co-chair of the CHAP Committee) wrote in a review paper published the same year as the CHAP Report (Braun et al., 2013) that any recommendations to reduce exposure to phthalates (one of the main conclusions of the Report) are not "evidence-based." Dr. Hauser is one of the authors of this review. Although Dr. Hauser signed off on the CHAP report recommending that phthalates be banned, he writes in this review of the epidemiological literature regarding early life phthalate exposure and pediatric health outcomes (which covers basically the same evidence) that any recommendations regarding exposure (what the authors describe as "anticipatory guidance") are not evidence-based.

He writes (Braun et al., 2013, p. 247):

> "**While anticipatory guidance is not evidence-based at this time**, providers can counsel concerned patients to reduce phthalate exposures in order to protect the developing fetus and child from potential adverse health outcomes." (emphasis added)

Perhaps as importantly, Dr. Hauser does not state in this peer-reviewed publication that there is a need to permanently ban or even reduce exposure to any phthalate at the population level. Rather, Dr. Hauser only believes that health providers can (if they so choose) to "counsel concerned patients" (i.e. not any and all patients) to reduce phthalate exposures.

The recommendations in this review paper contrast sharply with the recommendations of the CHAP Report. No justification is provided in the CHAP Report for this inconsistency. If the CHAP Report recommendations are not "evidence-based," then it is reasonable to ask "on what basis are these recommendations being made?" No answer to this question is provided in the CHAP Report as described in more detail in the next section.

What Method Was Used by CHAP to Assess the Possible Human Health Effects of Phthalates?

In the absence of a systematic approach to collecting, summarizing, and interpreting the scientific evidence relevant to the charge put to the CHAP committee, the question remains: what method (if any) did they use to evaluate the existence (or not) of adverse health effects of phthalates and to make recommendations to the CPSC?

No methods section was included in the CHAP Report. As a result, answering the question posed above (regarding the method (if any) used by the CHAP committee) was a time-consuming and challenging project. For example, the terms "search" or "PubMed" appeared only three times in the CHAP Report, in Appendix A ("Developmental Toxicity"). No documentation (or, for that matter, mention) of literature searches appears in the CHAP Report for epidemiological studies, including Appendix C, the appendix devoted to describing epidemiological studies.

I also attempted to find places in the CHAP Report where there approach to "reviewing the literature" was mentioned. That did occur on p. 12 of the CHAP Report, where the authors write:

> "The literature review performed by the CHAP covered all aspects of risk assessment. Thus, information and studies derived from toxicological experiments, exposure characterization, and human studies were targeted by the CHAP. Initially, these efforts were based upon previously published criteria documents, **literature reviews,** and reports.* These were then augmented by subsequently published or publicly available data, studies, and risk assessments."
>
> "* These include, but are not limited to, reports from the Agency for Toxic Substances and Disease Registry (ATSDR); European Chemicals Agency (ECHA); International Agency for Research on Cancer (IARC); Center for the Evaluation of Research on Human Reproduction (CERHR), National Toxicology Program (NTP); and the National Research Council (NRC). All references are cited in the text."

Note that the CHAP authors presumably examined earlier literature reviews but only for the purpose of identifying studies. As I will show in detail later in this review, the CHAP Committee chose to ignore the conclusions of several published reviews on the topic of the putative health effects of phthalates (including very recent examples), which for the most part, conflict with the CHAP conclusions.

Methodological Issues Mentioned by the CHAP Committee on Toxicology Data

Interestingly, the CHAP Committee chose to discuss some methodological concerns in their section on the Role of Animal (Toxicology) Data for the Assessment of Human Risk (CHAP Report, p. 19-21). Some issues in epidemiological methodology are mixed in with their discussion of toxicology. This approach is confusing.

They write:

> "The published literature on the toxicity of phthalates is extensive and varies widely in its usefulness for assessment of risks to humans. This section introduces the approach taken by the CHAP to evaluate such a broad and varied literature, and draws conclusions about potential risks to humans from individual chemicals or mixtures of chemicals."
>
> What is the basis for selecting key studies that provide a basis for assessment of risk for humans? What is the threshold for determining that studies in humans or animals are either helpful for assessment of risk or not? For example, the results of a pilot study in a small number of lab animals are usually not suitable for risk assessment. The study was designed to select the appropriate dose levels for a more definitive study. Similarly, case histories on individual persons are not a sufficient basis for a risk assessment because the individual case may not be representative of the population. For the same reason, reports of cluster effects of small numbers of humans are often difficult to extrapolate beyond the cluster. The most desired data are from appropriately designed studies in humans or animals that account for confounders and have reasonable power to detect an effect (e.g., 80% at 0.95 probability), with results replicated in another study of similar design and purpose.

> As an example of another threshold for acceptance of data, the CHAP's goal was to use data from studies that were published in peer-reviewed journals. There were times when the only available information was from a source other than published literature, for example, the results of a study submitted to a public docket of a regulatory agency as part of a data call-in or the results of a recently completed study that had not been submitted for review by a journal. In such cases, the CHAP has considered the data but has noted in its review that the results from the study on this particular chemical have not been published in the literature.
>
> Data from human studies of reasonable quality generally are a stronger signal of risk to humans than findings in animal studies. However, in the absence of other data, findings in animals should be assumed to be relevant for prediction of risk to humans.
>
> Animal or human studies that are negative must be examined closely for adequacy of experimental design, sufficient power, and presence of confounders that may have masked a possible effect of the test article.
>
> Animal or human studies that are positive must be examined closely for appropriateness of experimental design and presence of confounders that may have contributed to the effects reported.

Finally, the CHAP Report mentions the basis of their recommendations. See the CHAP Report, p.79, where they write:

> "The recommendations are based on a review of the toxicology literature, exposure data, and other information such as a calculated hazard index."

Note that, according to the CHAP Committee's own views, their overall recommendations are not based on a review of the epidemiological literature. This is a peculiar and nearly nonsensical approach. Clearly, the CHAP Committee has chosen to downgrade or downplay the epidemiological studies on actual human populations, in large part, I suspect, because the results of those studies do not provide adequate justification for their recommendations.

Some Additional Methodological Concerns

Although the CHAP Committee uses the term "weight of evidence" in many places (i.e. more than 20) in their Report, they never define it. I can only conclude that the use of this term is, therefore, purely metaphorical, without an objective foundation (Weed, 2005). Put another way, the CHAP Committee's use of the term means (in Krimsky's (2005) terms) that they performed a 'seat of the pants' review using a 'black box' method.

EPIDEMIOLOGY IN THE CHAP REPORT

I turn now to the presentation and discussion of epidemiological evidence in the CHAP Report.

Epidemiology studies are described, interpreted, and discussed in several sections of the CHAP report. The following sections are focused primarily on epidemiology:

1. Section 2.4 Epidemiology (See Chap Report, p. 27-33)
2. Appendix C

There are other places in the CHAP report where epidemiology is discussed or mentioned. These include:

1. Executive Summary (See Chap Report, p. 2-3)
2. Section 3: Risk Assessment

I begin with the Executive Summary.

A Critical Look at the CHAP view of the Relevance of Epidemiological Evidence in their "Executive Summary"

This is the statement made by CHAP in their Executive Summary Section on "Health Effects in Humans:"

> **"The phthalate syndrome in rats bears a resemblance to the "testicular dysgenesis syndrome" (TDS) in humans, which includes poor semen quality, testis cancer, cryptorchidism, and hypospadias, and which is hypothesized to have its origins during fetal life.** There is a rapidly growing body of epidemiological studies on the association of exposure to phthalates with human health. Most studies primarily focus on the association of maternal phthalate exposure with male reproductive tract developmental endpoints and neurodevelopmental outcomes. Two of three cohort studies found reduced AGD in male infants in relation to higher maternal urinary concentrations of phthalate metabolites. Other studies reported associations between reduced AGD and hypospadias, poor sperm quality, or reduced fertility. Seven prospective pregnancy cohort studies and two cross-sectional studies investigated associations of urinary phthalate metabolites with neurological measures in infants and children. Interestingly, although each publication utilized different neurological tests at different childhood ages, poorer test scores were generally, but not always, associated with higher urinary levels of some phthalates. Other studies found associations between reduced sperm quality and some phthalates in adult males.
>
> **Overall, the epidemiological literature suggests that phthalate exposure during gestation may contribute to reduced AGD and neurobehavioral effects in male infants or children.** Other limited studies suggest that adult phthalate exposure may be associated with poor sperm quality. The AGD effects are consistent with the **phthalate syndrome in rats.** However, it is important to note that the phthalates for which associations were reported were not always consistent and differed across publications. **In some cases, adverse effects in humans were associated with diethyl phthalate exposure, although diethyl phthalate does not cause the phthalate syndrome in rats.** None of these studies was designed to provide information on the specific sources of phthalate exposure or on the proportional contribution of exposure sources to body burden."

Note that this section does not begin with humans. It begins with rats. This section reveals a prominent theme—one of two key ideas that permeate the CHAP Report. The first key idea is that the CHAP authors are convinced that rats suffer from the "phthalate syndrome" and that humans may also be so affected, although the evidence for humans is far less convincing. Indeed, there are no published epidemiological studies reviewed by CHAP, or for that matter, in the current scientific literature, that have examined whether exposure to phthalates is associated with the testicular dysgenesis syndrome per se. The CHAP report fails to point out this important fact.

Most important for any review of the CHAP report is how to deal with these prominent inconsistencies: (1) different phthalates are involved in the rat syndrome and (2) the results across the human studies are not consistent. Indeed, some epidemiologic results are exactly opposite to the animal results.

Note too that the CHAP authors say very little about the "phthalate syndrome" in other species. After all, the rat is not necessarily the best animal to represent humans.

Regarding the "testicular dysgenesis syndrome" in humans, which the CHAP authors notes is characterized by poor semen quality, testis cancer, cryptorchidism, and hypospadias, there appears to be little evidence that testicular cancer, cryptorchidism, or hypospadias are associated with phthalate exposure in humans as a collection of events, much less as separate individual events. Hsieh et al. (2009), for example, is a preliminary study of the possible association between AGD and hypospadias/cryptorchidism without measuring phthalates.

A Critical Look at the CHAP Report on Epidemiology (Section 2.4)

Section 2.4 is a summary of what the authors describe as a "rapidly growing body of epidemiological studies on the potential association of exposure to phthalates with human health," with a focus solely on studies of male reproductive tract developmental endpoints and neurodevelopmental outcomes.

The use of the phrase "rapidly growing body of epidemiological studies" may give the false impression that there is an increasing number of "positive" results, i.e. an increasing number of studies demonstrating an association between exposure to phthalates and developmental outcomes. This is not the case. If anything, the "growing body of epidemiological studies" reveals inconsistent and incoherent results.

Exactly three studies are mentioned in the subsection 2.4.1 entitled, "Phthalates and Male Reproductive Tract Developmental Effects:" (1) Swan et al., (2005) with its extension described in Swan (2008), (2) Huang et al., (2009), and (3) Suzuki et al., (2012). The CHAP authors note that the results of these three studies are not "entirely" consistent (to be described in more detail below), yet nevertheless recommend that exposure to the following phthalates be reduced: DEP, DBP, and DEHP metabolites.

Incoherence of the CHAP report regarding the scientific relevance of amniotic fluid vs. urinary measurements of phthalates

Importantly, although the CHAP authors note that "amniotic fluid measurements of phthalate metabolites would provide the best estimate of internal dose for the fetus" they fail to rely on the study (Huang et al. (2009)) that used this type of measurement and observed no association between phthalates and AGD in male infants. In essence, the CHAP authors appear to favor the results of studies

with poorer exposure assessments (i.e. urinary phthalates). No explanation is provided for this approach that is incoherent with their own scientific views.

Inconsistencies Between and Within the Epidemiology Studies

It cannot be said that the two studies utilizing urinary metabolites of phthalates reported consistent results regarding AGD or AGI. Indeed, the reliability of AGD measurements is not particularly good (Salazar-Martinez et al., 2004). By the CHAP authors' own account, Suzuki et al. (2012) found no associations between AGI and urinary measurements of MMP, MEP, MBP, MBZP, MEHHP or MEOHP. Indeed, Suzuki et al. (2012) observed only one association, namely, between MEHP and AGI. Swan et al. (2005), on the other hand, found associations between AGI and MBP, MIBP, MEP, and MBZP but Swan (2008) failed to find associations between AGI and MIBP or MBZP but did report associations between MEP, MBP, MEHP, MEHHP, and MEOHP. Finally, as noted above, the Huang et al. (2009) study found no association between any phthalate (measured in the amniotic fluid) and AGD in males. Thus there is inconsistency both across these three studies and within the same study (i.e. Swan et al. (2005) and Swan (2008)).

See also the CHAP Report's Executive Summary (p. 2-3) where the authors note that the reported associations in the epidemiology studies "were not always consistent and differed across publications."

The authors of the CHAP Report recognize what can only be considered prominent inconsistencies but apparently do not believe they matter when it comes time to make recommendations. I turn now to the CHAP Report's failure to provide sufficient scientific justification for their recommendations.

Failure of CHAP to Provide Scientific Justification for Their Recommendations

Given that the CHAP relied on studies with less valid exposure measurements and prominent inconsistencies both across and within the studies they rely upon for recommendations, one would reasonably expect a discussion—a scientific justification at the least—for their recommendation to "reduce" exposure to DEP, DBP, and DEHP metabolites. However, they simply state the following (CHAP Report, p. 29):

> "Based on the human data on gestational exposure and reduced AGD, exposure to DEP, DBP, and DEHP metabolites should be reduced."

No justification—no discussion of why these prominent study limitations can be ignored, and thereby not affect the justification of, recommendations to reduce exposure to phthalates—appears in Section 2.4.1 or in Appendix C.

Indeed, there is no (zero) evidence presented in the CHAP sections on epidemiology showing that reductions in exposure to phthalates results in improvements in reproductive outcomes in children, e.g. in increased AGD or AGI.

It might be reasonable to consider whether the CHAP based its recommendations at least in part on the animal evidence of the so-called "phthalate syndrome" rather than the human evidence, given that they mention this issue in section 2.4.1. However, they note that "it is uncertain whether the phthalate syndrome occurs in humans" (CHAP report, p. 28). The authors also note (CHAP Report, p. 3) that the

"adverse effects in humans were associated with diethyl phthalate exposure, although diethyl phthalate does not cause the phthalate syndrome in rats."

In the end, the only justification for the CHAP recommendations appears to be the subjective judgment of the CHAP authors (at best) or, at worst, a belief among the members of the CHAP committee that recommendations to reduce exposure to phthalates were predetermined, independent of the scientific evidence.

A Critical Look at Appendix C "Epidemiology"

In Appendix C, the CHAP authors devote the bulk of their attention to a single study reported in two publications (Swan et al., (2005) and Swan (2008)). For the other studies, the CHAP authors provide negative (critical) descriptors of each study but no such descriptors for the Swan studies. Huang et al. (2009), for example, is called a "small study" and Suzuki et al. (2012) is criticized for having "23 examiners performing the AGD measures on the newborns" thus "contributing to possible measurement error and potential attenuation of associations" (CHAP Report, Appendix C-2). However, the CHAP authors fail to point out that most certainly the Swan studies also had multiple examiners performing the AGD measures, given that the study involves at least three different clinical study centers. Furthermore, it is not necessarily true that these measurement errors would lead to non-differential misclassification error and attenuation of associations. The CHAP authors' provide no discussion of this important methodologic issue.

Indeed, there is no presentation or discussion of basic, much less advanced, issues in epidemiological methodology in Section 2.4, Appendix C, or anywhere else in the CHAP report. The CHAP report is, to a large extent, devoid of a defined methodology for collecting, describing, and interpreting scientific evidence, as noted earlier.

See also CHAP's "Risk Assessment" Section 3 (CHAP Report, p. 69)

> "To arrive at transparent recommendations about restricting (or otherwise) the use of phthalates in children's toys and care products, the CHAP has employed a risk assessment approach that first analyzed the epidemiological evidence of associations between phthalate exposures and risk to human health. **Such data give valuable answers to questions about whether phthalates as a group of chemicals might be linked to human disorders. However, only in rare cases is it possible to pinpoint specific chemicals as associated with health effects, and no such case is currently available for phthalates.** At present, quantitative estimates of the magnitude of risks that stem from phthalate exposures cannot be derived directly from epidemiological data. For this reason, the CHAP had to rely primarily on evidence from tests with animals to underpin phthalate risk assessment."

Given this summary of the epidemiological evidence, one must conclude that the case for hazard identification (in humans) is extraordinarily weak. At best, the conclusion of CHAP is that phthalates "might be linked to human disorders."

EPIDEMIOLOGY IN THE CHAP REPORT: SPECIFIC STUDIES

In this section, I will examine specific studies mentioned by the CHAP Committee in their Report.

I begin with the CHAP Report's versions of the studies and findings regarding male reproductive tracts.

Discrepancies Between the CHAP Authors' Versions and the Study Authors' Versions of the Studies Described in the CHAP Report on Male Reproductive Tract Development

Swan et al. (2005) is the first epidemiologic study to examine the putative relationship between single prenatal maternal urine samples of phthalate ester metabolites and what the authors describe as "subtle patterns of genital morphology in humans," namely, anogenital distance (AGD), testicular descent, genital malformations, size of the scrotum, and penile width and volume, among others, including the anoscrotal distance (ASD).

The study participants were 85 mother-son pairs from an original study population of 346 families entered in the SFFI (Study for Future Families), a multicenter pregnancy study located in California, Minnesota, and Missouri. There were 172 boys born to the mothers in these families; thirty-eight (38) mother-son pairs were excluded, because there were twins, incomplete data, or no record of the AGD measurement. Importantly, the investigators noted that the AGD measurement is not reliable for "older boys" and for "boys with a higher activity level." See (Swan et al., 2005, p. 1058). Of the original 172 mother-son pairs, there remained 134 participants and "no frank genital malformations or disease" and "no parameters appeared grossly abnormal." See (Swan et al., 2005, p. 1058). Of the 134 mothers, there were 85 with prenatal urine samples, hence the final number of participants, i.e. 85 mother-son pairs. The mean age of the boys in the study was 12.6 months. In addition, height, weight, AGD (mm), ASD (mm), and AGI (mm/kg) were recorded and (when appropriate) calculated. The "AGI" is the "anogenital index" and is calculated by dividing the AGD by the weight of the boy. The AGD is the distance (in mm) from the center of the anus to the anterior base of the penis. The ASD is the distance (in mm) from the center of the anus to the poster base of the scrotum.

Phthalate metabolites were measured in the mothers' prenatal urine, in the mothers' postnatal urine, and in the babies; these were unadjusted for urine concentration. There were originally 214 samples, from which 85 prenatal samples were chosen for the analyses. **Note that the infant (sons') urinary phthalate metabolites were not included in the analyses.** Mothers' metabolite concentrations were categorized into low (<25th percentile), intermediate (between 25th and 75th percentile), and high (≥ 75th percentile). In addition, a summary phthalate score was created, representing the sum of phthalates most strongly associated with AGI.

AGD and AGI (but not ASD) were modeled as a function of age; with the best fitting model in hand, the investigators categorized the study participants (i.e. the boys) in two ways:

1. dichotomized boys as those whose AGI was smaller than or at least as large as expected
2. short (AGI < 25th percentile), intermediate (25th percentile ≤ AGI < 75th percentile), and long (AGI ≥ 75th percentile)

In addition, the investigators categorized the boys in terms of the proportion with normal testicular descent and normal scrotum (size and distinctness from surrounding tissue).

Potential confounding factors included: mother's ethnicity and smoking status, time of day and season when urine sample was collected, gestational age at sample collection, and baby's weight at examination.

Main et al. (2006)

In Appendix C (Epidemiology), the CHAP Report (p. Appendix C-2) describes a single study (Main et al., 2006) as "supporting evidence for anti-androgenic effects of phthalates." Their description of this study follows.

> "A Danish-Finnish study on 130 three-month-old male infants, 62 cases with cryptorchidism and 68 controls, explored the association of phthalate concentrations in breast milk with serum reproductive hormones (Main et al., 2006). Breast milk phthalate concentrations were not associated with cryptorchidism, but there were associations with hormones related to Leydig cell function. MMP, MEP, and MBP were positively associated with the luteinizing hormone (LH):free testosterone ratio (a 10-fold increase in MMP, MEP, and MBP concentrations raised the LH:free testosterone ratio from 18% to 26%). There were suggestive positive associations of MEHP and mono(isononyl) phthalate (MINP) with the LH:free testosterone ratio and suggestive positive associations of MMP, MEP, MBP, and MEHP with the LH:testosterone ratio. MINP was associated with increased LH (a 10-fold increase in MINP was associated with a 97% increase in LH), and there was a suggestive association with increased testosterone. MBP was inversely associated with free testosterone, whereas MEP and MEHP showed similar directions of association but were nonsignificant. For Sertoli cell markers (i.e., FSH and inhibin B), positive nonsignificant associations were found for MBzP and MEHP with inhibin B. All monoesters were negatively associated with the FSH:inhibin B ratio, which was significant for MEHP. Finally, MEP and MBP were positively associated with sex-hormone binding globulin (SHBG), and there were suggestive non-significant positive associations of MBZP and MINP with SHBG. The Main et al. results for MEP, MBP, and MEHP suggest that human Leydig cell development and function is affected following perinatal exposure. The reduced free testosterone and the increased LH:free testosterone ratio support the associations of phthalates with reduced AGD reported in Swan et al. (2005). Although the changes in hormones related to Leydig cell function may or may not pose a significant health effect in a single individual, such a shift on a population basis could presumably lead to potential adverse health outcomes."

The key question here is the following: did the CHAP Report accurately describe the results of Main et al. (2006)? The answer must be no. The CHAP Report committed the following methodological errors:

1. Describing an "association" as such even though the relationship between the two variables was not statistically significant. Note that Main et al. (2006) did not use this terminology. They use the term "correlation" rather than "association." Correlations and associations are vastly different notions; an association requires that the incidence of a condition in the exposed group exceeds that of unexposed group and is statisticaly significant. The Main et al. (2006) study is about correlations and rather weak correlations at that.

2. Failing to describe the overwhelming negative findings of the Main et al. (2006) study, preferring to emphasize the relatively few (and minor) findings which the CHAP committee reported as "positive" or as "associations," despite the fact that many were not statistically significant.

3. Failure to fully define the meaning of "association" in this study, which is not an association between the rate (or risk) of an event in one population relative to another, but rather a much simpler (and less informative concept) of an "association" as a Spearman correlation coefficient measured in boys with and without cryptorchidism.

4. Failure to emphasize that the only actual organic defect measured in this study (i.e. cryptorchidism) was not associated with any phthalate in breast milk and, furthermore, that these results conflict with animal (i.e. rodent) studies described by Main et al. (2006, p.274) as: Imajima et al. (2001), Jarfelt et al. (2005), and Kavlock et al. (2002a, 2002b).

5. Failure to mention the fact that Main et al. (2006) calculated 54 different Spearman correlation coefficients in two separate analyses (see Tables 3 and 4) yet did not correct for multiple hypothesis testing. Had they done so, the so-called "positive" results of Main et al. (2006) would likely have disappeared. Note that, in contrast to the CHAP Report, Main et al. (2006) mentioned their lack of adjustment for multiple testing of hypotheses.

   Consider, for example, Table 3 (Main et al., 2006, p. 273). In that table, Main et al. (2006) report Spearman correlations between concentrations of phthalate monoesters in human breast milk and reproductive hormones in serum of boys 3 months of age with and without cryptorchidism. Of the 54 comparisons made, only 8 were statistically significant. Put another way, 46/54 (85%) of the findings were negative (i.e. not statistically significant) in the absence of multiple hypothesis testing. The CHAP Report, however, adds to the 8 statistically significant findings an additional 17 results they describe as "associations."

   The CHAP version of the Main et al. (2006) results makes it appear that 25/54 comparisons (46%) are scientifically relevant, when in fact only 15% were so. Indeed, the CHAP committee provides no guidance to the reader (e.g. in a methods section) how they define an "association" which appears to be any finding that "fits" with their preconception of a relevant result, independent of statistical significance. There is no scientific justification for such an approach. Furthermore, the CHAP Report makes no mention of the fact that the correlation coefficients in Main et al. (2006) are, for the most part, very modest. Good examples are the so-called "negative associations" reported by the CHAP committee for "all monoesters with the FSH/Inhibin B ratio." Four of these so-called "negative associations" have correlation coefficients less than 0.1 (namely, 0.006, 0.027, 0.049, and 0.058) and none of the remainder are greater than 0.204. Inclusion of these findings as "associations" (negative or not) is inappropriate and misleading.

Hsieh et al. (2008)

Examining the Hsieh et al. (2008) study in terms of discrepancies is important because it examines the extent to which specific measures of anogenital distance are correlated (or not) with specific anogenital malformations, namely, hypospadias and cryptorchidism in young boys approximately 1.5-4 years of age. Other studies of exposure to phthalates and anogenital distance assume that these associations (if present) have negative consequences whether in terms of anogenital malformations, sexual function, and/or sexual development (**CHECK Swan et al. 2005 and Swan, 2008**).

According to Hsieh et al. (2008, p. 139) they "did not measure anogenital distance (i.e. the distance from the anus to the penopubic junction)" in their study of young boys. The authors examined the potential associations between various human male perineal measurements and hypospadias and cryptorchidism. They note that although the USEPA (in its guidelines for reproductive toxicology studies) identifies AGD as an endpoint, "disagreements exist over the ideal instruments for measurement and which forms of perineal length measurement best represent anogenital distance and associated endocrine disruption, if any" (Hsieh et al., 2008, p. 137). The authors note that Swan et al. (2005) and Salazar-Martinez et al. (2004) both used calipers placed on the patient rather than suture or flexible surgical rulers, thus creating the opportunity for "significant measurement discrepancies" arising from calipers that do not follow the contour of the scrotum.

Furthermore, Hsieh et al. (2008) mention that there are at least three different ways to measure "anogenital distance:" the posterior anoscrotal distance (PASD), the anterior anoscrotal distance (AASD), and anogenital distance. Regardless of the terminology, they note that "the biological significance and reproducibility of these various perineal measurements remain to be determined" (Hsieh et al., 2008, p. 138).

In this study, PASD and AASD were measured and compared among boys with hypospadias, cryptorchidism and normal genitals. As noted above, AGD (as the distance from the anus to the penopubic junction) was not measured because they believe it to be less reliable than PASD and AASD. Without adjusting for weight, the authors found that both PASD and AASD in boys with hypospadias but not cryptorchidism were significantly different than normals. After adjusting for body weight, only AASD but not PASD was significantly different than normal boys among both boys with hypospadias and cryptorchidism. In the end, the authors note that their "preliminary data indicate that human hypospadias and cryptorchidism may be associated with shortened anogenital distance" and that "further study is needed to corroborate or refute these findings" (Hsieh et al., 2008, p. 141).

The CHAP report's version of the Hsieh et al. (2008) preliminary study tells a very different story. They state (CHAP Report, p. 42) the following: "Hsieh et al. (2008) reported that boys with hypospadias had shorter AGD than boys with normal genitals." Missing from their account is the notion that these are preliminary data—i.e. not replicated— and that only one measure of anogenital distance—AASD but not PASD— was significantly different in the comparative cross-sectional analysis. No limitations of the study were mentioned much less discussed in the CHAP report.

Huang et al. (2009)

Examining the study by Huang et al. (2009) is important because its results (apparently) conflict with those of Swan et al. (2005) and Swan (2008) and its results conflict with the rat studies (upon which the CHAP bases its overall conclusions and recommendations). In the study by Huang et al. (2009), both amniotic and urine levels of five phthalate monoesters were measured in pregnant women, specifically MBP, MEHP, and MEP. The measurement of phthalates in the amniotic fluid is important because that is a better indication of exposure to the fetus than urinary phthalates. In addition, the newborns' birth weight, gestational age, and anogenital distance (AGD)—as PASD—were measured. The authors observed no associations between MBP, MEHP, or MEP and AGI (whether AGD or AG Indices adjusted for weight or length) in infant boys. In infant girls, on the other hand, the authors found associations between AGD, AGI-W and AGI-L and amniotic fluid levels of MBP and MEHP.

Note that these results are directly opposite those in rats, where male rats have abnormal AGD from exposure to phthalates but not female rats.

Here's what the CHAP Report says about Huang et al. (2009) in Appendix C (p. C-1 and C-2):

> "In a small study on 33 male and 32 female infants, researchers from Taiwan (Huang et al., 2009) explored associations of prenatal urine and amniotic fluid levels of MEHP, MBP, MBZP, MMP, and MEP with AGD measured at birth. AGD for female infants, after adjusting for birth weight or length, were significantly shorter among those above the median for amniotic fluid MBP or MEHP concentrations, as compared to those below the median. In female infants, urine concentrations of MBP had suggestive negative associations with AGD after adjustment for birth weight or length. Among male infants, birth weight, length, and AGD were not associated with amniotic fluid levels of MBP or MEHP."

Here's what the CHAP Report says (p. 28) about Huang et al. (2009) in their assessment of the human epidemiological evidence:

> "The Huang study (2009) did not find associations of any phthalate metabolite with reduced AGD in boys, but did in girls."
>
> "It is well known that in rodent studies some phthalates cause the phthalate syndrome, consisting of, among other endpoints, reduced AGD, increased prevalence of reproductive tract anomalies and poor semen quality (see Section 2.2 for further details). Although it is uncertain whether the phthalate syndrome occurs in humans, the data on phthalates and AGD are suggestive (Swan et al., 2005; Swan, 2008; Suzuki et al., 2012) and human data suggest that AGD is a relevant marker for reproductive health outcomes. Hsieh et al. (2008) reported that boys with hypospadias had shorter AGD than boys with normal genitals. Mendiola (2011) showed that shorter AGD was associated with poorer semen quality (i.e., lower sperm concentration and motility, and poorer morphology), while Eisenberg (2011) found shorter AGD among infertile men as compared to fertile men. **These human studies demonstrated that shortened AGD is associated with reproductive conditions that are similar to those observed in rats with the phthalate syndrome.** This observation supports the use of human AGD as a relevant measure to assess the antiandrogenic mode of action of phthalates during fetal development.
>
> **In conclusion, these studies provide the first human data linking prenatal phthalate exposure (specifically DEP, DBP and DEHP) with antiandrogenic effects in male offspring.**

Note however that the CHAP authors make no mention here of the results of Huang et al. (2009) which certainly do not demonstrate that "shortened AGD is associated with reproductive conditions that are similar to those observed in rats with the phthalate syndrome." Basically, the CHAP authors have chosen to ignore the contradictory results of Huang et al. (2009), further evidence that the CHAP authors prefer positive results and appear to be relying upon their preconceptions when making conclusions. And, as mentioned above, Huang et al. (2009) is the only study that uses amniotic fluid

measures of phthalates rather than urinary measures, which are widely considered to be better measures of actual exposure to the fetus during pregnancy.

Suzuki et al. (2012)

Examining the study by Suzuki et al. (2012) is important because the CHAP authors misrepresent their findings.

Here's what the CHAP Report (p. 28) says about Suzuki et al. (2012):

> "The Swan (2005; 2008) and Suzuki et al. (2012) publications reported reduced AGD in male infants in relation to higher maternal urinary concentrations of DEHP metabolites, whereas the Swan study also found similar associations of monoethyl phthalate (MEP) and MBP with reduced AGD."

This statement is false (at worst) or misleading (at best). According to their own table (2.2), the CHAP Report authors note that Suzuki et al. (2012) found evidence of only a "suggestive association" of AGI with DEHP metabolites. More importantly, Suzuki et al. (2012) make no such statement. According to Suzuki et al. (2012, p. 239) the correlation between DEHP metabolites and AGI was not significant in their study.

Note also that in this summary statement, the CHAP authors make no mention of the fact that Suzuki et al. (2012) did NOT find associations between the following phthalates and AGD/AGI: DEHP metabolites, MMP, MEP, MBP, MBZP, MEHHP or MEOHP, although this information appears in tabular form (Table 2.2, p. 29) and in Appendix C in the CHAP report.

In the end, the CHAP authors ignore contradictory data (found in their own report) and make, at best, misleading statements about results. This is in direct conflict with good scientific practice.

The CHAP Report's Version of the Findings and Relevance of Neurodevelopmental Studies

The CHAP report discussed the epidemiological studies on phthalates and neurodevelopmental outcomes in two places:

1. Section 2.4 Epidemiology (p. 29-33)
2. Appendix C-3 through C-6 in a section "Phthalates and Neurodevelopmental Outcomes"

The latter of these (Appendix C) is a narrative description of several studies, namely, Swan et al. (2010), Engel et al. (2009), Engel et al. (2010), Miodovnik et al. (2011), Cho et al. (2010), Kim et al. (2011), Whyatt et al. (2010), and Yolton et al. (2011). In this section, the authors of the CHAP report provide no formal assessment of the quality of these studies. Indeed, this section appears to be a straightforward summarization of what the original studies reported without any (or with a very limited amount of) critical assessment and interpretation on the part of the CHAP authors. I will not provide my own detailed descriptions of these same studies but will provide enough information to assess the extent to which the CHAP authors interpreted and reported the results of these studies appropriately.

In Section 2.4 the CHAP authors provide their assessment of the relevance and implications of these same studies, with an accompanying Table 2.3 on pages 32-3. They note the following:

1. That it is difficult for them to synthesize the results across these studies because different study designs, different sets of phthalate metabolites were assessed during different periods of time (e.g. during pregnancies), and finally, because these studies assessed different neurological outcomes at different ages using different tests.
2. That it is appropriate to conclude that the results of cohort studies should be given more "weight" than cross-sectional studies.
3. That poorer test scores were generally associated with higher urinary levels of some phthalates, although the phthalates differed across populations and were not always consistent.

Yet despite these fundamental and prominent differences, the CHAP authors concluded that "human exposure to DEHP, DBP, and DEP metabolites should be reduced."

A number of issues with these studies were either ignored by the CHAP authors or de-emphasized to the point of questionable scientific integrity. Consider, for example, the single cohort study from which three of the seven publications (**Engel et al., 2009; Engel et al., 2010; and Miodovnik et al. 2011**) emerged. Or, to put it another way, the CHAP is incorrect when they give the reader the impression that there are "seven prospective cohort studies" when in fact there are, at most, four cohort studies. Three investigators use the same basic dataset—the Mount Sinai Children's Environmental Health Study—and report their results in three separate publications.

The Mount Sinai Children's Environmental Health Study

The Mount Sinai Children's Environmental Health Study enrolled a multiethnic prenatal population (n = 404) in New York City between 1998 and 2002. Of these, only 188 (47%) returned for a 4-9 year follow-up study of phthalates and childhood behavior and executive functioning (Engel et al., 2010) and a smaller number (n = 137 or 34%) returned for a 7-9 year follow-up study of phthalates and childhood social impairment (Miodovnik et al., 2011). The third publication from this study (Engel et al., 2009) examined 295/404 (73%) infants at or near birth. Importantly, this third study revealed that for male infants (the boys) concentrations of high and low molecular weight phthalates were associated with *higher* (not lower) scores on orientation and motor scales and no apparent association for alertness. For girl infants, there was evidence of an association between concentrations of high and low molecular weight phthalates and lower scores on these same scales. Simply put, the study could be interpreted to mean that giving phthalates to pregnant women is a good idea, although I am not recommending that. Rather, it is important to point out that the CHAP version of these results (see CHAP Report, p. 30) does not mention the "positive" results for boys focusing only on the "negative" results for girls. This is a good example of selective reporting and skewed interpretation of results. Clearly, the "positive" results for boys contradict the CHAP committee's final recommendations to reduce exposure to phthalates.

Apparently, a number of chemicals in the maternal urines were measured during pregnancy including but not limited to phthalates. For example, the authors note that pesticide levels and PCBs (polychlorinated biphenyls) were evaluated in another publication from this same cohort but these chemicals were not evaluated as potential confounders in the studies examined in this matter (Engel et al., 2009; Engel et al., 2010; Miodovnik et al., 2011). Furthermore, the authors of these studies mention that the presumed mechanism of action of phthalates involves thyroid homeostasis, including thyroid hormone. But no measures of thyroid hormones were reported (or mentioned) in these studies.

In addition, the loss to follow-up reported in the Engel et al. (2010) and Miodovnik et al. (2011) publications deserves mention. Both authors claim that this loss to follow-up would not lead to a selection bias. Engel et al. (2010), for example, state specifically that "we do not believe selection bias can account for our findings." However, this is pure speculation on their part, devoid of an empirical basis. Both Engel et al. (2010) and Miodovnik et al. (2011) state that because the mothers did not know their prenatal phthalate concentrations, they could not evaluate their child's behavior based on that knowledge. But the issue remains unresolved without additional information or further studies.

The Study for Future Families (SSFI and SSFII)

Swan et al. (2010) reported on the relationship between maternal phthalate concentrations and "masculine play" in the same cohort of infants Swan et al. (2005) and Swan et al. (2008) examined with regards to anogenital distance (described earlier in this report). Here, the authors studied 74 boys and 71 girls from a total potential cohort of 477 mother-child pairs, representing a very large loss to follow up. The results of this study were, for all practical purposes, negative. There were no associations between phthalate concentrations and play behavior in girls. Only two phthalates were associated with "decreased masculine scores" in boys with no associations observed for the remaining phthalates. Not surprisingly, the CHAP authors failed to mention this negative study in their overall assessment of the epidemiological studies (CHAP Report, p. 30).

The Mothers and Children's Environmental Health Study (MOCEH)

Kim et al. (2011) reported the results of a study examining prenatal phthalate exposure and neurodevelopment in 460 mother-infant pairs from South Korea.

The Health Outcomes and Measures of the Environment (HOME) Study

Yolton et al. (2011) reported the results of a study examining the relationships between prenatal exposure to phthalates and infant neurobehavior in children 5 weeks old. In this study (called the "Health Outcomes and Measures of the Environment (HOME) Study," prenatal exposure to phthalates was measured in maternal urinary metabolites at 16 and 26 weeks during the pregnancies. At five weeks of age, infants (n = 332) were examined on the NICU Network Neurobehavioral Scale (NNNS). Results revealing a benefit of phthalate exposure were as follows: higher levels of DBP (di-butyl-phthalate) were associated with improved behavioral organization (i.e. decreased arousal, increased self-regulation, and decreased handling). Results revealing a hazard (or negative association) were as follows: higher levels of DEHP were associated with nonoptimal reflexes in 26 week old males but not females.

Note, however, that in CHAP Report's discussion of the epidemiological studies on phthalates and neurodevelopmental outcomes (CHAP Report, p. 29-33) the "positive" findings of Yolton et al. (2011)—revealing that exposure to some phthalates were associated with benefits—are not mentioned in the text. Only the "negative" findings are discussed by the CHAP authors. Yet despite these inconsistent findings (i.e. some "positive" and some "negative") the CHAP authors recommend that exposure to DEHP, DBP and DEP metabolites be reduced. No justification for these recommendations—given mixed results—is provided.

The CHAP Report and Studies on Gynecomastia and Precocious Puberty

In their overall assessment of epidemiology, the CHAP Report ignores three cross-sectional studies on phthalate measurements and gynecomastia and precocious puberty (Colon et al., 2000; Lomenick et al., 2009; and Durmaz et al., 2010). These studies are described in Appendix C.

STUDIES AND OTHER PUBLICATIONS NOT CITED BY CHAP INCLUDING REVIEWS PUBLISHED IN 2013

As noted by the CHAP, the stopping point for their analysis and interpretation of evidence relating to the health effects of phthalates was information available up to the end of 2012. In order to examine the extent to which the CHAP reviewed "all relevant data" regarding the possible harmful health effects of phthalates, the following analysis was performed.

A systematic search of the scientific literature was performed for publications examining the issue of phthalates and reproductive health, with a special focus on children and other potentially susceptible populations. The purpose of this search was to identify epidemiological studies as well as reviews, editorials, and commentary. The aim was to include all publications published through 2012, although I also included reviews published on the topic of the human health effects of phthalates published in 2013, the same year as the CHAP Report.

Search #1: Medline (PubMed) was searched for relevant publications using the following search terms: "phthalate" and "reproductive," limiting the search to publications in English and regarding infants (birth to 23 months) and children (birth to 18 years). This search, performed on August 7, 2014 identified 109 publications, of which 17 were published in 2013 and 2014, leaving 92 publications.

Search #2: Medline (PubMed) was searched for publications related to a recent review entitled "Exposure to phthalates: reproductive outcomes and children health. A review of epidemiological studies," by Jurewicz and Hanke (2011). This search, performed on August 12, 2014, identified 104 publications, of which 16 were published in 2013 and 2014, leaving 88 publications.

After removal of duplicates (n = 15), a total of (92 + 73) = 165 potentially relevant publications were identified. From search #1, the CHAP included (i.e. cited) 28/92 (30%). From search #2 (minus duplicates), the CHAP included (i.e. cited) 21/73 (29%). From these two searches alone, the CHAP did not cite 70% (116/165) of the publications identified in these two PubMed searches and published no later than 2012.

Abstracts of these 116 articles (not cited in the CHAP report) were examined for relevance to the topic of the CHAP review. Of these 116, 32 were identified as relevant and not cited in the CHAP report. A list of the remaining articles is available on request. Briefly described below are the studies, reviews, and other articles not cited much less discussed by the CHAP committee that relate directly to the issues regarding exposure to phthalates and reproductive or neurodevelopmental outcomes in children. Note that I also include three review articles published in 2013, the same year the CHAP committee completed their review. Although the CHAP committee may not have had access to these three articles, the years of the reviews are basically identical to the years reviewed by the CHAP committee. It is reasonable, therefore, to compare the CHAP conclusions with those of reviewers examining the same issues over the same time period. Clearly, some reviews were published in earlier years.

Epidemiology Studies Not Cited in the CHAP Report (in reverse chronologic order)

Chevrier et al. (2012) is the report of a nested case-control study of exposure to phthalates and the occurrence of hypospadias and undescended testis. Cases in the EDEN and PELAGIE mother-child cohort studies were identified during the first five days after birth. Three controls were selected per case and matched on residence area, gestational age and date and day of collection of urine. Urinary phthalates were determined without knowledge of case/control status. The results were overwhelmingly negative. In the authors' words (Chevrier et al., 2012, p. 355):

> "Our prospective study did not show evidence of increased risks of male genital anomalies with prenatal exposure to phthalates."

However, the CHAP Report failed to mention much less discuss these findings which directly contradict the notion that phthalates—if they were to reduce AGD—also cause male genital abnormalities.

Mieritz et al. (2012) is a study of phthalates measured in the urine of 555 healthy Danish boys and several male reproductive outcomes (e.g. age of puberty, serum testosterone levels, presence of gynecomastia), as a part of the Copenhagen Puberty Study. As these authors conclude in their abstract (Mieritz et al., 2012, p. 227):

> "The urinary levels of phthalate metabolites were not associated with age at pubertal onset, serum testosterone levels or presence of gynaecomastia. In conclusion, we did not find evidence of anti-androgenic effects of phthalates in our healthy boys. Thus, current phthalate exposure was not associated with pubertal timing, testosterone levels or with the presence of pubertal gynaecomastia in this cross-sectional study."

In sum, **Mieritz et al. (2012)** is a study that conflicts with the notion that phthalates have negative causal effects on reproductive outcomes in male children (an example of what the CHAP committee would consider "male developmental toxicity"), yet the CHAP committee did not include this study in their assessment.

Frederiksen et al. (2012) published a study of urinary phthalate levels in 725 healthy Danish girls and examined these values relative to the following outcomes: age, pubertal development (including a separate analysis of 25 girls with precocious puberty (PP)), and reproductive hormone levels. From the abstract, the authors conclude:

> "No association between phthalates and breast development was observed. In addition, there were no differences in urinary phthalate metabolite levels between girls with PP and controls. We demonstrated that delayed pubarche, but not thelarche, was associated with high phthalate excretion in urine samples from 725 healthy school girls, which may suggest anti-androgenic actions of phthalates in our study group of girls."

In sum, **Frederiksen et al. (2012)** reveal mixed results, i.e. both null and potentially negative effects of phthalates on reproductive outcomes in healthy girls. At most, the authors note that their results "suggest" anti-androgenic actions of phthalates in their study population of Danish girls.

Lin et al. (2011) is a study of maternal urinary phthalate levels and cord sex hormones in human infants. The authors report the following for male newborns (Lin et al., 2011, p. 1195):

> "No significant correlation was found between each steroid hormones and phthalate metabolites for male newborns, except MMP was marginally significantly correlated with E(2)."

In sum, another study with negative (i.e. null) results for the putative relationship between phthalate levels and male reproductive outcomes was not mentioned (much less discussed) by the CHAP.

Calafat et al. (2004) report the results of a study examining the extent to which premature neonates are exposed to di-2-ethylhexylphthalate in the neonatal intensive care unit. They note the following about the state of knowledge of health effects (Calafat et al., 2004, p. e429):

> "Although the overall benefits of medical procedures using PVC devices outweigh the risks associated with exposure to DEHP, more research is needed to determine whether infants and children who undergo intensive therapeutic interventions using DEHP-containing devices are at higher risk for altered health outcomes than infants and children who undergo similar treatments but are not potentially exposed to DEHP."

Clearly, at the time of this publication, the health effects were unknown.

Reviews and Other Related Publications not Cited in the CHAP Report

Bellinger (2013) reviewed the epidemiological literature on exposure to phthalates and neurodevelopmental outcomes. He concludes (Bellinger, 2013, p. 2):

> "Although these limited studies are consistent in suggesting poorer outcomes among children with higher biomarker levels of prenatal or concurrent phthalate exposure, it is impossible to draw strong inferences at this time."

This author concludes that inferences about causal relationships between exposure to phthalates and neurodevelopmental outcomes are "impossible."

Braun et al. (2013) reviewed the epidemiological literature examining the relationship between early life phthalate exposure and pediatric health outcomes. They conclude (Braun et al., 2013, p. 6):

> "Several studies suggest that gestational phthalate exposure may increase behavioral problems in childhood, but there is inconsistent pattern related to the specific phthalates and behavioral domains."

> "Currently, no evidence based methods to reduce exposures exist but many scientific and professional organizations have made recommendations to reduce exposure."

Gallinger and Nguyen (2013) reviewed the potential health effects of phthalates, given that these chemicals are found in some gastrointestinal medications. They conclude that the adverse health effects are not known. They write (Gallinger and Nguyen, 2013, p. 7045):

> "In order to further explore preliminary concerns, additional research with robust

methodology should be conducted. Longitudinal studies capable of demonstrating causation are required to determine whether phthalates actually cause negative health consequences. Studies with larger sample sizes will also help quantify how much DBP and DEHP is being absorbed through specific medications."

Kay et al. (2013, p. 200) in their review of the reproductive and developmental effects of phthalate diesters in females conclude:

> "The epidemiological literature is sparse for most outcomes studied and plagued by small sample size, methodological weaknesses, and thus fails to support a conclusion of an adverse effect of phthalate exposure."

The conclusions of these authors directly conflict with those of the CHAP authors.

Note also that these authors write (Kay et al., 2013, p. 215) that the "relevance of current animal models is questionable" striking at the heart of the CHAP argument that in the absence of human (epidemiological) evidence, the animal evidence is generalizable to humans.

Chakraborty et al. (2012) reviewed the relationships between biomarkers of phthalates and pubertal stages in girls. They describe inconsistent results among the epidemiologic studies with respect to pubertal development, citing (Wolff et al. 2010; Colon et al. 2000; Durmaz et al. 2010; and Lomenick et al., 2010). They (Chakraborty et al., 2012, p. 23) conclude the following:

> "The differences in results reported by different research groups could be due to the different locations of the studies, ethnicity, age, or a cumulative effect of other EDCs."

Grady and Sathyanarayana (2012) is a review of phthalates and male reproductive development and function. They note that the human studies published on phthalates and AGD (e.g. Swan et al., 2005, Swan, 2008, and Huang et al., 2008) are inconclusive. They write (Grady and Sathyanarayana, 2012, p. 309):

> "The implications of shortened male AGD are unclear and require further investigation."

Johnson et al. (2012), in their review of the mechanisms of phthalate toxicity in rats, mice, and humans note the following about the epidemiological investigations to date:

> "Epidemiology data linking *in utero* human phthalate exposure to male reproductive tract demasculinization or malformations are limited and somewhat inconsistent; for a review, see Jurewicz and Hanke (2011). These types of studies are difficult to perform because of the need to examine phthalate exposure during the critical window of male reproductive tract masculinization (presumed to be gestational weeks 8–14; Welsh *et al.*, 2008), the relatively low level of human phthalate exposure in pregnant women, and the lack of access to sensitive molecular endpoints during the masculinization window. Because increased male anogenital distance (AGD), testis descent, and the positioning of the urethral opening at the phallus tip require masculinization during the male programming window (van den Driesche *et al.*, 2011; Welsh *et al.*, 2008), these endpoints are the most relevant gross morphology measurements available in the human."

Polanska et al. (2012, p. 330), in their review of exposure to environmental and lifestyle factors potentially affecting (i.e. causing) attention-deficit hyperactivity disorder in children, note the following with respect to phthalate exposure:

> "On the other hand, the impact of phthalates, BPA, PFCs, PAHs and alcohol is less frequently investigated and does not allow a firm conclusion regarding the association with the outcomes of interest."

Jurewicz and Hanke (2011) is a review of epidemiologic studies that makes the following conclusions (see abstract):

> "Epidemiological studies, in spite of their limitations, suggest that phthalates may affect reproductive outcome and children health. Considering the suggested health effects, more epidemiologic data is urgently needed and, in the meantime, precautionary policies must be implemented."

Note that the reviewers only conclude that there are "suggestive" effects of phthalates on reproductive outcomes and that more epidemiologic studies are needed. Note too, however, that they believe "precautionary policies must be implemented." It follows that the CHAP recommendations are consistent with these earlier recommendations although the CHAP provides no justification for their stated policies, e.g. that they are "precautionary" in nature.

Pak et al. (2011) is a review of phthalate exposures and human health concerns with implications for nursing practice. They conclude (Pak et al., 2011, p. 232):

> "Despite animal studies demonstrating consistent reproductive toxicity, additional human studies are needed to explore health outcomes, especially affecting reproductive health."

Note the request for more, better, epidemiological studies.

Yen et al. (2011) is a review of the potential health effects of an event in Taiwan in which a phthalate was illegally added to foods and beverages. They note the following about those potential health effects:

> "Epidemiological studies have suggested associations between phthalate exposure and shorter gestational age, shorter anogenital distance, shorter penis, incomplete testicular descent, sex hormone alteration, precocious puberty, pubertal gynecomastia, premature thelarche, rhinitis, eczema, asthma, low birth weight, attention deficit hyperactivity disorder, low intelligence quotient, thyroid hormone alteration, and hypospadias in infants and children."

Note that these authors describe the epidemiological findings only as "suggestive of associations."

Hatch et al. (2010) is a review of the possible effects of endocrine disruptors (including but not limited to phthalates) on obesity. Their assessment of the methodological problems plaguing studies of endocrine disruptors is pertinent (problems, in general, not discussed by the CHAP committee):

> "The complexity of the etiology of obesity and related disorders poses numerous challenges for the field as it moves forward. While rodent models and in vitro assays play a critical role in advancing this research, the many differences between rodent and human physiology in regards to adipogenesis must be considered (Ben-Jonathan, 2009). As this review highlights, human studies of the association between EDCs and obesity are few and suffer from methodologic limitations. Data are particularly lacking for chemicals that the emerging animal literature points to as being of notable concern, including organotins and BPA. Epidemiologists must pay close attention to the difficulties in measuring diet and exercise, the "Big Two" risk factors that may cause residual confounding if they covary with exposure. Also difficult are the logistical and conceptual challenges in studying the effect of mixtures of early life exposures on outcomes much later in life. Another area in need of additional study is the effect that pharmacokinetic differences in metabolism of chemicals may have on observed associations. Cross-sectional studies may be subject to reverse causality."

Martino-Andrade and Chahoud (2010) review the available evidence on phthalates and reproductive toxicity. They make the following statement (Martino-Andrade and Chahoud, 2010, p. 154):

> "…uncertainties in the epidemiological database, difficulties in animal to human extrapolations and the lack of knowledge on the significance of low-dose effects for human health preclude a better understanding of the real risks for humans."

Clearly, they are unconvinced that exposure to phthalates is associated with human risk.

Yiee and Baskin (2010, p. 34) reviewed the role of environmental factors in genitourinary development and concluded:

> "In utero exposure to diethylstilbestrol has been shown to increase the risk of testicular dysgenesis syndrome. However, to our knowledge no other environmental factor has been shown to cause testicular dysgenesis syndrome."

Kamrin (2009) reviewed the potential health effects of phthalates and concluded that "there is no convincing evidence of adverse effects on humans." The author writes (Kamrin, 2009, p. 157):

> "This article summarizes recent evaluations of the risks of these phthalates, and addresses the public health implications of the regulations that were enacted. The analysis considers biomonitoring studies and epidemiological research in addition to laboratory animal evidence. Analysis of all of the available data leads to the conclusion that the risks are low, even lower than originally thought, and that there is no convincing evidence of adverse effects on humans. Since the scientific evidence strongly suggests that risks to humans are low, phthalate regulations that have been enacted are unlikely to lead to any marked improvement in public health."

Lyche et al. (2009) is a review of the reproductive and developmental toxicity of phthalates. They conclude (Lyche et al., 2009, p. 225):

> "The present human toxicity data are not sufficient for evaluating the occurrence of reproductive effects following phthalate exposure in humans, based on existing relevant animal data."

Note that this conclusion directly conflicts with both the conclusions and approach of the CHAP.

Talsness et al. (2009) review the toxicological effects of a variety of compounds found in plastics, including but not limited to phthalates and conclude the following about the putative effects of phthalates on humans (Talsness et al., 2009, p. 2082):

> "…some epidemiological data on possible associations between phthalate exposure and reproductive effects in humans have provided further evidence for concern."

Clearly, these authors are not convinced that the epidemiological evidence is convincing for adverse health effects of phthalates.

In their section entitled "general conclusions" they state (Talsness et al., 2009, p. 2090):

> "Difficulties are not only encountered with extrapolation from animal models to humans, but epidemiological studies are also thwarted by drawbacks such as controlling for confounding factors. In particular, subjects are exposed to an assortment of chemicals on a daily basis and, often, lack of data regarding the extent of exposure at what may have been the critical time frame."

Main (2008, p. S47) reviewed the Main et al. (2006) and Swan et al. (2005) studies and concluded:

> "…the studies suggest that human testicular development pre and perinatally may be vulnerable to phthalate exposure."

No recommendations or causal claims were made.

Matsumoto et al. (2008) reviewed the potential effects of phthalates on reproductive outcomes. They conclude (Matsumoto et al., 2008, p. 37:

> "…it is not yet possible to conclude whether phthalate exposure is harmful for human reproduction."

Sathyanarayana (2008) reviewed the evidence on phthalates and children's health, providing conclusions on the science and on practical recommendations for patients and their families. The author writes (Sathyanarayana, 2008, p. 46):

> "The effect of phthalates on children's health is still not yet known, but current research suggests that phthalates may cause developmental and reproductive toxicity, and that the developing fetus is the most susceptible to these effects."

Wigle et al. (2008) reviewed the potential effects of environmental chemicals on reproductive outcomes. Regarding phthalates, they concluded (Wigle et al., 2008, p. 425):

> "There was inadequate epidemiologic evidence for associations between male genital birth defects and exposure to the environmental contaminants (including phthalates) examined here."

Chou and Wright (2006, p. 127) reviewed the health effects of phthalates and concluded:

> "There is limited evidence for adverse health effects of phthalates in children."

Lottrup et al. (2006) reviewed the possible impact of phthalates on infant reproductive health. Based on the Main et al. (2006) and Swan et al. (2005) studies they conclude (Lottrup et al., 2006, p. 172):

> "Taken together, these studies suggest that … human testicular development may be vulnerable to phthalates."

No recommendations or causal claims were made.

Jaeger et al. (2005) is a review of the potential health risk of exposure to phthalates in the neonatal intensive care unit. The authors note (Jaeger et al., 2005, p. 54):

> "…the exact potential for harm, either subtle or overt, is unknown or disputed. Thus, the recording of exposure history and "dose" in the medical record is warranted."

Fisher (2004, p. 313), in his review of a variety of environmental anti-androgens and reproductive health, concludes:

> "The ability of phthalates to suppress androgen synthesis during development and to induce testicular dysgenesis together with cryptorchidism and hypospadias has close parallels with human TDS. However, the crucial question regarding whether the level of environmental chemicals is sufficient to impact on human male reproductive health remains unanswered, although advances will be made from studying the effects of multi-component EDC mixtures in both in vitro and in vivo test systems. It remains to be seen what consequences this research will generate for human risk assessment strategies."

Latini et al. (2004) is a review of the extent to which exposure to DEHP occurs with infant nutrition with a discussion of what is known about the health effects. The authors note (Latini et al., 2004, p. 27):

> "Although DEHP has been shown to induce toxicity in experimental animals, a limited but suggestive human exposure data causes a serious concern that an early in life DEHP exposure may adversely affect male reproductive tract development. Here, we report a review on dietary phthalate exposure in babies."

Shea and the American Academy of Pediatrics Committee on Environmental Health (2003) reviewed the literature on the potential health effects of phthalates and concluded (Shea et al., 2003, p. 1472):

> "No studies have been performed to evaluate human toxicity from exposure to these compounds."

AN ASSESSMENT OF THE ADEQUACY OF THE PEER REVIEW OF THE CHAP REPORT

In line with the request to review all sections of the formal Peer Review of that report, I have carefully examined the document entitled, "Peer Review of the CHAP Draft Report on Phthalate and Phthalate Substances" submitted to the Consumer Product Safety Commission (CPSC) in final form on August 12, 2013. In addition, I reviewed the CHAP response to the Peer Review in a letter dated July 17, 2014 to the Acting Chairman of the Consumer Product Safety Commission from Paul Lioy and Russ Hauser.

On page 60 of the Peer Review document, the charge questions to the peer reviewers are described. Oddly, these charge questions were generated by the CHAP, rather than from an independent body. Note that the CHAP, in requesting peer review, was "primarily interested in a review of those areas of the risk assessment process that employ novel methodologies." Note, however, that they also mention that it was not their intention "to dissuade the peer reviewers to comment on any aspect of the report that they deem significant."

There are at least three issues of central importance to the issue of the health effects of phthalates that the CHAP peer review should have been charged with but were not: (1) the relevance and limitations of the epidemiologic studies, (2) the over-arching methodological approach the CHAP used in their review of the evidence, and (3) the fact that there was no process to eliminate from the group of peer reviewers individuals with ties to pediatric, public health, consumer, or other advocacy groups with a vested interest in procuring recommendations to reduce exposure to phthalates, yet the peer reviewers were not permitted to have ties to any industry that manufactures or sells consumer products.

I examine each of these issues in turn.

Failure of the Peer Review to Address the Relevance and Limitations of Epidemiologic Studies

The eight charge questions provided to the peer reviewers of the CHAP report are missing any explicit mention of epidemiology. The word "epidemiology" does not appear in these charge questions, despite the fact that the primary goal of the CHAP report is to assess the risk to humans of exposure to phthalates. I take this to be a significant problem with the peer review process, i.e. with the charge to the peer reviewers. Certainly these peer reviewers could discuss the epidemiological studies if they chose to do so, but the CHAP did not request such a review. Rather, the CHAP only asked the peer reviewers if they thought it was appropriate to "regard male developmental effects in rodents as the critical endpoint for the cumulative risk assessment of phthalates in humans?"

By not specifically asking about the adequacy of the epidemiological studies to discern whether adverse health effects exist in the "sensitive" populations of actual interest to the public (i.e. human populations rather than rodents), the CHAP effectively avoided having the relevance and limitations of the epidemiological studies discussed in the peer review. This is unfortunate and inappropriate.

Note that the CHAP specifically asked the Peer Reviewers to comment on biomonitoring (a section within the CHAP Report) and the CHAP specifically asked the Peer Reviewers to comment on their approach to cumulative risk assessment (another section in the CHAP Report). In addition, the CHAP asked the Peer Reviewers to comment on their views on critical effect and reference doses and sensitive populations. But the CHAP did not ask the peer reviewers to comment on epidemiology. Given the obvious weaknesses of the epidemiologic studies, described in more detail earlier (see above), the CHAP

appears to be avoiding peer review of the weakest link in the chain of evidence in this issue. The CHAP should have insisted that the peer review comment on their review of the putative health effects of phthalates on the populations of pimary interest to the CPSC.

Failure of the CHAP to Appropriately Respond to a Request for a Systematic Review Methodology

It is important to point out that the peer reviewers were asked if the "CHAP adequately addressed their charge?" The peer reviewers were also asked if they had any other scientific issues they thought were important.

In response to the question about "other issues," Reviewer #4 noted that the CHAP failed to systematically review the literature. That reviewer wrote (Peer Review, p. 48-9):

> "The field of risk assessment is moving quickly to adopt the approach of systematic review as a guiding principle as well as a practical process for literature review, evidence gathering, and synthesis in support of risk assessment. As a gold standard, systematic review enhances objectivity, transparency, as well as credibility."

Reviewer #4 goes on to say that the CHAP report is not a systematic review. Specifically (Peer Review, p. 49):

> "The lack of description of the search scope, (and) inclusion and exclusion criteria makes it difficult to evaluate to what extend [sic] the current review is thorough and complete in identifying the latest and best scientific evidence."

In sum, Reviewer #4 and I agree that the CHAP report is not a systematic review of the scientific literature on the health effects of phthalates. The CHAP committee responded to this peer reviewer's concerns by arguing that a systematic review methodology was not appropriate. As I have discussed in detail, the CHAP committee is exactly wrong on this point. A systematic review methodology is precisely what was needed for a project of this scope and magnitude.

In the absence of a systematic methodology, the CHAP report is not objective, transparent, or credible. Rather, it is a personal and subjective review.

Failure of the Peer Review Process to Exclude Peer Reviewers with Ties to Public Advocacy Groups

It is important that the CHAP peer review process specifically excluded from consideration any peer reviewer who "received compensation or has any substantial financial interest in any manufacturer, distributor, or retailor of a consumer product" but did not explicitly exclude from consideration peer reviewers with financial (or other ties) to consumer, environmental, or public health advocacy groups.

ADDITIONAL QUALIFICATIONS

My primary research focus is the science and practice of disease causation. I have published peer reviewed papers on the methods used to assess causation, the practice of causal inference, theories of causation, the logic of causal inference, and the philosophies of science applicable to causation, the central problem of medicine, public health, and the law. For examples of papers on causality in the peer reviewed literature, see the following: Weed (1986), Koopman and Weed (1990), Weed and Gorelic

(1996), Weed and Hursting (1998), Weed (2000), Weed (2002), Weed (2005), and Parascandola and Weed (2006). I have also published peer-reviewed papers on the methods and practice of meta-analysis. See, for example: Weed (2000), Weed (2010), Alexander et al. (2011), and Althuis et al. (2014). Finally, I have also published peer-reviewed papers on the methods and practice of systematic reviews. See, for example, Breslow et al. (1998), Weed et al. (2011), Alexander et al. (2012), Weed (2013), and Alexander et al. (2014).

My research was supported by the National Cancer Institute, where I was employed for 25 years (1982-2007).

I have lectured on disease causation and related aspects of epidemiological methods at the National Cancer Institute, the Institute of Medicine, the United States Environmental Protection Agency, the National Academies of Science, Harvard University, Yale University, University of California (Berkeley), Imperial College (London), the University of Michigan, the University of North Carolina, Sloan Kettering Cancer Center, MD Anderson Cancer Center, the University of New Mexico, the University of Utah, and at The Ohio State University as well as at academic and research institutions around the world (e.g. China, Japan, Germany, Ireland, Norway, and Turkey) and at many scientific conferences.

I have trained and taught hundreds of physicians, nurses, public health scientists, and biomedical scientists in the principles and practice of disease causation. In addition, I have designed epidemiological studies, meta-analyses, and systematic reviews, analyzed the results, and published my findings in peer-reviewed journals.

I have also written extensively and lectured on bioethics, with special interest in the application of bioethical principles and methods to biomedical research, epidemiology, preventive medicine, and public health. Topics of special interest have been scientific misconduct and the ethics of cancer screening.

Finally, I have extensive experience in peer review of manuscripts submitted for publication. I have been (and continue to be) asked to review manuscripts for at least 28 different scientific journals. Examples include: the Journal of the American Medical Association (JAMA), Cancer, Critical Reviews in Toxicology, the American Journal of Public Health (AJPH), the American Journal of Epidemiology (AJE), the American Journal of Preventive Medicine, Nutrition and Cancer, and the Journal of the National Cancer Institute (JNCI). In addition, I serve on the editorial board of the JNCI where I manage this same peer review process. I have been a Reviews Editor for JNCI for the past 18 years.

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Review of CHAP Final Report on Phthalates and Phthalate Alternatives (July, 2014)

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Introduction

Under the direction of the Consumer Product Safety Improvement Act of 2008 (CPSIA) a Chronic Hazard Advisory Panel (CHAP) was convened "to study the effects of all phthalates and phthalate alternatives as used in children's toys and child care articles." Among the tasks specified in the CPSIA, CHAP was mandated to critically and objectively review all of the available data on potential health effects of all phthalates, alone and as mixtures, with the goal of determining with reasonable certainty safe levels of exposure for children, pregnant women, or other susceptible individuals. Upon examination of all available literature CHAP focused on the effect of phthalates on male developmental toxicity in the rat which they considered to be the "most sensitive and extensively studied endpoint" consistent with a position taken previously by other bodies such as the National Research Council (NRC, 2008).

In Section 2.2 of their report, CHAP reviews the research surrounding "phthalate syndrome" in the rat, a series of reproductive abnormalities observed in male offspring when pregnant dams are exposed to select phthalate diesters during late pregnancy from gestation days (GD) 15 to 20 (Foster, 2006). Among the characteristics of phthalate syndrome in the rat are malformations in the epididymis, vas deferens, seminal vesicles, prostate, hypospadias of the external genitalia, cryptorchidism (undescended testes), retention of nipples/areolae, and reduced

anogenital difference (AGD) reflecting demasculinization of the perineum (Mylchreest *et al.*, 1998; 1999). The effects appeared to be dose-related where more malformations were observed at higher dose levels of phthalate while lower dose levels were characterized by AGD and nipple retention (Mylchreest *et al.*, 2000). Mechanistically, the primary target in phthalate-induced abnormalities is the Leydig cell of the fetal testes which exhibits a significant reduction in the production of fetal testosterone followed by evidence of Leydig cell hyperplasia or aggregation. The reduced testosterone production is consistent with decreases in the expression of genes associated with cholesterol homeostasis and steroidogenesis. Reduced testosterone is believed to impair Wolffian duct development leading to the abnormalities in the vas deferens, epididymis, and seminal vesicles. Reduced serum testosterone also results in decreased formation of dihydrotesterone (DHT) via 5α-reductase in target cells which is required for prostate and external genitalia development, widening of the AGD, and nipple disappearance via apoptosis. Gene expression of another Leydig cell product, insulin-like factor 3 (Insl3), which participates with testosterone in testicular descent is also altered by phthalate exposure (Parks et al., 2000; Barlow and Foster, 2003; Foster, 2006; Wilson *et al.*, 2004). The active phthalate is not the diester administered but a monoester which results from hydrolysis of the parent compound. The potency of phthalate esters to produce phthalate syndrome appears to have a chemical structural basis. Based upon the ability to impair fetal testosterone production, the activity is restricted to phthalates with ortho substitutions containing three to seven (or eight) carbon atoms in the alkyl side chain backbone, the most potent compound containing five carbon atoms and the weakest containing seven to eight carbons (Foster et al., 1980; Gray et al., 2000).

As noted in the CHAP report, phthalate syndrome in the rat is reminiscent of a condition in humans referred to as "testicular dysgenesis syndrome" (TDS) which is characterized by hypospadias, cryptorchidism, as well as poor semen quality and testicular cancer. It has been hypothesized that the mechanism of TDS is similar to that observed for phthalate syndrome in the rat, impaired fetal testosterone production during the critical period of sexual differentiation for humans (late first trimester of pregnancy). Furthermore, it has been suggested that TDS might be a consequence of in utero exposure to endocrine disruptors (Skakkebaek et al., 2001). In their report the CHAP notes that there is an increase in epidemiologcal studies on the effect of

phthalate exposure with human health. Among these, several have reported an association between maternal urinary phthalate metabolite concentrations and reduced AGD in male offspring. CHAP concludes that these studies linking prenatal phthalate exposure with antiandrogenic effects in male infants "have important relevance to the hypothesized testicular dysgenesis syndrome (TDS) in humans."

The purpose of this review of the CHAP Final Report is to critically analyze the opinions and conclusions of the report as it relates to the expertise of this reviewer, endocrine and reproductive physiology and toxicology. While I attempted to examine the entire report, I focused my attention on the following sections: 1. Executive Summary; 2. Background and Strategy; 3. Phthalate Risk Assesment; 4. Discussion; Appendix A. Developmental Toxicity; and Appendix B Reproductive Toxicity. My specific opinions will relate to the following issues: 1) The rat as a model for estimating risk of phthalate exposure; 2) Species specificity of phthalate syndrome; and 3) Strength of epidemiologic evidence associating neonatal phthalate exposure with decreased AGD.

The rat as a model for estimating risk of phthalate exposure

The CHAP expresses little enthusiasm for the rat as a model for estimating risk of phthalate exposure, individually or as mixtures, in producing inhibition of testosterone production by the Leydig cells of the fetal testes. This concern relates to an accurate determination of the NOAEL (no observed adverse effect level) which can then be used to estimate risk to humans by such measures as margin of exposure (MOE) or reference dose (RfD) for determination of hazard quotients (HQ). With regard to the utility of the rat model, several issues have been raised in the CHAP report. For example, there is concern that since studies employing rats were mechanistic in nature, there usually were inadequate numbers of phthalate ester (PE) doses employed particularly in the low dose range. In the same vein, studies that are primarily investigative in nature, rather than regulatory, usually contain inadequate numbers of animals per dose. With these two shortcomings there is concern that accurate NOAELs have not been derived. According to the CHAP many studies failed to expose animals during the

sensitive periods associated with the onset of phthalate syndrome, i.e., late gestation (GD15 to term) when testosterone secretion by the fetal testes is elevated and supports male reproductive organ development. The CHAP also notes that assessment of phthalates is not complete, since not all phthalate esters (PE) or PE substitutes have been screened for this particular form of anti-androgenic activity. Finally, the CHAP points out that many studies lack replication and most of the information on phthalate syndrome is limited to the rat as a species.

With all due respect to CHAP, this reviewer disagrees with these concerns, although admittedly this opinion comes from an endocrine and reproductive physiologist with an interest in endocrine disruption and not from a regulatory toxicologist with expertise in risk assessment. My opinion is based upon the plausibility and reproducibility of the published data. Use of the rat has provided reliable and reproducible information with regard to the identity and relative potency of several phthalate esters, as well as providing insights into the biological mechanisms by which in utero reproductive development is disrupted. The science behind phthalate syndrome in the rat appears very sound and has applicability in risk assessment. While the relative potency of every PE or PE substitute has not been determined to date, there is considerable information in this regard which has utility in risk assessment. Furthermore, recent studies, as discussed below, have added to this data base as well as providing new mechanistic insights. Admittedly, some studies have employed an inadequate number of doses and insufficient number of animals per dose for the determination of NOAEL. However, these shortcomings can be rectified with modification of the original assay designs. As noted below much of the mechanistic and relative potency data have been replicated. Furthermore, the majority of studies have administered compounds of interest during the appropriate period of gestation, otherwise phthalate syndrome would not have occurred. It is true that most of the data on phthalate syndrome have been obtained in only one species, the rat. However, there is a reason for this since phthalate syndrome appears to be species specific in which the rat is the most sensitive to adverse effects of PE on male reproductive development. The issue of species specificity with regard to phthalate syndrome will be discussed in the next section.

Whereas virtually all of our understanding about phthalate syndrome came about from studies in the rat, the utility of the rat as a model for risk assessment is exemplified by the study

of Howdeshell et al. (2008). In this study pregnant SD rats were dosed with PE orally from GD8 to GD18 with the endpoint of interest being ex vivo testosterone (T) production from testes of male offspring at GD18. Using this design a dose-response assay was conducted on 5 PEs namely benzylbutyl phthalate (BBP), di(n)butyl phthalate (DBP), diethylhexyl phthalate (DEHP), diethyl phthalate (DEP), diisobutyl phthalate (DiBP), and dipentyl phthalate (DPP). Depending upon the compound tested, 4 to 7 dose levels were used with doses ranging from 25 to 900 mg/kg/day, 100 to 900 mg/kg/day, or 25 to 900 mg/kg/day. While DEP was inactive in lowering T production up to a dose of 900 mg/kg/day, the remaining 5 compounds dose-dependently decreased fetal T production Sufficient data were available to determine ED50's for this anti-androgenic activity of the active PEs where 4 compounds were equipotent (BBP, DBP, DEHP, DiBP) with ED50s at about 440 mg/kg/day while DPP was about 3-fold more potent with an ED50 of 130 mg/kg/day. The relative potencies obtained from these data confirmed structure activity relationships suggested by earlier experiments (that activity resides in phthalates containing 3 to 7 carbons in the alkyl sidechain backbone with 5 carbons being the most active). After verifying the relative potency of the active compounds the dose additivity hypothesis was tested by preparing a mixture of these five active compounds in which each constituent was of equivalent potency (equal amounts of BBP, BDP, DEHP, and DiBP and 1/3 the amount of DPP). The mixture was then tested in the model at varying dilutions from 100% down to 5%. The observed dose-response curves were consistent with the predicted curves confirming earlier reports of dose additivity, underscoring the reliability of the rat model as a means of estimating potency, and suggesting that the model would have utility in cumulative risk assessment, as well. The authors of this study also noted an additional advantage of this approach. Fetal T production as an endpoint can be determined at a much shorter duration (GD18) than postpartum endpoints associated with phthalate syndrome, such as AGD, nipple retention, organ weight, malformations, or histopathology. This approach also revealed that while higher doses of PE can produce evidence of maternal or fetal toxicity (e.g., decrease maternal weight, increased fetal mortality) the dose range of PE can be adjusted downward to obtain phthalate syndrome type effects without evidence of maternal and fetal toxicity (Howdeshell et al., 2008).

More recent studies from same research group have optimized the design of rat model to

increase its practicality and cost-effectiveness. Employment of this modified assay has provided more mechanistic insight, expanded the data base with regard to the activity and relative potency of PE and PE substitutes, and has provided further evidence of the utility of the rat model. The assay has been modified to produce a short-term in vivo screen, referred to as Fetal Phthalate Screen (FPS) and has been used to detect absence or presence of this specific form of anti-androgenic activity in PEs, PE substitutes, or other chemicals. In the modified assay the dosing period has been shortened from 11 days to 5 days. Pregnant rats are dosed orally from GD 14 to 18 and fetal testes T production is measured ex vivo on GD18 (Hannas et al., 2011a; 2011b; 2012; Furr et al., 2014). In the course of developing this protocol it was found that duration of exposure influences the potency of PE. For example, one day of exposure of DPP significantly reduced T production at doses of 300 mg/kg/day or higher whereas with 5-day exposure T production was reduced at 33 mg/kg/day or higher (Hannas et al., 2011a). The FPS was employed to determine the existence of this specific form of anti-androgenic activity in 27 compounds, namely PEs, PE substitutes, as well as other xenobiotics. In this screen, a single dose of test compound was administered at a level usually below that known to produce fetal-maternal toxicity (depending on the compound, the doses ranged from 150 to 750 mg/kg/day). The FPS correctly identified all known active and inactive compounds, as well as 7 unknowns as negative (Furr et al., 2014). The FPS assay also employed a multiple dose protocol to determine the ED50s of 11 compounds. These assays revealed that ED50s varied 25-fold (from 45 to 1100 mg/kg/day). DPP was revealed to be the most potent and DiNP (diisononyl phthalate) the least potent of the PEs, being about 2-fold less potent than DEHP (Hannas et al., 2011a, 2011b, 2012). These relative potencies correlated with relative potencies obtained previously using classical endpoints of phthalate syndrome (reproductive organ malformations) as well as the previous estimates of Howdeshell et al. (2008). Furthermore, with this FPS design a mixture containing 9 PE constituents produced a dose-response curve consistent with a predicted one based upon the dose addition model (Hannas et al., 2011b).

The optimized assay design was also used to compare decreased fetal T production with genetic markers (mRNA expression) after exposure to individual PEs as well as mixtures containing 9 PEs (Hannas et al., 2011a; 2012). Genes linked to testicular steroidogenesis (such

as SR-B1, StAR, Cyp17-1, Cyp11a) as well insl3, a protein involved in testicular descent, decreased dose-dependently to individual PEs or mixtures in a fashion comparable to that seen with T production, consistent with the previous literature. Gene analysis appeared to rule out the involvement of the PPARα pathway in phthalate syndrome (Hannas et al., 2012). As an endpoint, T production was found to be as sensitive as, if not more sensitive than, genetic markers (Hannas et al., 2011a; 2012). Furthermore, T production appeared to be much less variable between litters than that seen for gene expression (Hannas et al., 2011a). T production was also found to be more sensitive than traditional markers of phthalate syndrome. For example, the ED50s for DPP with AGD or nipple retention as endpoints were 4 to 5 fold that of the estimated ED50s for DPP when T production was used as the endpoint (Hannas et al., 2011a).

The developers of the FPS approach suggest that the shortened design (5 day dosing in the rat and T production ex vivo) might have value for risk assessment of PEs both individually or as mixtures for cumulative risk assessment (Hannas et al., 2011a; Furr et al., 2014). Furthermore, they recommend that more litters per dose would make it suitable for establishing NOAELs. Alternatively they suggest that benchmark dose (BMD) analysis may be more appropriate than NOAEL since BMD relies more on the shape of dose-response curve rather than statistical comparison of low dose and control (Hannas et a., 2011a). The CHAP has suggested that molecular endpoints have value in determining NOAEL. In view of its consistency and reliability, it would appear that fetal rat testes T production is preferable to gene expression for purposes of risk assessment. Furthermore, changes in gene expression in response to a toxicant exposure might not necessarily reflect an adverse effect, but rather a transient response to a minor perturbation. On the other hand, a decrease in fetal T production is clearly linked to the adverse effects associated with phthalate syndrome.

In conclusion, the rat appears to be potentially, if not presently, a reliable model for estimating risk of phthalate-induced adverse effects on male reproductive development. Furthermore, the implementation of recent modifications, as done for the FPS, make it efficient and cost-effective for both screening and potency estimates of individual phthalates as well as estimating the cumulative potency of phthalates mixtures. With the use of ex vivo testosterone

production as an endpoint, in particular, this system should be useful for determining both MOEs and BMDs. As will be discussed in the next section, the rat also appears to be the most sensitive species exhibiting adverse effects of phthalate. This would provide the lowest ED50s and NOAELs which leading to the most conservative estimates of safe exposure.

Species specificity of phthalate syndrome

While major events associated with phthalate syndrome are well established in the rat, effects of PE are not that clear-cut among other species. As noted in the CHAP report, guinea pigs and rabbits appear responsive to phthalates while limited data on hamsters suggest that this species is resistant (Gray et al., 1982; Higuchi et al. 2003). The data appear conflicting with regard to the existence of phthalate syndrome in mice. Gaido et al (2007) reported that while DBP in utero produces morphological changes in the testes such as increases in the number of multinucleated gonocytes (MNG) and number of nuclei per MNG, no apparent effect was observed on testicular testosterone concentration. While some genetic responses in the mouse testes were observed, none involved cholesterol homeostasis and steroidogenic enzymes, as were reported in the rat. The CHAP also cites a study by Marsman (1995) that appeared only in abstract form where there were "no treatment-related gross lesions at necropsy and no histopathological lesions associated with treatment in male or female mice." as a result of exposure to DBP. A recent study by Heger et al. (2012) involving testicular xenografts also tends to support the absence of phthalate syndrome response in mouse testes. In this study fetal rat (GD 16) and fetal mouse (GD 15) testes were xenografted to immunodeficient rodent hosts. Hosts were gavaged with multiple doses of DBP (100, 200, 500 mg/kg/day) for 2 days. In response to DBP, the rat xenograft exhibited a dose-dependent decline in the mRNA expression of steroidogenic enzymes with Cyp17a1 and Scarb 1 being significantly decreased, while Cyp11a1 and StAR decreased without achieving statistical significance. Ex vivo testosterone production by grafts was also significantly decreased. The mouse xenograft showed no significant effect on gene expression or ex vivo T production. Both species exhibited increased MNG in xenografts consistent with previous reports in vivo.

On the other hand, Moody et al (2013) reported evidence in mice consistent with phthalate syndrome. Varying doses of DBP (1-500 mg/kg/day) were administered orally to male mice (wild type C57BL/6J) from PND 4 to PND 14. This treatment produced dose dependent effects on testes growth which were correlated with morphological changes, such as evidence of impaired Sertoli cell maturation and delayed spermatogenesis, as well lower serum testosterone levels at the highest dose of DBP. This study also revealed evidence of decreased AGD and disrupted spermatogenesis in these mice when they reached adulthood even at the lowest dose of DBP. While phthalate syndrome observed in rats pertains to in utero exposure, it should be noted that this particular study involved postnatal exposure. (This study was cited only in Executive Summary but not the body of the CHAP report).

Furr et al. (2014) employed the FPS system described earlier to examine phthalate effects in the mouse. In this study pregnant CD-1 mice were exposed orally to varying doses of DPP (50-600 mg/kg/day) from GD 13 to GD 17. Ex vivo T production by the testes of male fetuses was examined at GD17. Dose dependent decreases in T production were observed with DPP doses of 100 mg/kg/day or higher. The ED50 for DPP in mice (193 mg/kg/day) was 4-fold that found in the rat (48 mg/kg/day). Furthermore, the dose related decline in T production in mice reached a plateau at about 50% of control compared to a plateau at 10-15% of the control in the rat. This study provides evidence that both species exhibit the basic phthalate syndrome response. However, the mouse appears much less sensitive to the xenobiotic than does the rat. The mechanism for this species difference is unexplained. However, the data are more reflective of a quantitative difference rather than a qualitative (all or none) difference between the species.

The CHAP report also addresses the issue of the possibility of phthalate syndrome in humans. Several studies have examined the effect phthalate esters on human fetal testis explants in vitro. Hallmark et al. (2007) explored the effects of varying concentrations of DBP or MBP (10 μM, 100 μM, 1 mM) in both cultured fetal rat (GD 19.5) and fetal human (15 to 20 wks gestation) testes on basal and hCG stimulated testosterone production. MBP produced a statistically significant but modest (25%) decline in cultured rat testes at the highest concentration only. No phthalate effects were observed with cultured human testes. The

authors of this study suggested that the system employed was too insensitive and unreliable to reflect a response in vivo and considered the results inconclusive. Lambrot et al. (2009) incubated human fetal testes (7 to 12 weeks gestation) for 4 days with varying concentration of MEHP (1, 10, 100 μM) in the absence or presence of LH. No effect of MEHP on basal or LH-stimulated T production was observed. Furthermore, no effects of MEHP were observed on mRNA expression of key steroidogenic enzymes (P450scc, CYP17, or StAR) or of Insl3, as well as on Sertoli cell proliferation or apoptosis. At the highest dose of MEHP reduced expression of Mullerian inhibiting substance and increased germ cell apoptosis were observed. A major shortcoming of this study is the absence of a positive control (e.g., rat fetal testes). In addition, effects of MEHP at a dose of 100 μM would appear be of little environmental relevence since such concentrations are unlikely to be achieved in vivo. Desdoits-Lethimonier et al. (2012) examined the direct effects of varying concentration of DEHP and MEHP on organ culture of adult human testes and the human adrenocortical cell line (NCI-H295R). In both models, DEHP and MEHP significantly inhibited T production at concentrations of 10 and 100 μM, whereas no significant effect was observed at 1 μM. The effect appears to be specific for steroidogenesis as there were no alterations of Leydig cell Insl3 production, Sertoli cell inhibin B production or germ cell apoptosis. This observation is of questionable relevance to the in vivo situation in view of the concentrations required to achieve adverse effects in this system. In addition, it should be noted that these experiments were conducted on adult testes and may have little relevance to phthalate syndrome which involves phthalate exposure in utero. Finally, this study would have benefitted from the presence of cultured rat testes (perhaps both adult and fetal) to provide some point of reference as to whether there may differences in species and age sensitivity to phthalate esters.

As noted in the CHAP report several studies have explored effects of phthalates in vivo in a primate species, the marmoset. Hallmark et al. (2007) conducted two in vivo studies. In one study, they reported that a single oral dose of MBP (500 mg/kg) to marmosets aged 2 to 7 days exhibited an acute suppression of serum testosterone. In the other study, 4 day old marmosets exposed to MBP (500 mg/kg) daily for 14 days exhibited no suppression of serum testosterone, although histology revealed an increase in Leydig cell volume per testis, suggestive of LH

stimulation. Based upon the findings of both studies, the authors suggest that MBP-induced inhibition of T production leads to compensatory increase in LH secretion (via negative feedback) and the elevated LH, in turn, stimulates the testes to restore T production. It should be noted that MBP exposure was administered postnatally rather than prenatally. Accordingly, in a follow-up study McKinnell et al. (2009) exposed pregnant marmosets to 500 mg/kg/day MBP from about week 7 to week 15 of gestation and male offspring were examined post-partum (PND 1 to PND 5). No effect was observed on numerous endpoints, namely gross testicular morphology, reproductive tract development, germ cell number, and germ cell:Sertoli cell ratio, as well as testosterone levels. The authors also suggest that the marmoset is preferable to the rat as a model for phthalate effects in the human in view of similarity with regard to phases of testicular development and germ cell differentiation which are distinctly different from the rat. The authors note that the interval of treatment of marmosets in this study (weeks 7 to 15 of gestation) correspond to the critical window of androgen-dependent masculine programming in the rat. However, it is also noteworthy that the treatment terminates 12 weeks before birth when data collection occurs, which does not rule out the possibility of recovery from transient effects of MBP. From these data the authors conclude that MBP exposure of pregnant marmosets do not affect steroidogenesis in the fetal testes "sufficient to cause any detectable downstream effects; nor is there any evidence for focal or wider testicular dysgenesis."

Two reports have examined the effect of phthalates on human fetal testes xenografts in vivo and were noted in the CHAP report. As discussed previously in reference to mouse fetal testes, Heger et al., (2012) studied the effect of varying doses of DBP (100, 250, 500 mg/kg/day) for 2 days via oral gavage on fetal human testes (gestation weeks 10-24, avg 18.6 wks) to grafted to immunodeficient adult rat hosts. No effect of DBP was observed on gene expression of Leydig cell steroidogenic enzymes (Cyp11a1, Cyp 17a1, Scarb1, and StAR), as well as insl3. Ex vivo testosterone production by these xenografts was not measured. As noted previously, the positive control, rat fetal testes (GD 16) xenografted onto immunodeficient rat hosts, exhibited decreased ex vivo decrease in testosterone production as well as decreases in steroidogenic and Insl3 gene expression in response to exposure to DBP for 2 days. As observed previously for fetal rat and mouse testes, DBP exposure increased the MNG. In the other study, Mitchell et al.

(2012) examined castrated nude mice bearing xenografts of human fetal tests (14-20 weeks of gestation). To simulate pregnancy, hCG (human chorionic gonadotrophin) was administered to these hosts, a treatment which produced a robust increase in serum testosterone and in the weight of the seminal vesicle (SV), a testosterone target. These responses indicate that the xenografts were functional in the hosts. Treatment of hosts with DBP or MBP (500 mg/kg/day) failed to significantly decrease serum T or SV weight. DBP treatment of positive controls, castrated male mice bearing rat fetal testes (GD 17.5) xenografts, significantly decreased SV weight, and mRNA expression of two steroidogenic enzymes, mRNA of Cyp11a1, StAR. Serum T was also decreased but this response was of marginal statistical significance (p=0.06).

The CHAP report noted that in both xenograft studies, human fetal testes were obtained beyond 14 weeks of gestation which is after the critical window for androgen-induced development of the male reproductive tract. This raises the possibility that phthalates may inhibit testosterone synthesis in human fetal testes but the effect was missed due to the age of the explants. On the other hand, CHAP notes that this argument is countered by the evidence in cultured fetal explants which failed to respond to phthalates in vitro, independent of whether the tissue was obtained during the first or second trimester of pregnancy (Hallmark *et al.*, 2007; Lambrot *et al.*, 2009). Mitchell et al. (2012) also acknowledge the fact that xenografts employed were obtained after the masculinization programming window (MPW) raising the possibility that the action of DBP in the xenograft study might have been missed. While they indicate that this possibility cannot be excluded, they consider it unlikely for a variety of reasons: 1) that fetal rat testes are more responsive to adverse effects of DBP after the MPW than during it; 2) that MBP has no effect on steroidogenesis in vitro in cultured human testes obtained during the first or second trimesters (same point that was addressed by the CHAP); and 3) that their xenograft findings concur with in vivo data in the marmoset which exhibited no adverse effects of MBP exposure in utero.

The CHAP report also expressed additional concerns about the xenograft study of Mitchell et al., 2012. They note, for example, that even though serum testosterone was not significantly decreased in animals bearing human testes xenografts with MBP, the mean level was decreased from control by about 50%. CHAP suggests that this failure to achieve statistical

significance was due to " high experimental variation and the small number of repetitions." With all due respect to CHAP, I disagree with this particular criticism. Review of the data (SV weight, serum testosterone) in animals bearing human xenografts does not seem usually variable. The animals bearing xenografts of human testes showed robust responses to hCG as exemplified by increases in serum testosterone and SV weight (Fig. 1 of paper) indicating that the grafts were functional. In addition, these animals exhibited highly significant correlations between serum testosterone and SV weight. The results with DBP in hosts bearing human testes xenografts were very clear cut and do not seem unusually variable with regard to serum testosterone or SV. Furthermore, the statistical analysis appeared rigorous involving ANOVA irrespective of the fetal donor and paired t-tests between vehicle or exposed xenografts from the same fetus. In either case no significant difference due to DBP exposure was observed (Fig. 2 of paper). For MBP exposure, the mean serum testosterone level was decreased, but the magnitude of this difference appears more like 30% than the 50% stated by CHAP, the difference being non-significant (Fig. 3 of paper). Furthermore it is unlikely that this is a "false negative" since there is no accompanying decrease in SV weight. While the positive control data are not perfect, overall they are consistent with the literature indicative that phthalates inhibit T production in fetal rat testes. Serum testosterone is decreased modestly with very narrow SEM and the difference is marginally statistically significant ($p=0.06$). This might be a shortcoming of the study. However, the statistically significant decrease in SV weight is respectable and the decrease in mRNA expression of the steroidogenic enzymes StAR, Cyp11a1 are very robust (Fig. 4 of paper). As for the number of replications in this study, the "n" for most comparisons is 6 or more which is typical of most hypothesis driven studies. The "n" for the MBP set is 3 or 4, which is small.

Based upon their assessment the two xenograft studies, CHAP suggests that the data have to be interpreted with great caution and at this stage, "the outcome of these studies has to be regarded as inconclusive." CHAP also states that "observations of associations between phthalate exposure in fetal life and anogenital distance (Swan *et al.*, 2005; Swan, 2008) are difficult to reconcile with the results of the xenograft and human fetal explant experiments. Changes in anogenital distance are a robust read-out of diminished androgen action *in utero,* and

these observations give strong indications that phthalates are capable of driving down fetal androgen synthesis in humans." As noted in next section this reviewer believes that this argument is flawed.

While more studies are recommended to resolve some inconsistencies and replicate certain findings, the weight of evidence indicates that the rat is more sensitive than the mouse with regard to phthalate-induced suppression of testosterone production by the fetal testes. This species difference appears most evident in the recent studies involving FPS design (Furr et al., 2014) and immunodeficient hosts bearing rat and mouse fetal testicular xenografts (Heger et al., 2012). While in vivo observations with marmosets and immunodeficient hosts bearing human fetal testes xenografts should be replicated, the weight of evidence suggests that the rat is more sensitive to the in utero effects of phthalates than primates. As suggested previously the more sensitive rat model would be beneficial in terms of risk assessment as it would tend to lead to lower (thus more conservative) estimates of safe exposure levels for people. The mechanistic basis for species differences in the production of phthalate syndrome, while provocative, is unexplained. Further research into understanding the mechanisms defining species specificity are encouraged as they would provide greater insights into the physiology and toxicology behind phthalate syndrome.

Strength of epidemiologic evidence associating neonatal phthalate exposure with decreased AGD

According to the CHAP report, the literature suggests that prenatal exposure to phthalates is associated with a decrease in anogenital distance (AGD) in human male offspring, evidence consistent with the existence of "phthalate syndrome" in humans. Their conclusion is based upon data from four epidemiologic studies (Swan et al., 2005; Swan, 2008; Huang et al., 2009; Suzuki et al., 2012) which report occasional inverse statistically significant relationships between phthalate metabolites in body fluids (maternal urine or amniotic fluid) and a measurement of AGD in mother-son cohorts. Recently, a fifth paper not mentioned in the CHAP report has been published that has examined this issue, that of Bustamante-Montes et al. (2013) which employed

a mother-son cohort from Mexico. A close scrutiny of these studies indicates that the data do not support the conclusion of the CHAP report. While statistically significant negative associations between the concentration of a particular phthalate monoester and an estimate of AGD are evident, they occur sporadically, are in some cases toxicologically irrelevant, and are very inconsistent from one study to the next, even internally inconsistent in the case of different publications from the same laboratory.

For example, while a statistically significant inverse relationship was shown for the monoester, MEP, and AGD by two studies from Swan's group (Swan et al., 2005; Swan, 2008), this particular relationship was not confirmed by Huang et al. (2009) and Suzuki et al., (2012). Incidentally, a statistically significant inverse relationship between MEP and AGD would be of little toxicologic significance since the parent compound, DEP, does not produce phthalate syndrome in rats even at extremely high doses (Howdeshell et al., 2008). In another example of external inconsistency, two studies report a statistically significant inverse relationship between the urinary concentrations of MEHP and AGD (Swan, 2008; Suzuki et al., 2012) which was not confirmed in the remaining three studies (Swan et al., 2005; Huang et al., 2009; Bustamante-Montes et al., 2013). The parent compound of MEHP, DEHP does produce phthalate syndrome in rats (Howdeshell et al., 2008) . Swan (2008) also reported statistically significant inverse associations between two other metabolites of DEHP, MEOHP and MEHHP, and AGD which was not consistent with their earlier study on a smaller sampling of the same cohort (Swan et al., 2005) as well as the report of Suzuki et al. (2012).

One important shortcoming of this particular data base is the marked methodological differences from study to study. Among these methodological disparities are the particular times when phthalate levels are estimated in the mother, when AGD are measured in offpsring,, and the method by which AGD was measured. The variation in AGD measurement among these studies is particularly noteworthy. While all measurements start from center of the anus, they differ with regard to where the measurement ends. Furthermore, there are differences in how these measurements are processed further. For example, the measurement ended at the junction of perineum and the rugated skin of the scrotum in three studies (Bustamante-Montes et al., 2013; Huang et al., 2009; Suzuki et al., 2012) but, depending on the study this measurement was

adjusted for birth weight (Huang et al., 2009; Suzuki et al., 2012) or birth length (Huang et al., 2009) or used without adjustment (Bustamante-Montes et al., 2013). In one study the measurement ended at the posterior base of the penis and was not processed further (Bustamante-Montes et al., 2013). In three studies the measurement extended to the anterior base of the penis (Bustamante-Montes et al., 2013; Swan et al. 2005; Swan, 2008; Suzuki et al., 2012) and this measurement was normalized for body weight of offspring aged 2-36 months (Swan et al., 2005), adjusted for weight percentile of offspring aged 2-36 months (Swan, 2008), adjusted for birth weight (Suzuki et al., 2008), or was used without adjustment (Bustamante-Montes et al., 2013). In studies which used more than one estimate of AGD internal inconsistencies were also evident. For example, as noted above, Suzuki et al. (2012) employed two methods of AGD measurement both adjusted for birth weight, one extending to rugated skin of the scrotum and the other to the anterior base of the penis. Only the latter exhibited a statistically significant inverse relationship with MEHP, a relationship not confirmed in three other studies.

On the basis of occasional sporadic statistically significant associations, some of which are toxicologically insignificant, as well as severe methodologic inadequacies, it would appear that occasional associations are artifactual and, at best, inconclusive. Certainly the weight of evidence does not support a causal relationship between phthalate exposure during gestation and decreased AGD in human offspring.

Conclusions

While the CHAP is commended for a very scholarly and in depth review of the literature pertaining to the adverse effects prenatal pththalate exposure on the development male reproductive system, this reviewer noted three issues that deserved further discussion. First of all, this reviewer seems more optimistic than the CHAP about the utility of the rat as a model for risk assessment of exposure to phthalates both individually and as mixtures. Secondly, the weight of evidence indicates that the rat is more sensitive to the effects of phthalate than the mouse and possibly than primates, as well. Finally, in contrast to the opinion expressed by

CHAP, the epidemiologic data associating maternal phthalate levels in body fluids with decreased AGD in human male offspring are inconclusive.

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human fetal testis? Exposure of human fetal testis xenografts to di-n-butyl phthalate. J Clin Endocrinol Metab 97, E341–348.
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Suzuki, Y., Yoshinaga, J., Mizumoto, Y., Serizawa, S., Shiraishi, H., 2012. Foetal exposure to phthalate esters and anogenital distance in male newborns. Int J Androl 35, 236–244.

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Wilson, V.S., Lambright, C., Furr, J., Ostby, J., Wood, C., Held, G., Gray, L.E., Jr., 2004. Phthalate ester-induced gubernacular lesions are associated with reduced insl3 gene expression in the fetal rat testis. Toxicol Lett 146, 207–215.

Appendix C

Curriculum Vitae of Expert Peer Reviewers

Curriculum Vitae
Of
Dr. Christopher J. Borgert
Monday, April 14, 2014

EDUCATION

Ph.D. Medical Sciences: Pharmacology — December 1991.
Phosphorylation of type I and type II DNA topoisomerases in a human tumor cell line. Ph.D. dissertation. University of Florida College of Medicine, Department of Pharmacology and Therapeutics.

Artium Baccalaurei; Major in Biology — June 1980.
Kenyon College, Gambier, Ohio.

CURRENT POSITION & ADDRESS

Applied Pharmacology and Toxicology, Inc. — President & Principal Scientist, 1996 – Present

2250 NW 24th Avenue
Gainesville, Florida 32605
Telephone: (352) 335-8334
Facsimile: (352) 335-8242
cjborgert@apt-pharmatox.com

Product Safety Assessments & Registration
Risk Assessment, Risk Management & Risk Communication
Study Design & Causation Analysis
Litigation Support
Teaching
Experimental Research

ADJUNCT FACULTY POSITION

Department of Physiological Sciences — Courtesy Assistant Scientist, 1998 - Present
Center for Environmental and Human Toxicology
College of Veterinary Medicine, University of Florida
Gainesville, Florida

EXPERIENCE

Representative List of Consulting & Professional Experience — 1992 – Present

Co-Chair, Society of Toxicology Continuing Education Program, *Toxicology and Risk Assessment of Chemical Mixtures*. 50th Annual Meeting, March 6, 2011.

Evaluation Group Leader: Data Quality. National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), National Institutes of Health (NIH) Independent Scientific Peer Review, Special Emphasis Panel to review the validation status of two assays for measuring in vitro estrogen receptor activity. January - March, 2011.

Expert Panelist: ILSI Health and Environmental Sciences Institute Risk 21, Cumulative Risk Panel, 2010-2011.

Expert Panelist: American Association for the Advancement of Science, the American Chemical Society, and the Georgetown University Program on Science in the Public Interest. Discussion Series on Science & Society: *Global Challenges: Coming to the Table on Food Safety (Bisphenol A and Beyond)*. November 1, 2010, Washington, D.C.

Discussant: U.S. Environmental Protection Agency Workshop: Cumulative Risk Assessment of Phthalates," December 8-9, 2010, Arlington, Virginia.

Testimony before the U.S. Consumer Product Safety Commission's Chemical Hazard Assessment Panel on phthalates: *Uncertainty versus Certain in Cumulative Risk Assessment: Anti-Androgens.* July 26, 2010. Washington, D.C.

Testimony before U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Energy and Environment, hearing entitled, "Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment," Thursday, February 25, 2010, rm. 2123, Rayburn House Office Building, Washington, D.C.

Associate Scientific Coordinator; Endocrine Policy Forum (EPF): 2010-2012; assists member companies responding to Test Orders pursuant to the U.S. EPA's Endocrine Disruptor Screening Program (EDSP).

Development of safety assessments based on quantitative structure activity analysis (SAR/QSAR) for novel chemical entities used in cosmetics.

Evaluations of claims made for labeling and advertisement of dietary supplements and weight loss formulations.

Co-Chair, Society of Toxicology Continuing Educations Course: *Toxicological Evaluation of Drug and Chemical Mixtures.* 46th Annual Meeting, Charlotte, NC. March, 2007.

Steering Committee, International Society for Regulatory Toxicology and Pharmacology Workshop: Progress and Barriers To Incorporating Alternative Toxicological Methods in the U.S. Marriott Waterfront Hotel, November 17-18, 2005.

Organizing Committee, Society of Toxicology Contemporary Concepts In Toxicology Workshop: Charting the Future: Building the Scientific Foundation for Mixtures Joint Toxicity and Risk Assessment. Crowne Plaza Ravinia, Atlanta, GA. February 16–17, 2005.

Expert Panelist, SOT Mixtures Project, 2002 – 2005.

Steering Committee, International Society for Regulatory Toxicology and Pharmacology Workshop: Understanding Human Biomonitoring. Hyatt Regency Hotel, Sacramento, CA, June 16, 2005.

Steering Committee, International Society for Regulatory Toxicology and Pharmacology Workshop: EPA's New (Proposed) Guidance for Assessing Cancer Risks from Early Life Exposures: Genotoxic Mode of Action and Implications for Human Health-Based Standards. Wyndham Hotel, Baltimore MD, February 10, 2005.

OECD Peer-Review Panel for Validation of the Uterotrophic Assay, September-December, 2004.

SETAC Pellston Workshop on Science for Assessing the Impacts of Human Pharmaceuticals on Aquatic Ecosystems Workshop, Snowbird, UT, June 3-8, 2003 (invited panelist)

ILSI Health and Environmental Sciences Institute Workshop on Dose-Dependent Transitions in Mechanisms of Toxicity, invited expert participant. February 12-13, 2003. Washington, DC.

SOT Expert Panel on Mixtures Research Agenda, Workshop Expert Participant. Sept 8-9, 2002, Atlanta, GA.

EPA External Peer Reviewer of Documents Identifying Chemicals for Cumulative Risk Assessment Based on Common Mechanisms of Action and Toxicity for 1) Organotin Pesticides, 2) Urea Herbicides, and 3) Triazine Herbicides. July 9-10, 2002.

Expert Panel on Breast Milk Monitoring for Environmental Chemicals in the United States, workshop member. Milton S. Hershey Medical Center, Dept. of Pediatrics, Pennsylvania State University College of Medicine, February 15 – 17, 2002.

U.S.E.P.A. Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) member. 1996-1998. EDSTAC, a Federal Advisory Committee to the U.S.E.P.A., developed recommendations for toxicity testing requirements for pesticides, industrial and agricultural chemicals pursuant to requirements of the 1996 Food Quality Protection Act and 1996 Amendments to the Safe Drinking Water Act.

EDSTAC Screening & Testing Workgroup member.

EDSTAC Communication & Outreach Workgroup, Co-Chair.

Developed detailed protocols for the 20 EDSTAC-recommended screens and tests for use in a cost estimate survey that is published in Appendix S of the EDSTAC final report, August 1998, and is also included in the Federal Docket for the EDSTAC. Updated this survey in 2003 for Endocrine Screening assays under validation by EPA and OECD.

Critical analysis and detailed comments submitted on draft regulatory and technical documents released by various agencies, including EPA, ATSDR, OECD, and EU.

Served as peer-reviewer for ATSDR Interaction Profiles for: Persistent Chemicals in Breast Milk; Benzene, Toluene, Ethylbenzene and Xylene (BTEX); Uranium, Fluoride, Cyanide and Nitrate.

Directed and composed several product safety assessments of adjuvants and fertilizers for registration in Canada under the Fertilizers Act (Client: Aquatrols Corporation of America).

Study monitor for numerous toxicity studies on formulations and ingredients of agricultural and turfgrass chemicals for product development and registration in Canada, Europe and the U.S.

Technical assistance in risk assessment for a wide array of environmental and industrial pollutants.

Critical analysis of medical scientific literature on prescription medications, drugs of abuse, chlorinated solvents and pesticides, fluorinated hydrocarbons, terpenes, polyaromatic hydrocarbons,

pesticides, herbicides and their environmental degradation products, fluorescent dyes used in groundwater tracing studies, and soil wetting agents used in turf grass management.

Pharmacological and toxicological causation analyses for environmental contaminants and drugs. Examples include:
- cancer etiology related to insecticides, fungicides, herbicides, toluene, methyl ethyl ketone, methyl isobutyl ketone, formaldehyde, bis-chloromethyl ether, benzene, chlorinated and fluorinated hydrocarbons, phthalate esters, glycol ethers;
- reproductive toxicity of phthalates, phthalate esters, pesticides;
- ethylene glycol, carbon monoxide and pesticide toxicity to the brain and nervous system;
- injury from domestic and occupational pesticide applications;
- fluorinated hydrocarbon toxicity and occupational exposure;
- lead poisoning and reduced IQ in children;
- acid-base burns;
- inhalation exposure to gases, vapors, cleaners, and solvents, dusts, mineral fibers;
- birth defects and various prescription medications;
- death related to ipecac alkaloids, antidepressants, anti-anxiety agents, anti-psychotics, sedative hypnotics, stimulants, alcohol and other drugs;
- marijuana (cannabinoids), cocaine, opiates, benzodiazepines, sedative hypnotics, CNS stimulants, opioids, sedatives, alcohol and performance impairment;
- multiple chemical sensitivity and consumer products.
- chemical interactions among drugs, pesticides, consumer product formulations.

Served as expert witness and consulting expert for civil and criminal litigations concerning: drugs, OTC medications, and dietary supplements; medical, occupational, marine, recreational, residential and environmental exposures and poisonings; and, environmental contamination issues.

Developed an indoor air quality and safety assurance feasibility study for an indoor ballpark with natural turfgrass playing field (Client: Seattle Mariners Baseball Club).

Conducted employee health interviews and health assessments for indoor air quality evaluations in offices and in a hospital pharmacy.

Provided technical assistance in Risk Assessment to the United States Golf Association for its Environmental Research Program.

Assessed biological and chemical hazards and directed human health evaluation of a large wastewater treatment plant.

Provided technical assistance in volatilization exposure and human health risks from chlorinated solvents in a shallow, coastal aquifer.

PAST POSITIONS

Department of Pathology and Laboratory Medicine — Courtesy Research Assistant Professor
College of Medicine, University of Florida — 1995 - 1997
Gainesville, Florida

TERRA, Inc. — Pharmacologist / Toxicologist
6241 NW 23rd Street — July, 1992 - August, 1996
Gainesville, Florida — (850) 309-1330

Managed branch office of TERRA, Inc. in Gainesville, Florida.
Responsible for consulting services and client development in:
- Product Safety & Registration
- Litigation Support
- Risk Assessment
- Health, Safety & Education Programs

Center for Environmental and Human Toxicology — Postdoctoral Associate
University of Florida Research and Technology Park — December 1991 - January 1994
One Progress Boulevard, Alachua, Florida — (352) 392-4700/ext. 5500

- Conducted critical review of risk assessments for Florida Department of Environmental Protection. Developed general and site-specific clean-up levels for contaminants in various environmental media.
- Refined and improved risk assessment methodologies.
- Researched and wrote toxicant profiles and summaries.
- Prepared and presented lectures in Ph.D.-level Toxicology courses.
- Directed laboratory research on molecular mechanisms of toxicity.

Supervised graduate student research and technical staff.
Provided training workshops in risk assessment to regulators and environmental professionals.
Directed the development of computer software that automates dose and risk calculations for EPA risk assessments.

Molecular Biology Laboratory — Graduate Research Assistant
Department of Pharmacology and Therapeutics — June 1986 - December 1991
University of Florida, College of Medicine, Gainesville, Florida
Antibody development for DNA topoisomerases (enzymes targeted by cancer chemotherapy)
Studied regulation and post-translational modification of DNA topoisomerases (immunoprecipitation and immunodetection; metabolic radiolabeling of tumor cells; one and two-dimensional SDS-PAGE & two-dimensional thin layer electrophoresis; DNA transfection of cells and bacteria; DNA analysis by Southern blotting and nucleoid sedimentation.
Prepared and presented antibiotic and anti-viral drug lectures in Principles of Pharmacology course. Trained and supervised research of veterinary student and premedical student. Prepared and presented research seminars and journal clubs.

Toxicology Laboratory — Graduate Research Assistant
Department of Pharmacology and Therapeutics — July 1985 - June 1986
University of Florida College of Medicine, Gainesville, Florida
Amino acid transport studies in primary hepatocyte cell cultures; hormonal tumorigenesis studies in rats; organ perfusion, hepatocyte isolation; partial hepatectomy of rats.

Pharmacology and Toxicology Laboratory — Graduate Teaching Assistant
Department of Pharmacology and Toxicology, — January 1985 - June 1985
Purdue University, West Lafayette, Indiana
Prepared and instructed Pharmacology and Toxicology laboratory sessions for pharmacy students.

Laboratory of Renewable Resource Engineering — Technician, Analytical Group
Purdue University, West Lafayette, Indiana — April 1984 - January 1985
Developed HPLC, GPC, and GC separations for bio-polymers; alcohols from plant materials; liquefied coal samples; Operated analytical core facility for five research groups.

Plant Physiology Laboratory — Technician
Department of Agronomy, — November 1981- July 1984
Purdue University, West Lafayette, Indiana
Established and operated HPLC core facility. Supervised technical staff (2) and undergraduate students (2). Conducted studies on the transport of sugars and carbohydrates in wheat plants.

COMPETITIVE FUNDING AWARDS

2001-2005	$899,998	PI	American Chemistry Council Long Range Research Initiative: Investigation of Chemical Mixtures in the Upper Ocklawaha River Basin: Reproduction, Development and Endocrine Status in Alligators, Fish, and Mussels

REFEREED PUBLICATIONS

Borgert CJ, Stuchal LD, Mihaich EM, Becker RA, Bentley KS, Brausch JM, Coady K, Geter DR, Gordon E, et al. 2014. Relevance Weighting of Tier 1 Endocrine Screening Endpoints by Rank Order. Birth Defects Res B Dev Reprod Toxicol *101*, 90-113.

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Borgert CJ, Sargent EV, Casella G, Dietrich DR, McCarty LS, Golden RJ. 2012. The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. *Regulatory Toxicology and Pharmacology* 62:313-328.

Borgert CJ, Mihaich EM, Ortego LS, Bentley KS, Holmes CM, Levine SL, Becker RA. 2011. Hypothesis-driven weight of evidence framework for evaluating data within the U. S. EPA's Endocrine Disruptor Screening Program. *Regulatory Toxicology and Pharmacology* 61:185-191.

Borgert CJ, Mihaich EM, Quill TF, Marty MS, Levine SL, Becker RA. 2011. Evaluation of EPA's Tier 1 Endocrine Screening Battery and recommendations for improving the interpretation of screening results. *Regulatory Toxicology and Pharmacology* 59:387-411.

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Muller JK, Scarborough JE, Sepúlveda MS, Casella G, Gross TS, Borgert CJ. 2007. Dose verification following topical treatment of alligator eggs. *Environmental Toxicology & Chemistry,* 26(5): 908-913.

Muller JK, Gross TS, Borgert CJ. 2007. Topical dose delivery in the reptilian egg treatment model. *Environmental Toxicology & Chemistry, 26*(5): 914-918.

Johnson KG, Muller JK, Price B, Ware A, Sepúlveda MS, Borgert CJ, and Gross TS. 2007. Influence of seasonality on the accumulation and reproductive effects of *p,p*'-dichlorodiphenyldichloroethane and dieldrin in largemouth bass. *Environmental Toxicology and Chemistry,* 26(5): 927-934.

McCarty LS, Borgert CJ. 2006. Review of the toxicity of chemical mixtures: theory, policy and regulatory practice. *Regulatory Toxicology and Pharmacology, 45(2)*:119-143.

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LaKind JS, Birnbach N, Borgert CJ, Sonawane BR, Tully MR, Friedman L. 2002. Human milk surveillance and research of environmental chemicals: Concepts for consideration in interpreting and presenting study results. *Journal of Toxicology & Environmental Health Part A, 65*: 1909-28.

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Price B, Borgert CJ, Wells C, Simon GS. 2002. Assessing toxicity of mixtures: the search for economical study designs. *Human and Ecological Risk Assessment, 8*(2): 305-326.

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Borgert CJ, Roberts SM, Harbison RD, James RC. 1995. Influence of soil half-life on risk assessment of carcinogens. *Regulatory Toxicology and Pharmacology, 22*: 143-151.

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COMMENTARIES & LETTERS

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Borgert CJ, Koller RC, Housley TL. Transport of sucrose in wheat endosperm. Abstract for The American Society of Plant Physiology annual meeting, Springfield, Illinois, 1983.

INVITED PRESENTATIONS

Basics of Product Safety Testing for Green Chemists and Engineers; Can Biological Activity be Designed Out? Christopher J. Borgert, Ph.D. and Ted Simon, Ph.D., DABT. 18th Annual Green Chemistry & Engineering Conference. Washington, DC. June,2014. Technical Session: Endocrine Disruption: Its Potential Impact on Green Chemistry.

The need to modernize problem formulation for risk assessment. Workshop: A Review of Weight-of-Evidence (WoE) Frameworks, American Chemistry Council (ACC), Center for Advancing Risk Assessment Science and Policy (ARASP), December 4-5, Washington, DC.

Why disclosure is insufficient to assure research integrity. Scientific Approaches to Strengthening Research Integrity in Nutrition and Energetics. Hosted by the University of Alabama at Birmingham Nutrition Obesity Research Center, Mohonk Mountain House, August 7-8, 2012.

Scientific Weight of Evidence: Qualitative or Quantitative? CropLife America Science Forum: Judging Weight of Evidence Approaches, Focus on Chemical Evaluation, *May 17, 2012, Marriott Metro Center, Washington, DC*

Hypothesis-driven weight of evidence framework for evaluating data in the context of the U.S. EPA's Endocrine Disruptor Screening and Testing Program. Endocrine Disruptors, 2nd International Conference. Die Akademie Fresenius, Frankfurt, Germany, June 7-8, 2011.

What is "Scientific Quality" and How Do We Judge It? Plenary Lecture, CropLife America Science Forum: Judging the Quality of Scientific Work. Washington, DC. May 13, 2011.

The Intersection of Design and Interpretation of Mixtures, Toxicology and Risk Assessment of Chemical Mixtures. Society of Toxicology Continuing Education Program, 50th Annual Meeting, March 6, 2011.

Setting the Scene on the Mixtures Discussion. Cumulative risk assessment: how and when? - Approaches for future strategies on mixtures" organized by Cefic – the European Chemical Industry Council. Brussels-Silken Berlaymont Hotel, Brussels, Belgium, 16 December, 2010.

Weight of Evidence Determinations for EPA's EDSP. ISRTP Endocrine Workshop: EDSP Compliance. December 13, 2010. Lister-Hill Auditorium, National Institutes of Health, Bethesda, MD.

Comments On: *Courage for Simplification and Imperfection in the 21st Century Assessment of "Endocrine Disruption."* 21st Century Validation Strategies for 21st Century Tools. July 14, 2010, Johns Hopkins Bloomberg School of Public Health - 615 N Wolfe St., Baltimore MD.

Objective or Subjective? Should the Scientist Be Judged? Session on Research Funding and Scientific Integrity: Conflicts and Criteria, Society for Risk Analysis Annual Meeting, Baltimore, MD, December 7, 2009.

Limitations of EDSP Data for Evaluating Cumulative Risk. Workshop on Scientific Methods for Evaluating Endocrine Disruptor Screening Program Data and Estimating Dose Response, Society for Risk Analysis Annual Meeting, Baltimore, MD, December 6, 2009.

Combination Effect Models, Mode of Action, and Risk: Is There Any Relationship? Society of Toxicology of Canada, 41st Annual Symposium. Montreal, Quebec, Dec 1, 2009.

Staging Screening and Testing, in Session I: Strengths and Weaknesses of the EDSP Assays. And

Limitations of EDSP Data. in Session III, Assessing Cumulative Effects of Endocrine Active Substances.

ISRTP Workshop: The Endocrine Disruptor Screening Program: What Can Screening Results Tell Us About Potential Adverse Endocrine Effects? Lister Hill Auditorium, Bethesda, MD, September 9-10, 2009.

Relative Potency Factors in Drug Safety Assessment. in Current Approaches in Mixture Risk Assessment, Society of Toxicology Continuing Education Program, 48th Annual Meeting, March 15-19, 2009, Baltimore, Maryland.

Considerations for Single Chemical Versus Mixture Risk Assessment: Concepts and Caveats. National Academies of Science, National Research Council, Board on Environmental Studies & Toxicology, Workshop on Pharmaceuticals in Drinking Water, December 11-12, 2008. Washington, DC.

Cumulative Risk: The Case Against Estrogen Equivalents. Session III. ISRTP Workshop: Conducting and Assessing the Results of Endocrine Screening. February 19-20, 2008. Lister Hill Center Auditorium, NIH. Bethesda, MD.

Regulatory Assessment of Chemical Mixtures: Concepts & Caveats. Symposium IV: Combination Toxicology. American College of Toxicology (ACT), 28th Annual Meeting. Charlotte, NC. November 12, 2007.

Food-Drug Interactions, Theory and case studies. Institute of Food Technologists (IFT) Annual Meetings, Symposium entitled: *Health Food Ingredients: When is a food really a drug?* July 29, 2007, Chicago, IL.

Interpretation of mixtures data – case studies of the good, the bad, and the ugly. Society of Toxicology Continuing Education Program, 46th Annual Meeting, March 25-29, 2007, Charlotte, NC.

Biological plausibility and application to risk assessment: Human relevance and dose response analysis. Society of Toxicology Annual Meeting, March 5-9, 2006, San Diego, CA.

Perspectives on development and use of screens and tests for endocrine activity. Chemical Producers & Distributors Association, Mid-Year Meeting February 27 – March 1, 2006. Arlington, VA.

Epidemiology of Benzene in the Toxicogenomic Era: Omic Technologies & Causation. Benzene Litigation 101 Conference, February 2-3, 2006, Westin Riverwalk Hotel, San Antonio, TX.

Causality Assessment of Herbal-Drug Interactions: Scientific Data vs. Diagnostic Scales. International Conference on Quality and Safety Issues Related to Botanicals, Sponsored by CFSAN/ FDA and International Society for Horticultural Sciences. National Center for Natural Products Research, August 15 – 18, University, MS.

Causality Assessment: Is There a Role for Biomonitoring? ISRTP Workshop: Understanding Human Biomonitoring. June 16, 2005. Hyatt Regency, Sacramento, CA.

Predicting Interactions from Mechanistic Information (Pharmacokinetic & Pharmacodynamic). Workshop Session: Dose-Additivity of Mixtures: Where Are We Going With The Science? SOT Annual Meeting, New Orleans, LA. March 7, 2005.

Interactivity Toxicity – Information from Pharmacodynamics and Toxicokinetics to Predict Interactions. SOT Contemporary Concepts In Toxicology Workshop: Charting the Future: Building the Scientific Foundation for Mixtures Joint Toxicity and Risk Assessment. Crowne Plaza Ravinia, Atlanta, GA. February 16–17, 2005.

Synergism, Antagonism, or Additivity of Dietary Supplements with Hemostasis and Antithrombotic Therapies. National Institutes of Health Office of Dietary Supplements, Conference on Dietary Supplements, Coagulation, and Antithrombotic Therapies, Masur Auditorium, Clinical Center, NIH, Bethesda, MD. January 13-14, 2005.

Synergism, Antagonism, or Additivity of Dietary Supplements. National Capitol Areas Society of Toxicology and National Capitol Area Society for Risk Analysis Fall Symposium, Lister Hill Auditorium, NIH, Bethesda, MD. November 2, 2004.

Update: CDC's *National Report on Human Exposure to Environmental Chemicals.* The Toxicology Forum, Summer Meeting. Aspen, Colorado, July 14, 2003.

TEFs for Environmental Estrogens: Theoretical and Practical Challenges. Society of Environmental Toxicology and Chemistry 23rd Annual Meeting Salt Lake City, Utah, November 18, 2002.

Synergism, antagonism, or additivity: What's in the mix for dietary supplements? Symposium III - Toxicology and Pharmacology of Nutraceuticals. American College of Toxicology (ACT) 23rd Annual Meeting, Nov. 10-13, 2002, Hershey PA.

Biomonitoring and Health Tracking; Implications at the State Level. State Affairs Meeting of the American Chemistry Council, November 13, 2002.

Screening and Testing for Endocrine Disruptors; Chemical Mixture Issues. Presented at the International workshop on Endocrine Disruptors and Pharmaceutically Active Chemicals in Drinking Water, Chicago, Illinois, April 19-21, 2000.

Endocrine Disruptor Screening and Testing; Not Yet Ready for Prime Time. Chemical Right to Know Initiatives: HPV, Kid's Health, and Endocrine Disruptors. American Bar Association Section of Environment, Energy, and Resources. April 6, 2000, Washington, D.C.

Endocrine Active Mixtures; Approaches and Pitfalls. Presented to the Adjuvants and Inerts Meeting; Chemical Producers and Distributors Association, Arlington, VA. June, 1999.

Implications of the U.SEPA's Endocrine Disrupter Screening and Testing Program. American Industrial Hygiene Association, Philadelphia Chapter, April 13, 1999.

Review of EDSTAC Activity. 19th Symposium on Pesticide Formulations and Application Systems. E--35 Committee on Pesticides & Subcommittee on Pesticide Formulations and Application Systems, American Society for Testing and Materials (ASTM). 1998.

Endocrine Disruptors: Science and Sound Bites. Presentation to the Minnesota Pollution Control Agency Conference on "The Endocrine Disruptor Debate", St. Paul Minnesota, October 17, 1997.

The EDSTAC Process; Where to from Here? Presented to the AlkylPhenol Ethoxylates Panel of Chemical Manufacturer's Association, Arlington, VA, July 24, 1997.

Human Toxicology of Lead. Presentation to the National Oil Recyclers Association, April 1994, Orlando, Florida.

Clean Closure on a RCRA Site. 11th Biannual Hazardous Waste Management RCRA Compliance Course. University of Florida Continuing Education Center for Training, Research and Education for Environmental Occupations (TREEO) and The Florida Center for Solid and Hazardous Waste Management. TREEO Center, Gainesville, Florida, March 5, 1993.

A Turfgrass Pesticide Risk Assessment. C.J. Borgert, S.M. Roberts, R.D. Harbison, J.L. Cisar and G.H. Snyder. Poster Presentation; Seventh International Turfgrass Research Conference, Palm Beach, Florida. July 19, 1993.

Risk Assessment Techniques. Toxicology and Risk Assessment Workshop. University of Florida Continuing Education Center for Training Research and Education for Environmental Occupations and University of Florida Center for Environmental and Human Toxicology. Orange County Convention Center, Orlando, Florida, May 19, 1992.

JOURNALS REFEREED

ALTEX
Chemosphere
Dose Response
Environmental Research
Environmental Toxicology and Chemistry
Environmental Pollution
Food and Chemical Toxicology
Human and Ecological Risk Assessment
International Journal of Obesity
International Journal of Toxicology
International Workshop on Quantitative Structure-Activity Relationships (QSARs) in Environmental Sciences
Journal of Agricultural and Food Chemistry
Nonlinearity in Biology, Toxicology, and Medicine
Regulatory Toxicology and Pharmacology
Social Science and Medicine
Toxicological Sciences
Toxicology
Toxicology and Applied Pharmacology

MEMBERSHIPS

Toxicology Forum, 2003-present
Southeastern Pharmacology Society, 1991.
Society of Environmental Toxicology and Chemistry, Southeast Chapter, 1992 - present.
Society of Environmental Toxicology and Chemistry, 1995 - present.
Society of Toxicology, full member 1999-present
Society for Risk Analysis, 2006
International Society for Experimental Hematology, 2006-2007
International Society of Regulatory Toxicology & Pharmacology, 1997-present:
- Governing Council, 2001-2006; 2009-present
- Treasurer, 2003-2006
- President, 2007-2008

American Chemical Society 2010-present

Kathryn E. Clark, Ph.D., P.Eng.

EDUCATION

Ph.D. (Chemical and Environmental Engineering, minor in Toxicology) 1990, University of Toronto
M.A.Sc. (Chemical Engineering) 1986, University of Toronto
B.A.Sc. (Chemical Engineering) 1984, University of Toronto
B.Sc. (Pharmacy, completed two years of study) 1979-1981, University of Toronto

EXPERTISE

Dr. Clark has more than 25 years of experience in the development and application of models for quantifying the movement of chemicals in the environment. Her research interests include the evaluation of human exposure to phthalate esters, through multi-media fate modelling and probabilistic analysis, and characterization of bisphenol A in the environment. She is an environmental consultant and has also completed more than 250 site-specific risk assessments for contaminated sites, encompassing a wide variety of contaminants and land uses. Her role has included environmental fate modelling, evaluations of toxicological and physical chemical property information, and exposure assessment for human and ecological receptors.

EXPERIENCE

2000-present **BEC Technologies Inc., Aurora, ON**

Principal

Conducted numerous studies to evaluate human exposure to phthalate esters, through multi-media fate modelling and probabilistic analysis. Compiled a database summarizing reported concentrations in the environment, food, biological media, and consumer products for 21 phthalate esters based on a review of approximately 1000 references. Completed extensive literature reviews in order to characterize the concentration of bisphenol A in the environment.

On behalf of Health Canada, conducted a critical review of environmental fate and human exposure models used in completing risk assessments. The models were ranked, based on their applicability to risk assessment, acceptance by regulatory agencies, usability, and availability. Developed a guidance document and checklist for Health Canada staff to use when reviewing human health risk assessments. Developed and conducted more than fifteen multi-day training courses for staff of federal government departments on the methods for conducting risk assessments and the application of probabilistic methods to risk assessment. Assisted in the development of an online training course for conducting human health risk assessments. Prepared fact sheets and use profiles for various chemicals.

Performed risk assessments to assess human and ecological exposures due to the presence of chlorinated organic compounds, petroleum related hydrocarbons, and inorganic constituents at numerous industrial and institutional facilities. Performed risk assessments to support risk management plans for the redevelopment of many sites, including industrial facilities, highway lands, and a landfill. Conducted peer reviews of risk assessments evaluating human and ecological exposure to a variety of chemicals.

1994-2000 **O'Connor Associates Environmental Inc., Oakville, ON**

Associate (1999-2000), Senior Engineer (1994-1999)
Responsible for site-specific risk assessments leading to the development of risk management plans at contaminated sites across Canada. Site-specific risk assessments included chemical distribution facilities, numerous sites impacted with chlorinated solvents or arsenic, a chlor-alkali facility, hydrometric stations impacted by mercury, a former steel fabricating facility, parks and golf courses impacted by historical use of pesticides, an agricultural area impacted by metals from a spill of mine tailings, and coal tar leaching into a lake. Most of these risk assessments included the application of uncertainty analysis. Performed a study to evaluate the environmental fate and human exposure to diethylhexyl phthalate. Participated in a study to evaluate the natural attenuation of petroleum hydrocarbons in soil and groundwater. Performed an evaluation of the relative importance of site-specific and non-site-specific parameters in developing generic guidelines for soil and groundwater. Participated in the development of soil and groundwater remediation guidelines for upstream oil and gas sites and in the development of soil guidelines for petroleum hydrocarbons. Provided technical support for the in-house Research and Development group. Conducted seminars and training courses on the application of risk assessment.

1989-1994 **SENES Consultants Limited, Richmond Hill, ON**

Senior Environmental Engineer
Responsible for managing human health and ecological risk assessments, the development of clean-up guidelines, chemical fate modelling, and air monitoring measurements. Responsible for the ongoing redevelopment of a computer program known as AERIS© (Aid for Evaluating the Redevelopment of Industrial Sites) and for the production of the commercialized version of this software which determines clean-up guidelines for soil by estimating the human health risks posed by contaminants. Project Manager of numerous studies applying the AERIS© model to develop site-specific clean-up guidelines. Project Manager of environmental monitoring programs for volatile organic chemicals, total suspended particulate matter, and dustfall.

PROFESSIONAL AFFILIATIONS

- Professional Engineers of Ontario
- Registered Qualified Person (Risk Assessment) with the Ontario Ministry of the Environment

PUBLICATIONS AND PRESENTATIONS

"Relevance of Drinking Water as a Source of Human Exposure to Bisphenol A" (2013) with S.M. Arnold, C.A. Staples, G.M. Klecka, S.S. Dimond, N. Caspers, and S.G. Hentges, J. Expos. Sci. Environ. Epidem., 23:137-44.

"The Case for Activity and Fugacity Based Environmental Risk Assessment: The Example of the Plasticizer DEHP" (2012) with F. Gobas, V. Otton, and M. Ikonomou. SETAC North America 33rd Annual Meeting, Long Beach, California.

"Modeling Human Exposure to Phthalate Esters: A Comparison of Indirect and Biomonitoring Estimation Methods" (2011) with R.M. David, R. Guinn, K.W. Kramarz, M.A. Lampi, and C.A Staples. Human and Ecological Risk Assessment, 17(4):923–65.

"Comparison of Indirect and Biomonitoring Estimation Methods" (2011). 36th Annual Winter Meeting of The Toxicology Forum, Washington, DC.

"Exposure Analysis of Bisphenol A in Surface Water Systems in North America and Europe" (2009) with G.M. Klecka, C.A. Staples, N. van der Hoeven, D.T. Thomas, and S.G. Hentges. Environ. Sci. Technol., 43(16):6145-50.

"Evaluating Bisphenol A Concentrations in North American and European Environments: Comparison with Predicted Environmental Fate" (2007) with G.M. Klecka, C.A. Staples, N. van der Hoeven, and D.T. Thomas. SETAC North America 28th Annual Meeting, Milwaukee, Wisconsin.

"Evaluation of Bisphenol A in the European and North American Environments and Comparison with Predicted Environmental Fate" (2007) with C.A. Staples, N. Caspers, U. Friederich, G.M. Klecka, and N. van der Hoeven. SETAC Europe 17th Annual Meeting, Porto, Portugal.

"Development of Refined Predicted No-Effect Concentrations for Bisphenol A using Statistical Methods for Aquatic Risk Assessment" (2006) with C.A. Staples, K. Woodburn, and G.M. Klecka. SETAC North America 27th Annual Meeting, Montreal, Quebec.

"Critical Review of Available Environmental Fate and Exposure Models for Chemicals at Federal Contaminated Sites" (2006) with I. Mitchell, D. Williams, and S. Petrovic. Federal Contaminated Sites National Workshop, Ottawa, Ontario.

"An Examination of the Accumulation of Phthalate Esters using the Fugacity Approach" (2004). Fourth SETAC World Congress, Portland, Oregon.

"Estimating the Uncertainty in Predicting Environmental Fate of Phthalate Esters versus PCBs" (2004) with M. Comber and C. Cowan-Ellsberry. Fourth SETAC World Congress, Portland, Oregon.

"Observed Concentrations in the Environment" (2003) with I. Cousins and D. Mackay. In Phthalate Esters: The Handbook of Environmental Chemistry, Volume 3 Anthropogenic Compounds, Part Q. Ed. C.A. Staples. Springer-Verlag, Heidelberg, Germany, p125-177.

"Assessment of Critical Exposure Pathways" (2003) with I. Cousins and D. Mackay. In Phthalate Esters: The Handbook of Environmental Chemistry, Volume 3 Anthropogenic Compounds, Part Q. Ed. C.A. Staples. Springer-Verlag, Heidelberg, Germany, p227-262.

"Boxes, Cylinders and Parallel Plates: An Examination of Current Methods Employed to Predict Indoor Infiltration of Volatile Soil Contaminants" (2000) with G.M. Richardson, M. Mah-Paulson and D.R. Williams. Presented at: Atlantic Canada Environmental Business and Municipal Expo, Halifax, N.S.

"Preliminary Estimates of Adult Exposure to Bisphenol-A from Dental Materials, Food and Ambient Air" (1999) with G.M. Richardson and D.R. Williams. Environmental Toxicology and Risk Assessment: Standardization of Biomarkers for Endocrine Disruption and Environmental Assessment: Eighth Volume. ASTM STP 1364, pp 286 - 301.

"Natural Attenuation of Petroleum Hydrocarbons in a Rural Area" (1999). Remediation by Natural Attenuation, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Remediation Planning" (1999). Environmentally Acceptable Decommissioning, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Why Decommissioning is Necessary" (1999). Environmentally Acceptable Decommissioning, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Mass Distribution of Contaminants in the Subsurface" (1999). Remediation Processes for Contaminated Soil and Groundwater, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Fate and Exposure Models - Selecting the Appropriate Model for a Specific Application" (1998) with G.M. Richardson. Invited Debate/Commentary. J. Soil. Contam., 7(3), 267-274.

"Chlorosolvent-Impacted Low-Permeability Soil: Implications for Successful In Situ Cleanup" (1998) with G.S. Karp, A.V. Krishnayya, and R.C.E. McKee. Remediation of Chlorinated and Recalcitrant Compounds, Monterey, California.

"Risk Management" (1998). 4th Annual Groundwater Contamination and Remediation Techniques, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Environmental Fate and Exposure to Diethylhexyl Phthalate (DEHP)" (1997) with J.C. Paslawski and D.R. Williams. 24th Annual Aquatic Toxicity Workshop, Niagara Falls, Ontario.

"How Much Site Characterization is Necessary?" (1997) with G.M. Richardson and D.R. Williams. Air & Waste Management Association's 90th Annual Meeting and Exhibition, Toronto, Ontario.

"Consultant's Roles and Responsibilities" (1997). Environmentally Acceptable Decommissioning, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Risk Management" (1997). Groundwater Contamination and Remediation Techniques, EPIC Educational Program Innovations Center, Toronto, Ontario.

"Site-Specific Risk Assessment" (1996). Ontario's New Guidelines for the Clean-Up of Contaminated Sites, INSIGHT Information Inc., Toronto, Ontario.

"Assessing the Uncertainty in Uncertainty Analysis: Application of Stochastic Uncertainty Analysis to Exposure Assessment" (1996) with G.M. Richardson, J.C. Paslawski, and D.R. Williams. 3rd National Hazardous and Solid Waste Convention, Sydney, Australia.

"Computer Models for Developing Remediation Guidelines: A Comparison of MEPAS® and CalTOX™" (1996) with G.M. Richardson and D.R. Williams. 3rd National Hazardous and Solid Waste Convention, Sydney, Australia.

"The Relative Importance of Site-Specific and Exposure Parameters in Developing Generic Remediation Guidelines" (1996) with G.M. Richardson and D.R. Williams. 3rd National Hazardous and Solid Waste Convention, Sydney, Australia.

"Risk Management: The Consultant's Role" (1996). Environmentally Acceptable Decommissioning, EPIC Educational Program Innovations Center, Toronto, Ontario.

"The Application of Risk Management to the Remediation of Soil and Groundwater" (1995) with R.C.E. McKee and J.C. Paslawski. Environment and Energy Conference of Ontario, Toronto, Ontario.

"Potential Discrepancies Between Generic Guidelines for Chlorinated Organic Chemicals and Those Derived from Risk Assessments" (1995) with R.C.E. McKee. 5th Annual Symposium on Groundwater and Soil Remediation, Toronto, Ontario.

"The AERIS© Model: Its Use in Risk Assessments of Contaminated Sites" (1993) with C.L. Robins. Site Investigations for Contaminated Sites Conference, London, U.K.

"AERIS© Model As An Aid in Evaluating Human Exposure to Site Contamination" (1993) with C.L. Robins. Air & Waste Management Association - Ontario Section, Spring Conference, Guelph, Ontario.

"Analysis of Strategies for the Assessment of Hazardous Waste Sites" (1992) with J.A. Wyman, B.E.Halbert and B. Jessiman. ECO World '92 Conference and Exhibition, Washington, D.C.

"AERIS© Model as an Aid in Remedial Action Decisions at Contaminated Sites" (1992) with C.L. Robins. 1992 International Association of Hydrogeologists Conference, Hamilton, Ontario.

"Linking - Integrated Pathways Models" (1992). CIRAC/AWMA-OS Joint International Conference on Atmospheric Chemistry, Toronto, Ontario.

"A Quantitative Evaluation of 10 Approaches to Setting Site-Specific Cleanup Objectives" (1992) with B. Jessiman, G.M. Richardson, and B.E. Halbert. Hydrocarbon Contaminated Soils - Volume II, ed. P.T. Kostecki, E.J. Calabrese, M. Bonazountas, Lewis Publishers Inc., Chelsea, MI. Proceedings of the Sixth Annual Conference on Hydrocarbon Contaminated Soils, Amherst, Massachusetts.

"Predicting the Environmental Partitioning of Organic Contaminants and their Transfer to Biota" (1991) with D. Mackay. Organic Contaminants in the Environment: Environmental Pathways and Effects, ed. K.C. Jones, Elsevier Applied Science Publishers, London, 159-188.

"Dietary Uptake and Biomagnification of Four Chlorinated Hydrocarbons by Guppies" (1991) with D.Mackay. Environ. Toxicol. Chem., 10, 1205-17.

"Ecological Risk Assessments to Develop Cleanup Criteria for Soil and Groundwater" (1990) with B.E. Halbert, D.M. Gorber and J.M. Southwood. Air & Waste Management Association International Specialty Conference: How Clean is Clean? Cleanup Criteria for Contaminated Soil and Groundwater, Boston, Massachusetts.

"Model of Organic Chemical Uptake and Clearance by Fish from Food and Water" (1990) with F.A.P.C. Gobas and D. Mackay. Environ. Sci. Technol., 24(8), 1203-1213.

"Bioconcentration of Polybrominated Benzenes and Biphenyls and Related Superhydrophobic Chemicals in Fish: Role of Bioavailability and Elimination into the Feces" (1989) with F.A.P.C. Gobas, W.Y. Shiu and D. Mackay. Environ. Toxicol. Chem., 8, 231-245.

"Partitioning of Persistent Organic Chemicals in the Lake Ontario Ecosystem" (1988) with T. Clark, S. Paterson, D. Mackay and R.J. Norstrom. 31st Conference on Great Lakes Research, IAGLR, Hamilton, Ontario.

"Wildlife Monitoring, Modeling, and Fugacity" (1988) with T. Clark, S. Paterson, D. Mackay, and R.J. Norstrom. Environ. Sci. Technol., 22(2), 120-127.

"A Model of Organic Chemical Bioaccumulation by Fish" (1987) with D. Mackay and F. Gobas. Fourteenth Annual Aquatic Toxicity Workshop, Toronto, Ontario.

"Bioaccumulation of Super-Hydrophobic Chemicals in Fish" (1987) with F. Gobas, W.Y. Shiu and D. Mackay. Eighth Annual Meeting of the Society of Environmental Toxicology and Chemistry, Pensacola, Florida.

Curriculum Vitae

WARREN G. FOSTER, Ph.D.

August 20, 2014

PERSONAL:

Residential Address:

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Ancaster, Ontario, Canada
L9K 0A1

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Cellular: 905-975-9051

Business Address:

McMaster University
Department of Obstetrics & Gynecology
1280 Main Street West, HSC-3N52D
Hamilton, Ontario, Canada
L8S 4K1

Telephone: 905-525-9140 ext. 22822
Facsimile: 905-524-2911

E-mail: fosterw@mcmaster.ca

Citizenship: Canadian

EDUCATION:

1991	Ph.D.	McMaster University, Hamilton, ON	Health Sciences
1986	M.Sc.	University of Guelph, Guelph, ON	Biomedical Sciences
1979	B.Sc.(Hon.)	University of Guelph, Guelph, ON	Human Biology

MEMBERSHIP IN PROFESSIONAL SOCIETIES:

1. Society of Toxicology, 1999 – present.
    - President, Lake Ontario Regional Chapter, 2012 – present.
    - Secretary Treasurer, Reproductive Developmental Toxicology Specialty Section, 2010 – 2012.
    - Member, Scientific Program Committee, 2010 – 2012.
2. Society for the Study of Reproduction, 1994 – present.
    - Member, Membership Committee, 2012 – present.
    - Member, Scientific Program Committee, 2010 – 2012.
    - Chair, Committee on Reproduction and the Environment (CoRE), 2010 – 2012.
    - Member, Committee on Reproduction and the Environment (CoRE), 2009 – 2012.
    - Member, Animal Care Committee, 1995.
3. The Canadian Fertility and Andrology Society, 1991 – present.
    - Member, Scientific Program Committee, 2007 – 2011.
    - Past President 2008 – 2009.
    - Chair, Scientific Program Committee, 2007 – 2008.
    - President 2007 – 2008.
    - Vice-President, 2006 – 2007.
    - Industrial Liaison Committee, 2005 – 2006.
4. World Endometriosis Society, 2010 – present.
    - Member, Scientific Organizing Committee, World Congress of Endometriosis, Vancouver BC, 2012 – present.
5. European Society for Human Reproduction and Embryology, 2007 – present.
6. American Society for Reproductive Medicine, 2004 – present.
7. Association of Professors of Obstetrics & Gynaecology, 2003 – 2009.
8. Society of Obstetricians & Gynaecologists of Canada, 2001 – present.
9. Society of Toxicology of Canada, 1992 – present.
    - Vice-President (President Elect), 1998 – 1999.
    - Chairperson, Scientific Program Committee, 1997.
    - Member, Scientific Program Committee, 1996.
10. American Association for the Advancement of Science, 1988 – present.
11. International Federation of Placenta Associations, 2007.
    - Abstract Reviewer, 2007.

AWARDS:

1. Graduate Student Supervision Award, Faculty of Health Sciences, Research Plenary, McMaster University, 2014.
2. Mid-career Award, CIHR/Ontario Women's Health Council, 2006 – 2010.
3. Career Award, Ontario Women's Health Council, 2005.

4. Co-author of the best CFAS paper (oral presentation) in basic science category and Alpha Award. Neal MS, Petrik J, **Foster WG**, Holloway AC. *In utero* and lactational exposure to nicotine: ovarian effects. Conjoint American Society for Reproductive Medicine and the 51st Annual Meeting of the Canadian Fertility & Andrology Society, Montreal, QC, October 16 – 19, 2005.
5. Co-author of the best CFAS paper (oral presentation) in basic science category. Van Vugt DA, Krzemien A, Roy BN, **Foster W**, Lundhal S, Marcus S, and Reid RL. Photodynamic ablation in non-human primates. 42nd Annual Meeting of the Canadian Fertility & Andrology Society, Lake Louise, AB, 1996.
6. Senior author of the best CFAS paper (oral presentation) in basic science category. **Foster WG**, Rice DC, McMahon A. Suppression of luteal function in the chronically lead exposed cynomolgus monkey (*Macaca fascicularis*). 40th Annual Meeting of the Canadian Fertility & Andrology Society, St. John, NB, September 7 – 10, 1994.
7. Medical Research Council of Canada Studentship, 1988 – 1990.
8. Medical Sciences Programme Scholarship, 1987 – 1990.
9. Ontario Graduate Scholarship, 1985 – 1986; 1987 – 1988.

EMPLOYMENT EXPERIENCE:

1. Adjunct Professor, Herbert Wertheim College of Medicine, Florida International University, Miami, FL, April 2013 – present.
2. Professor, Reproductive Biology Division, Department of Obstetrics & Gynecology, McMaster University, Hamilton, ON, June 2005 – present.
3. Affiliate Scientist, Institute of Population Health, University of Ottawa, Ottawa, ON, 2003 – present.
4. Director, Reproductive Biology Division, Department of Obstetrics & Gynecology, McMaster University, Hamilton, ON, 2002 – March 2010.
5. Medical Director, Centre for Reproductive Care, Hamilton Health Sciences, Hamilton, ON, April 2005 – March 2008.
6. Coordinator, Resident Research Program, Department of Obstetrics & Gynecology, McMaster University, Hamilton, ON, 2003 – 2010.
7. Adjunct Assistant Professor, Department of Obstetrics & Gynaecology, Foothills Hospital, University of Calgary, Calgary, AB, 1993 – 2008.
8. Associate Professor, Reproductive Biology Division, Department of Obstetrics & Gynecology, McMaster University, Hamilton, ON, June 2001 – June 2005.
9. Senior Science Advisor, Bureau of Chemical Hazards, Health Canada, Ottawa, ON, September 2000 – June 2001.
10. Adjunct Assistant Professor, Department of Obstetrics & Gynaecology, McMaster University, Hamilton, ON, 1997 – 2001.
11. Associate Director/Director of Research, Center for Women's Health, Cedars-Sinai Medical Center, Los Angeles, CA, January 1999 – September 2000.
12. Acting Division Chief, Environmental & Occupational Toxicology Division, Environmental Health Directorate, Health Protection Branch, Health Canada, Ottawa, ON, May – October

1997; June 1998 – January 1999
13. Head, Reproductive Toxicology Section, Environmental & Occupational Toxicology Division, Environmental Health Directorate, Health Protection Branch, Health Canada, Ottawa, ON, 1992 – June 1998.
14. Reproductive Toxicologist, Reproductive Toxicology Section, Environmental & Occupational Toxicology Division, Environmental Health Directorate, Health & Welfare Canada, Ottawa, ON, 1990 – 1992.

SCHOLARLY, AND PROFESSIONAL ACTIVITES:

i) **editorial boards** –

BioMed Research International, 2014 – present.
Guest Editor, Obstetrics and Gynecology, 2014 – present.
Journal of Clinical Toxicology, 2013 – present.
Journal of Environmental & Analytical Toxicology, 2012 – present.
ISRN Toxicology, 2011 – present.
Journal of Toxicology and Environmental Health: B Critical Reviews, 2010 – present.
Journal of Applied Toxicology, 2008 – present.
Editor, Journal of Applied Toxicology, 2010 – present.
Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry, 2009 – present.
Faculty of 1000, 2008 – present.
Reproductive Toxicology 2004 – 2008.

ii) **grant panels and committees** –

Canadian Breast Cancer Fund Grants Review Committee, 2014 – present.
Development and Reproductive Toxicology (DART) Technical Committee, ILSI Health and Environmental Sciences Institute (HESI), Scientific Advisor, 2012 – present.
The ANTI-NMDA Receptor Encephalitis Foundation, Inc, Board of Directors, 2012 – present.
Medical Research Council, Ad hoc Grant Reviewer, UK, 2011 – present.
CIHR Training Program in Reproduction, Early Development, and the Impact on Health (REDIH), Program Advisory Committee Member, 2009 – present.
CIHR Training Program in Reproduction, Early Development, and the Impact on Health (REDIH), Member and Mentor, 2009 – present.
Faculty of Health Sciences, McMaster University, Graduate Curriculum Committee, 2006 – present.
US-National Toxicology Program, Center for the Evaluation of Risk to Human Reproduction, Member of Expert Registry, 2005 – present.
CIHR Strategic Training Program in Tobacco Research (CIHR-STPTR), University of Waterloo, Mentor, 2005 – present.
College of Reviewers, Canada Research Chairs Program, Member, 2000 – present.
Canadian Institutes of Health Research (CIHR) Gender, Sex & Health Peer Review Committee, December 4 – 5, 2013.
Canadian Institutes of Health Research (CIHR) Catalyst Grant Committee, Genes and Chronic

Disease, July 17 – 18, 2013.
National Sciences and Engineering Research Council (NSERC), Undergraduate Research Student Awards (URSA) Scholarship Review Committee, Member, March 13, 2013.
National Center for Environmental Assessment, US Environmental Protection Agency, Improving the risk assessment of persistent, bioaccumulative and toxic (PBT) chemicals in breast milk, Invited participant, Expert Workshop, October 24 – 26, 2012.
NICHD site visit, Division of Epidemiology, Statistics & Prevention Research, Expert Panel Member, October 22 – 24, 2012.
Council of Canadian Academies Panel, Integrating Emerging Technologies into Chemical Safety Assessment, Member, 2010 – 2012.
Centre for Disease Control, Infertility Research Working Group, Member, 2009 –2012.
Society for the Study of Reproduction, Committee on Reproduction and the Environment, Member, 2008 – 2012.
Strategic Training in Research in Reproductive Health Sciences (STIRRHS), University of Montréal, Mentor, 2006 – 2011.
ASRM ERSIG Advisory Board Member, June 2005 – 2011.
College of Physicians and Surgeons of Ontario, Obstetrics & Gynecology Task Force - *In vitro* Fertilization, Mentor, 2008 – 2010.
CIHR Clinical Investigation A Panel, Member, 2007 – 2010.
Canadian Breast Cancer Fund Grants Review Committee, Member, 2007 – 2010.
Environment and Health, Collaborations for Health, McMaster University, Co-theme Team Leader, 2005 – 2010.
US Environmental Protection Agency, the National Institute of Environmental Health Sciences, and the California Breast Cancer Research Program, Mammary Gland Evaluation and Risk Assessment Workshop, Invited participant, November 16 – 17, 2009.
NIH Study Section, Integrative and Clinical Endocrinology and Reproduction Study Section, Member, October 5 – 6, 2009.
Canadian Children's Environmental Health Research Workshop. Health Canada sponsored workshop, Invited Participant and Session Chair, Ottawa, ON, March 17 – 19, 2002; February 9 – 10, 2009.
Preimplantation Genetic Diagnosis and Related Activities in Canada, Steering Committee Member, 2008 – 2009.
The Society of Obstetricians and Gynaecologists of Canada (SOGC), Research Committee, Member, 2003 – 2008.
Assisted Human Reproduction Research Workshop: Developing a National Research Agenda, Scientific Planning Committee member, Montreal, QC, October 15 – 16, 2008.
National Institute of Child Health and Human Development, National Children's Study (NCS) Centers, Member of RFP review panel, April 2008.
CIHR Institute of Human Development and Child and Youth Health Workshop – Environmental Toxicology, Invited Participant, February 2008.
Ontario Tobacco Research Unit, Small Grants Committee, Member, 2007.
NICHD, Study Section member, Effects of Aspirin on Gestation and Reproduction panel, 2006.
US Environmental Protection Agency – Star program, grant review panel member, 2004; 2005.

NICHD, Child Study; Study Section member, 2005.
National Cancer Institute of Canada, Canadian Tobacco Control Research Initiative peer review panel member, 2004.
Toxic Substances Research Initiative, Health Canada, Healthy Environments and Consumer Safety Branch, 1999 – 2003.

- Chairman, Endocrine Disrupters Technical Review Committee, 1999 – 2000.

CIHR-Institute of Human Development, Child and Youth Health sponsored Pre and Post Implantation Consensus Workshop, Invited participant, April 5 – 7, 2002.
WHO/IPCS Steering Group on Endocrine Disruptors, 1998 – 2002.

- Global Inventory of Endocrine Disruptor Research.
- International Assessment of the State of Knowledge on Endocrine Disruptors.

Natural Sciences and Engineering Research Council (NSERC) Grant Selection, 1996 – 2001.

- Past chair, 2001
- Committee chair person, 1999 – 2000.
- Committee Member, 1996 – 2000.

National Institutes of Environmental Health Safety, National Institutes of Health, and National Toxicology Program sponsored expert meeting on low-dose effects of endocrine disruptors, Invited panelist, October 2000.
US Environmental Protection Agency, Atrazine, Science Advisory Panel Member, June 2000.
SETAC-SOT co-sponsored Workshop on Environmental-Human Interconnections, Snowbird, UT, Invited participant, June 10 – 15, 2000.
US Environmental Protection Agency – Endocrine Disruptor Screening and Testing Standardisation Committee, Mammalian Test Working Group Member, 1999 – 2000.
Joint US/EU Endocrine Disruptor Research, Expert Panel Member, 1999.
US-EPA ORD Strategy for Research on Environmental Risks to Children, Peer Reviewer, 1999.
Organisation for Economic Co-operation and Development (OECD), 1997 – 1999.

- Working Group on Endocrine Disruptor Testing and Assessment, 1997 – 1999.
- Health Canada Endocrine Disruptor Committee, 1997 – 1999.
- National Co-ordinator, Test Guideline Program, 1997 – 1998.

National Sanitation Foundation - International, Health Effects Task Group, 1996 – 1998.

iii) **executive positions** –
Member, Advisory Board, The Endometriosis Association, 2014 – present.
President, Society of Toxicology, Lake Ontario Regional Chapter, 2012 – present.
Member, Membership Committee, Society for the Study of Reproduction, 2012 – present.
Member, Scientific Program Committee, Society for the Study of Reproduction, 2010 – 2012.
Chair, Core Committee, Society for the Study of Reproduction, 2010 – 2012.
Secretary Treasurer, Reproductive Developmental Toxicology Specialty Section, Society of Toxicology, 2010 – 2012.
Member, Scientific Program Committee, Canadian Fertility and Andrology Society, 2006 – 2010.
Member of the Association of Professors of Obstetrics & Gynaecology, Science Committee,

2003 – 2009.
President, Canadian Fertility and Andrology Society, 2007 – 2008.
Chair, Scientific Program Committee, Canadian Fertility and Andrology Society, 2007 – 2008.
Vice-president, Canadian Fertility and Andrology Society, 2006 – 2007.
Chair, Science Panel, EM-COM web site, www.EMCOM.ca, 2002 – April 2005.
Member, Board of Directors, Infertility Awareness Association of Canada, 1998 – 2004.
Vice-president, President-elect, Society of Toxicology of Canada, 1998 – 1999.
Chair, Scientific Program Committee, Society of Toxicology of Canada, 1997.
Member of Scientific Program Committee, Society of Toxicology of Canada, 1996.
Member of Animal Care Committee, Society for the Study of Reproduction, 1995.

iv) **journal referee** –

Biology of Reproduction
Comparative Biochemistry & Physiology
Endocrinology
Environmental Health Perspectives
Environmental Research
Environmental Toxicology
Fertility & Sterility
Food & Chemical Toxicology
Human Reproduction
Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry
International Journal of Cell Biology
Journal of Applied Toxicology
Journal of Clinical Investigation
Journal of Toxicology & Environmental Health
Pesticide Biochemistry & Physiology
Placenta
Regulatory Toxicology and Pharmacology
Reproductive Biomedicine Online
Reproductive Toxicology
Systems Biology in Reproductive Medicine
The Journal of Urology
Toxicological Sciences
Toxicology and Industrial Health

v) **external grant reviews –**

Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada
Canadian Tobacco Control Research Initiative
Hospital for Sick Children, Toronto, ON
College of Reviewers for Canadian Research Chairs
Research Grants Council of Hong Kong
Canterbury Medical Research Foundation
Netherlands Organisation for Scientific Research - Earth and Life Sciences

AREAS OF RESEARCH INTEREST:

My research interests fall primarily into three categories as follows: (1) reproductive epidemiology and biomonitoring; (2) reproductive and development toxicity of environmental and dietary chemicals; and (3) the cellular and molecular mechanisms of endometriosis. Small teams of postdoctoral fellows and graduate students are assigned to each area carrying out focused studies as described below.

Reproductive epidemiology and biomonitoring studies are carried out in my laboratory to provide an accurate assessment of exposure to environmental contaminants (persistent organic

pollutants, endocrine toxicants and metals) and dietary chemicals such as phytoestrogens in women attempting to achieve pregnancy and maternal infant pairs. Data generated in these studies provide essential data for risk assessment, government and regulatory policy development, and dose selection in animal studies. A highlight from studies in the area was demonstration that pesticides, organic pollutants, and phytoestrogens can be quantified in human amniotic fluid.

Animal studies and tissue culture experiments are routinely employed in my laboratory to elucidate the cellular and molecular mechanisms underlying changes in reproductive outcomes with primary attention on ovarian regulation. An ongoing project in my laboratory is focused on elucidating the mechanisms of cigarette smoking induced subfertility, impaired response to ovulation induction, premature reproductive failure, and loss of primordial follicles. Our results to date have shown that contrary to existing dogma, follicle loss is not driven by apoptosis but rather toxicants present in cigarette smoke attenuate follicle development and induce autophagy of granulosa cells. Ongoing studies are designed to determine if the adverse effects of cigarette smoking on ovarian function and fertility are reversible.

Endometriosis is an enigmatic disease whose treatment is best characterized as fragmented. Diagnosis is often delayed for a decade from the onset of symptoms and current therapeutic strategies are sub-optimal. To address these weaknesses in the literature innovative tools such as proteomics and metabolomics together with conventional approaches are being employed in ongoing studies designed to identify novel diagnostic and therapeutic markers of endometriosis. In addition, the efficacy of novel therapeutic agents in regulating angiogenesis, apoptosis, and the growth of human endometrial cells transplanted to the abdominal cavity of a novel mouse model of endometriosis is being studied in several different studies.

COURSES TAUGHT:

i) **undergraduate –**
Pharmacology 4C03 Principles of Toxicology, Lectures on Endocrine Disruption
Undergraduate Medicine MF3 – Reproductive Biology

ii) **graduate –**
MS712 Reproductive Endocrinology
MS714 Industrial and Environmental Toxicology
MS720 Tobacco and Health: From Cells to Society
MS799 Independent Study in Reproductive Biology

SUPERVISORSHIPS:

i) **master** –

- Anne Doedée, Visiting Student (Netherlands), Neurotrophins and trks – novel reproductive tract proteins. (Supervisor, 2010).

- Alex Lagunov, Mechanisms regulating oocyte activation. (Supervisor, 2008 – 2010).
- Dana Anger, Tyrosine kinase receptor B expression in human endometrium. (Supervisor, 2005 – 2007).
- Katie Stys, Mechanisms of AhR-ligand induced changes in inappropriate estrogen production in the endometrium. (Supervisor, 2003 – 2005).
- Katie Edmunds, Proliferative effects of dietary isoflavones in the human endometrium. (Supervisor, 2002 – 2004).
- Megan Miller, Effects of benzo[a]pyrene on matrix metalloproteinase expression and activity in breast cancer. (Supervisor, 2002 – 2004).

ii) **doctoral –**

- Jocelyn Wessels, Brain derived neurotrophic factor (BDNF), a novel diagnostic marker for endometriosis. (Supervisor, 2011 – present).
- Mike Neal, M.Sc., The effect of environmental agents on follicle dynamics and oocyte quality. (Supervisor, 2002 – present).
- Mahmoud Aarabi, Queen's University, Characterization of post-acrosomal sheath protein PAWP. (Co-supervisor, 2008 – 2013).
- Anne Gannon (Mulligan Tuttle), M.Sc., The effect of cigarette smoke constituents on ovarian follicle growth and apoptosis. (Supervisor, 2006 – 2013).
- Nakpangi A Johnson, Duquesne University – Does DDE shorten time to tumor formation in MMTV-neu mice? (Co-supervisor, 2008 –2011).
- Ebrahim Nasir, Reproductive toxic effects of bilirubin on testicular function. (Co-supervisor, 2002 – 2003).

iii) **post-doctoral –**

- Jean Clair Sadeu, Ph.D., Effect of environmental toxicants on folliculogenesis. (2009 – 2013).
- Heather Cameron, Ph.D., Effects of environmental toxicants on estrogen dependent mammary tumor development in mice. (2006 – 2008).
- Rocio Monroy, M.D., Cigarette smoking during pregnancy and glucose transport protein expression in the human placenta. (2006 – 2008).
- Alison Holloway, Ph.D., Cellular and molecular mechanisms of inappropriate estrogen production in endometriosis. (2001 – 2004).
- Gentao Liu, Ph.D., The reproductive effects of dietary galactose in the rat. (1999 – 2000).
- Jack Yang, Ph.D., The role of environmental pollutants in the pathophysiology of endometriosis in rodents and non-human primate models. (1996 – 1999).
- Michael Wade, Ph.D., The effect of environmentally relevant concentrations of priority contaminants on ovarian follicle differentiation, steroidogenesis and ovulation. (1996 – 1998).
- Daniel Cyr, Ph.D., The effects of methyl mercury on male reproduction. (1994 – 1995).

iv) **professional –**

- Sandra Gregorovich, M.D., Research Coordinator, 2009 – 2011.
- Heather Cameron, Ph.D., Research Associate, 2009 – 2010.
- Miguel Dominguez, D.V.M., Ph.D., Visiting Scientist, from Mexico, 2006 – 2009 & 2013.
- Mehrnoosh Faghih, M.D., OBS & GYN Resident research project, McMaster University, 2006 – 2008.
- Myoung-seok Han, M.D., OBS & GYN, Visiting Scientist, from Korea, 2006 – 2007.
- Greg Athaide, M.D., OBS & GYN Resident research project, McMaster University, 2005 – 2006.
- Julie Francis, M.D., OBS & GYN Resident research project, McMaster University, 2004 – 2005.
- Pezhman Mirshokraei, D.V.M., Ph.D., Visiting Scientist, from Iran, 2003 – 2004.
- Anna Chomej, M.D., OBS & GYN Resident research project, McMaster University, 2003.

v) **supervisory committees –**

- Jennifer Fazzari, 2014 – present, M.Sc. candidate, McMaster University.
- Michael Tsoulis, 2013 – present, M.Sc. candidate, McMaster University.
- Stephanie Zantinge, 2012 – present, M.Sc. candidate, McMaster University.
- Jonathan Lockwood, 2012 – 2013, M.Sc. candidate, McMaster University.
- Robert Berger, 2007 – 2010, M.Sc. candidate, McMaster University.
- Ayesha Khan, 2006 – 2009, Ph.D. candidate, McMaster University.
- Jenny Bruin, 2005 – 2009, Ph.D. candidate, McMaster University.
- Carolyn Cesta, 2007 – 2009, M.Sc. candidate, McMaster University.
- Jordan Shaw, 2007 – 2008, M.Sc. candidate, McMaster University.
- Rochelle Fernandez, 2004 – 2005, M.Sc. candidate, McMaster University.

vi) **others (summer/co-op students) –**

- Alia Tewari, (January 2014 – present) 3rd yr. Health Sciences, University of Waterloo, Project Title: Environmental obesogens, what's the skinny?
- Garima Aryal, (January 2014 – present) 3rd yr. Health Sciences. Project Title: Human developmental exposure to BPA: developmental effects.
- Aamer Somani, (January 2014 – present) 3rd yr. Biochemistry. Project Title: Dietary chemical effects on endometrial epithelial cell aromatase activity.
- Anna Parackal, (January 2014 – present) 3rd yr. Biopharmacology. Project Title: Effects of cigarette smoke on markers of autophagy in the mouse ovary.
- Trevor Patch, (September 2013 – present) 4th yr. Psychology. Project Title: Mechanisms of stress induced pregnancy loss in the mouse.
- Piraveena Sivapatham, (September 2013 – present) 4th yr. Life Sciences. Project Title: Connexin-26 expression in the endometrium and spontaneous abortion.
- Kabir Toor, (Summer 2013) 4th yr. Bachelor of Health Sciences. Project Title: Clinical

markers in endometriosis.

- Alia Tewari, (Summer 2013) 2nd yr. Bachelor of Health Sciences, University of Western Ontario. Project Title: Neurotrophins in endometiosis.
- Vanessa Kay, (Summer 2011; Sept. 2011 – 2013) 4th yr. Thesis student. Project Title: Measurement of urinary phthalate metabolites.
- Vanessa Kay, (Summer 2010) 3rd yr. Bachelor of Health Sciences. Project Title: Identification of a novel diagnostic marker for endometriosis.
- Vanessa Kay, (Summer 2009) 2nd yr. Bachelor of Health Sciences, Project Title: Identification of a novel diagnostic marker for endometriosis.
- Natalie Cho, (Summer 2009) 4th yr. Bachelor of Health Sciences. Project Title: Ovarian effects of Bisphenol A exposure.
- Mary Peric, (Summer 2009) 2nd yr. Bachelor of Health Sciences. Project Title: Placenta change induced by in utero nicotine treatment in the rat.
- Melissa Coubrough, (Summer 2009) 2nd yr. Midwifery. Project Title: Neurotrophic expression in breast cancer cell lines.
- Otis Kryzanauskas, (Summer 2009) 2nd yr. Midwifery. Project Title: Effects of maternal smoking on placenta glucose transport.
- Mary Peric, (Summer 2008) 1st yr. Bachelor of Health Sciences. Project Title: Developmental effects of nicotine exposure in the rat.
- Vivian Ho, (Summer 2008) 3rd yr. Bachelor of Health Sciences. Project Title: Developmental effects of nicotine exposure in the rat.
- Rami Elias, (Summer 2007) 3rd yr. Bachelor of Health Sciences. Project Title: Neurotrophin and cognate receptor expression in endometriosis associated ovarian cancer.
- Mary Peric, (Summer 2007) Gr. 12 Hon. Student. Project Title: Brain derived neurotrophic factor and Tyrosine receptor kinase B expression in the reproductive tract of sexually mature BALB/c mice.
- Derek Chaves, (Fall 2004) 4th yr. Hon. Pharmacology & Toxicology Thesis Project, McMaster University. Project Title: Cyclooxygenase-II and matrix metalloproteinase expression in breast cancer cell lines.
- John Agzarian, (Summer 2004) 2nd yr. Hon. Bachelor of Health Sciences. Project Title: Environmental toxicant mixture effects on thyroid gland morphology. (Funded by a scholarship from the Thyroid Foundation of Canada).
- Alex Petre, (Summer 2004) 1st yr. Hon. Bachelor of Science. Project Title: Toxicant induced changes in tissue remodelling enzyme expression in granulosa cells. (NSERC scholarship).
- Dana Anger, (Summer 2004) 4th yr. Hon. Pharmacology & Toxicology Thesis Project, McMaster University. Project title: Mechanisms of methylchloranthene-induced changes in ovarian apoptosis.
- Gareth Lim, (Summer 2003) 4th yr. Hon. Pharmacology & Toxicology Thesis Project, McMaster University. Project Title: Developmental toxicity of in utero exposure to drinking water disinfection by-products in the rat. (Graduate student, University of

Toronto).

- Sarah Sinasac, (Summer 2002) 3rd yr. Hon. B.H.Sc., Medical Student, McMaster University. Project Title: Toxicant effects on granulosa cell steroidogenesis.
- Donna Grant, (Summer 1994) 3rd yr. Biochemistry/Toxicology, University of Guelph. Project Title: Ovarian apoptosis in the PMSG primed immature rat ovary. Location & activity unknown.
- Carmen Mertineit, (Winter 1992) 4th yr, Hon. Biology Thesis Project, McMaster University. Project Title: The effect of Hexachlorobenzene on the ovariectomized rat. Ph.D., Research Scientist, Astra Pharmaceuticals.
- Pete Ecclestone, (Winter 1991) 4th yr, Hon. Biology Thesis Project, McMaster University. Project Title: The effect of Lead intoxication on serum radioimmunoreactive vs. bioactive levels of pituitary gonadotropins and serum testosterone levels in the male cynomolgus monkey. Pharmaceutical sales.
- Greg Major, (Summer 1991) 2nd yr. Biology, University of Western Ontario. Project Title: Modification of an enzyme fluorescent method for quantification of DNA in subcellular fractions. Residency in Orthopedic Surgery, University of Colorado.
- Julie Pentick, (Fall 1990) 3rd yr. Biochemistry, University of Waterloo. Project Title: Tissue distribution and subcellular localization of Hexachlorobenzene in the rat ovary. Contract researcher, Health Canada.
- Greg Major, (Summer 1990) 1st yr. Biology, University of Western Ontario. Project Title: Mating induced changes in the distribution of immunoreactive GnRH neural elements in the female rabbit. Orthopedic Surgeon, University of Colorado.

vii) **graduate examining committees –**

- Jennifer Fazzari, M.Sc., Transfer Examiner, McMaster University, 2014.
- Stephanie Ondovcik, Ph.D., External Thesis Examiner, University of Toronto, 2013.
- Kristy Roth, Ph.D., Comprehensive Examiner, McMaster University, 2011.
- Jessica Kafka, Ph.D., Comprehensive Examiner, McMaster University, 2011.
- Robert Berger, M.Sc., Thesis Examiner, McMaster University, 2010.
- Ayesha Khan, Ph.D., Thesis Examiner, McMaster University, 2009.
- Jenny Bruin, Ph.D., Thesis Examiner, McMaster University, 2009.
- Arkadiusz (Eric) Hul, Ph.D., Thesis Examiner, McMaster University, 2009.
- Carolyn Cesta, M.Sc., Thesis Examiner, McMaster University, 2009.
- Jordan Shaw, M.Sc., Thesis Examiner, McMaster University, 2008.
- Navkiran Gill, Ph.D., Thesis Examiner, McMaster University, 2008.
- Anne Ellis, M.D., M.Sc., Thesis Examiner, McMaster University, 2008.
- Sudha Bhavanam, M.Sc., Thesis Examiner, McMaster University, 2008.
- Lorna Ryan, Ph.D., Thesis Examiner, McMaster University, 2007.
- Sherri Fernandez, M.Sc., Thesis Examiner, McMaster University, 2007.
- Alexandera Kollara, Ph.D., External Thesis Examiner, University of Toronto, 2006.
- Caleb Zavitz, M.Sc., Transfer Examiner, McMaster University, 2006.

- Rochelle Fernandez, M.Sc., Thesis Examiner, McMaster University, 2006.
- Tamara Lee Jocelyn, Ph.D., External Thesis Examiner, McGill University, 2005.
- Michael Cyr, M.Sc. Thesis Examiner, McMaster University, 2005.
- Erin McDonald, M.Sc., Thesis Examiner, McMaster University, 2005.
- Anthony Wood, Ph.D., External Thesis Examiner, University of Guelph, 2004.
- Julang Li, Ph.D., External Thesis Examiner, University of Ottawa, 1998.

RESEARCH FUNDING:

1. **Foster WG**, Leyland NA, Agarwal SK, Villeneuve P. Characterization of a novel clinical marker of endometriosis. CIHR Institute of Gender and Health $100,000. (***Awarded***). 2014 – 2015.
2. Fraser W, Arbuckle T, **Foster WG,** et al., (9 co-applicants). Maternal-Infant Research on Environmental Chemicals – Child Development Plus (MIREC-CD+). Health Canada $149,165. (***Awarded***). 2013 – 2015.
3. **Foster WG** and Zhu, J. Mechanism(s) of cigarette smoke-induced ovarian follicle loss. CIHR $873,835. (***Awarded***) 2011 – 2016.
4. Tayade C and **Foster WG**. A novel anti-angiogenic therapy for endometriosis. CIHR $483,410. (***Awarded***). 2011 – 2016.
5. Baltz JM, **Foster WG**, et al., (30 co-applicants). Training Program in Reproduction, Early Development, and the Impact on Health (REDIH). CIHR Human Development, Child and Youth Health $1,787,598. (***Awarded***) 2009 – 2015.
6. Cameron R, **Foster WG**, et al., (58 co-applicants). Population Intervention for Chronic Disease Prevention: A Pan-Canadian Program. CIHR $1,950,000. (***Awarded***) 2009 – 2014.
7. **Foster WG**. Evaluation of a dietary treatment for endometriosis. Concourse Health Sciences LLC $68,525 USD. (***Awarded***). 2012 – 2013.
8. **Foster WG.** Neurotrophins and Trks: Novel reproductive tract proteins. NSERC $185,000. (***Awarded***). 2008 – 2013.
9. Fraser W, Arbuckle T, **Foster WG,** et al., (9 co-applicants). Maternal-Infant Research on Environmental Chemicals – Infant Development (MIREC-ID). Health Canada $2,084,968. (***Awarded***). 2008 – 2011.
10. Fraser W, Arbuckle T, **Foster WG**, et al., (9 co-applicants)**.** Maternal-Infant Research on Environmental Chemicals (MIREC): A National Profile of *In Utero* and Lactational Exposure to Environmental Contaminants. CIHR $1,248,126. (***Awarded***) 2006 – 2012.
11. **Foster WG** and Cameron H. Dieldrin increases breast cancer metastasis via dysregulation of neurotrophin expression. CIHR $100,000. (***Awarded***) 2009 – 2010.
12. **Foster WG,** Yauk C, Quinn J, Robaire B, and McCarry B. Urban air particulate pollution & genetic instability. CIHR Team Grant LOI $10,000. (***Awarded***) 2009 – 2010.
13. **Foster WG**. Cellular and molecular mechanisms of toxicant-induced changes in ovarian follicular atresia. CIHR $616,408. (***Awarded***) 2006 – 2010.
14. **Foster WG**. Cellular and molecular mechanisms of toxicant-induced changes in follicular

dynamics and ovarian regulation. Ontario Women's Health Council/CIHR Institute of Gender and Health Mid-career Award $375,000. (***Awarded***) 2005 – 2010.

15. Oko R and **Foster WG.** Improvement of ICSI treatment by co-injection of recombinant PAWP protein. CIHR RxND $100,000. (***Awarded***) 2007 – 2008.
16. **Foster WG.** Toxicant-induced resistance to ANOIKIS in estrogen sensitive target tissues. NSERC $35,136. (***Awarded***). 2007 – 2008.
17. **Foster W**, Holloway A, Krewski D, Kourti T. Surrogate biomarkers of *in utero* exposure to xenobiotics. American Chemistry Council $878,418. (***Awarded***) 2003 – 2007.
18. **Foster WG**. Toxicant induced tissue remodelling in estrogen sensitive target tissues. NSERC $144,000. (***Awarded***) 2003 – 2007.
19. **Foster W**, Holloway A, Krewski D, Muller W. Biomarkers of breast cancer. American Chemistry Council $941,751. (***Awarded***) 2002 – 2007.
20. Casper R and **Foster WG.** Identification of early pathogenetic events leading to endometriosis and discovery of novel therapeutic strategies. CIHR – Operating $415,794. (***Awarded***) 2003 – 2006.
21. **Foster WG**. AhR ligands and endometriosis: towards understanding their mechanism of action. CIHR – Operating $345,601. (***Awarded***) 2002 – 2006.
22. **Foster WG**. Ontario Women's Health Council Career Award $100,000. (***Declined***) 2005.
23. **Foster W**, Holloway A. Effect of binary mixtures on estrogen sensitive target tissues. Canadian Network of Toxicology Centers $55,000. (***Awarded***) 2003 – 2004.
24. **Foster WG**. Hormonally active chemicals: cellular and molecular mechanisms of action. CFI-OIT $422,096. (***Awarded***) 2002 – 2003.
25. Holloway A, and **Foster WG.** Effects of *in utero* chemical insult on postnatal health. Canadian Chlorine Coordinating Council $48,000. (***Awarded***) 2002 – 2003.
26. **Foster WG**, Hughes CL, and Chan S. Human developmental exposure to endocrine disruptors. New York Community Trust Fund $105,000 USD. (***Awarded***) 2002 – 2003.
27. **Foster WG**. Dietary factor modulation of endometrial tissue production of IL-6 and IL-6sR and angiogenic factors *in vitro*. Dow Chemical $25,000 USD. (***Awarded***) 2001 – 2002.
28. Davis V, **Foster WG**, and Hughes CL. Influence and localized DDT exposure on breast cancer. California Breast Cancer Research Program $305,989 USD. (***Awarded***) 2000 – 2002.

PEER REVIEWED PUBLICATIONS:

i) **books** –

1. Ritter L, Austin CP, Bend JR, Brunk CG, Caulfield T, Dellarco VL, Demers P, **Foster W**, Infante-Rivard C, Jumarie C, Kacew S, Kavlock RJ, Krewski D, Mezey PG, Shultz T. (2012) Integrating Emerging Technologies into Chemical Safety Assessment. Council of Canadian Academies. Ottawa, Canada.

ii) **contributions to books** –

1. Valez MP, Monnier P, **Foster WG**, Fraser WD. (2014) Chapter 7:The impact of phthalates on women's reproductive health: Current state-of-the-science and future directions. In: Part

III, Endocrine Disruption Hormones as the 'Messengers of Gender'. (*In-press*).
2. Gannon AM, Sadeu JC, Agarwal SK, Hughes CL, **Foster WG**. (2013) Chapter 10:Cigarette smoking and ovarian function. In: Ovarian Toxicology, Patricia Hoyer, Editor. CRC Press. Part II, Ovotoxic Chemical Classes. 231-250.
3. Peery HE, Day GS, Doja A, Xia C, Fritzler M, **Foster W**. (2013) Chapter 129:Anti-NMDA receptor encephalitis in children: the disorder, its diagnosis, and treatment. In: Handbook of Clinical Neurology, Vol. 112, Pediatric Neurology Part II. 1229-1233.
4. Rier S and **Foster WG**. (2003) Environmental dioxins and endometriosis. Semin. Reprod. Med. 21(2):145-154.
5. **Foster W** and Hughes C. (2002) Chapter 2:Review of Normal Human Reproduction. In: Principles for Evaluating Human Reproductive Effects of Chemicals. International Programme on Chemical Safety of the World Health Organization.
6. Van Vugt DA, Krzemien A, **Foster W**, Lundhal S, Marcus S, Reid RL. (2000) Photodynamic endometrial ablation in non-human primates. In: Photomedicine in Gynecology and Reproduction. (P. Wyss, Tadir Y, Tromberg BJ, Haller U, eds.) Karger, Basal, Switzerland. 213-218.

iii) **journal articles** –
1. Sadeu JC, Doedée AMCM, **Foster WG**. (2013) Ovarian neurotrophins and effect of bisphenol A (BPA) exposure. Toxicol. Appl. Pharmacol. (*Submitted*).
2. Adlard B, Needham L, **Foster WG,** Rodriguez-Dozal S, Riojas-Rodriguez H, Hernandez M, Weber JP, Walker M, Davis K, Liang CL, Marro L, Wong LY, Curren M, Leech T, Van Oostdam J. (2013) Persistent organic pollutants (POPs) and metals in primiparous women: A comparison from Canada and Mexico. Sci. Total Environ. *(In revision)*.
3. Lehmann GM, Verner MA, Luukinen B, Henning C, Assimon SA, LaKind JS, McLanahan ED, Phillips LJ, Verner MA, Davis MH, Powers CM, Erin HP, Haddad S, Longnecker MP, Poulsen MT, Farrer DG, Marchitti SA, Tan YM, Swartout JC, Sagiv SK, Welsh C, Campbell Jr. JL, **Foster** WG, Yang RSH, Fenton SE, Tornero-Valez R, Francis BM, Barnett JB, El-Masri HA, Simmons JE. (2014) Improving the risk assessment of lipophilic persistent environmental chemicals in breast milk. Crit. Rev. Toxicol. 44(7):600-617.
4. Kay VR, Bloom MS, **Foster WG**. (2014) Reproductive and Developmental Effects of Phthalate Diesters in Males. Crit. Rev. Toxicol. 44(6):467-498.
5. Kubwabo C, Kosarac I, Lalonde K, **Foster WG**. (2014) Quantitative determination of free and total bisphenol A in human urine using labelled BPA-glucuronide and isotope dilution mass spectrometry. Anal. Bioanal. Chem. 406(18):4381-4392.
6. Wessels J, Leyland N, **Foster WG**. (2014) The brain-uterus connection: Brain derived neurotrophic factor (BDNF) and its receptor (Ntrk2) are conserved in the mammalian uterus. PLoS One. 9(4):e94036.
7. Arbuckle TE, Davis K, Marro L, Fisher M, Legrand M, LeBlanc A, Gaudreau E, **Foster WG**, Choeurng V, Fraser WD and the MIREC Study Group. (2014) Phthalate and bisphenol A exposure among pregnant women in Canada – Results from the MIREC study. Environ. Int. 68:55-65.
8. Curren MS, Davis K, Liang CL, Adlard B, Thuppal V, Said F, **Foster WG**, Donaldson S,

Van Oostdam J. (2014) Comparing plasma concentrations of persistent organic pollutants in primiparous women from Northern and Southern Canada. Sci. Total Environ. 1:479-480.

9. Toor K, Wessels JM, Agarwal SK, Leyland NA, **Foster WG**. (2014) Clinical markers of endometriosis: Have we been too quick to judge? Med. Hypotheses. 82(4):493-501.
10. Lamb JC 4th, Boffetta P, **Foster WG**, Goodman JE, Hentz K, Rhomberg LR, Staveley J, Swaen G, Van Der Kraak G, Williams AL. (2014) Critical comments on the WHO-UNEP state of the science on endocrine disrupting chemicals – 2012. Regul. Toxicol. Pharmacol. 69(1):22-40.
11. Rajabi N, Thorpe JB, **Foster WG**, deCatanzaro D. (2013) Novel male exposure reduces uterine e-cadherin, increases uttering luminal area, and diminishes progesterone levels while disrupting blastocyst implantation in inseminated mice. J. Steroid Biochem. Mol. Biol. 139:107-113.
12. Felker AM, Chen Z, **Foster WG**, Croy BA. (2013) Receptors for non-MHC ligands contribute to uterine Natural Killer cell activation during pregnancy in mice. Placenta. 34(9):757-764.
13. Arbuckle TE, Fraser WD, Fisher M, Davis K, Liang CL, Lupien N, Bastien S, Velez MP, von DadelszenP, Hemmings DG, Wang J, Helewa M, Taback S, Sermer M, **Foster W**, Ross G, Fredette P, Smith G, Walker M, Shear R, Dodds L, Ettinger AS, Weber JP, D'Amour M, Legrand M, Kumarathasan P, Vincent R, Luo ZC, Platt RW, Mitchell G, Hidiroglou N, Cockell K, Villeneuve M, Rawn DFK, Dabeka R, Cao XL, Becalski A, Ratnayake N, Bondy G, Jin X, Wang Z, Tittlemier S, Julien P, Avard D, Weiler H, LeBlanc A, Muckle G, Boivin M, Dionne G, Ayotte P, Lanphear B, Séguin JR, Saint-Amour D, Dewailly É, Monnier P, Koren G, Ouellet E. (2013) Cohort Profile: The maternal-infant research on environmental chemicals (MIREC) research platform. Paediatr. Perinat. Epidemiol. 27(4):415-25.
14. Sadeu JC and **Foster WG**. (2013) The cigarette smoke constituent benzo[a]pyrene disrupts metabolic enzyme, and apoptosis pathway member gene expression in ovarian follicles. Reprod. Toxicol. 40:52-59.
15. Siddique S, Sadeu JC, **Foster WG**, Feng YL, and Zhu J. (2013) In vitro exposure to cigarette smoke induces oxidative stress in follicular cells of F1 hybrid mice. J. Appl. Toxicol. 34(2):224-226.
16. Mirshokraei P, Hassanpour H, Rahnama A, **Foster WG**. (2013) Gene expression of BDNF and its receptors, TrkB and p75 in the uterus and oviduct of pregnant and non-pregnant ewes. Res. Vet. Sci. 95(1):164-68.
17. Kay VR, Chambers C, **Foster WG**. (2013) Reproductive and developmental effects of phthalate diesters in females. Crit. Rev. Toxicol. 43(3):200-19.
18. Gannon AM, Stämpfli MR, **Foster WG**. (2013) Cigarette smoke exposure elicits increased autophagy and dysregulation of mitochondrial dynamics in murine granulosa cells. Biol. Reprod. 88(3):63.
19. **Foster WG**, Cheung AP, Davis K, Graves G, Jarrell J, Leblanc A, Liang CL, Leech T, Walker M, Weber JP, Van Oostdam J. (2012) Circulating metals and persistent organic pollutant concentrations in Canadian and non-Canadian born primiparous women from five Canadian centres: results of a pilot biomonitoring study. Sci. Total Environ. 435-436:326-

336.
20. Khoufache K, Bondza PK, Harir N, Daris M, Leboeuf M, Mailloux J, Lemyre M, **Foster W,** Akoum A. (2012) Soluble human IL-1 receptor type 2 inhibits ectopic endometrial tissue implantation and growth: identification of a new potential target for endometriosis treatment. Am. J. Pathol. 181(4):1197-205.
21. Jarrell J, **Foster WG**, Kinniburgh DW. (2012) Phytoestrogens in human pregnancy. Obstet. Gynecol. Int. 2012:850313.
22. Khoufache K, Bazin S, Girard K, Guillemette J, Roy MC, Verreault JP, Al-Abed Y, **Foster W**, Akoum A. (2012) Macrophage migration inhibitory factor antagonist blocks the development of endometriosis in vivo. PLoS One. 7(5):e37264.
23. Rhomberg LR, Goodman JE, **Foster WG**, Borgert CJ, Van Der Kraak G, (2012) A critique of the European Commission document, "State of the Art Assessment of Endocrine Disrupters". Crit. Rev. Toxicol. 42(6):465-73.
24. Clafshenkel WP, King TL, Kotlarczyk MP, Cline JM, **Foster WG,** Davis VL, Witt-Enderby PA. (2012) *Morinda cirtifolia* (Noni) Juice Augments Mammary Gland Differentiation and Reduces Mammary Tumor Growth in Mice Expressing the Unactivated c-*erb*B2 Transgene. Evid. Based Complement Alternat. Med. 2012:487423.
25. Kosarac I, Kubwabo C, Lalonde K, **Foster W**. (2012) A novel method for quantitative determination of free and conjugated bisphenol A in human maternal and umbilical cord blood serum using a two-step solid phase extraction and gas chromatography/tandem mass spectrometry. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 898:90-4.
26. Johnson NA, Ho A, Cline JM, Hughes CL, **Foster WG,** Davis VL. (2012) Accelerated Mammary Tumor Onset in HER2/*Neu* Mouse Model Exposed to DDT Metabolites Locally Delivered to the Mammary Gland. Environ. Health Perspect. 120(8):1170-6.
27. Peery HE, Day GS, Dunn S, Fritzler MJ, Prüss H, De Souza C, Doja A, Mossman K, Resch L, Xia C, Sakic B, Belbeck L, **Foster WG**. (2012) Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev. 11(12):863-72.
28. Sadeu JC, Doedée AM, Neal MS, Hughes EG, **Foster WG**. (2012) Neurotrophins (BDNF and NGF) in follicular fluid of women with different infertility diagnoses. Reprod. Biomed. Online 24(2):174-179.
29. Gannon AM, Stämpfli MR, **Foster WG**. (2012) Cigarette smoke exposure leads to follicle loss via an alternative ovarian cell death pathway in a mouse model. Toxicol. Sci. 125(1):274-284.
30. McCarver G, Bhatia J, Chambers C, Clarke R, Etzel R, **Foster W**, Hoyer P, Leeder JS, Peters JM, Rissman E, Rybak M, Sherman C, Toppair J, Turner K. (2011) NTP-CERHR expert panel report on the developmental toxicity of soy infant formula. Birth Defects Res. B Dev. Reprod. Toxicol. 92(5):421-68.
31. Nethery E, Wheeler AJ, Fisher M, Sjödin A, Li Z, Romanoff LC, **Foster W**, Arbuckle TE. (2012) Urinary polycyclic aromatic hydrocarbons as a biomarker of exposure to PAHs in air: a pilot study among pregnant women. J. Expo. Sci. Environ. Epidemiol. 22(1):70-81.
32. **Foster WG,** Gregorovich S, Morrison KM, Atkinson SA, Kubwabo C, Stewart B, Teo K. (2011) Human maternal and umbilical cord blood concentrations of polybrominated diphenyl ethers. Chemosphere. 84(10):1301-9.

33. Sadeu JC and **Foster WG**. (2011) Cigarette smoke condensate exposure delays follicular development and function in a stage-dependent manner. Fertil. Steril. 95(7):2410-17.
34. Lagunov A, Anzar, M, Sadeu JC, Kahn MI, Bruin JE, Woynillowicz AK, Buhr M, Holloway AC, **Foster WG**. (2011) Effect of *in utero* and lactational nicotine exposure on the male reproductive tract in peripubertal and adult rats. Reprod. Toxicol. 31(4):418-23.
35. Sadeu JC and **Foster WG**. (2011) Effect of *in vitro* exposure to benzo[a]pyrene, a component of cigarette smoke, on folliculogenesis, steroidogenesis and oocyte nuclear maturation. Reprod. Toxicol. 31(4):402-8.
36. Dominguez MA, Cho N, Zhang B, Neal MS, **Foster WG**. (2011) Brain-derived neurotrophic factor expression in granulosa lutein cells. Reprod. Biomed. Online. 22(1):17-24.
37. **Foster WG** and Hughes CL. (2011) Gene expression in oogenesis and implications for transgenerational effects of environmental toxicants. Biol. Reprod. 84(1):2-4.
38. Sadeu JC, Hughes CL, Agarwal S, **Foster WG**. (2010) Alcohol, drugs, caffeine, tobacco, and environmental contaminant exposure: reproductive health consequences and clinical implications. Crit. Rev. Toxicol. 40(7):633-52.
39. Wright D, Gregorovich S, Hamilton S, Lukas P, **Foster WG**. (2010) Environmental chemical exposure research and characteristics of study subjects recruited from midwifery vs. hospital based clinics. CJMRP. 9(3):31-35.
40. Berger RG, **Foster WG**, deCatanzaro D. (2010) Bisphenol-A exposure during the period of blastocyst implantation alters uterine morphology and perturbs measures of estrogen and progesterone receptor expression in mice. Reprod. Toxicol. 30(3):393-400.
41. Neal MS, Mulligan Tuttle AM, Casper RF, Lagunov A, **Foster WG**. (2010) Aryl hydrocarbon receptor antagonists attenuate the deleterious effects of benzo[a]pyrene on isolated rat follicle development. Reprod. Biomed. Online. 21(1):100-108.
42. **Foster WG**, Maharaj-Briceño S, Cyr DG. (2010) Dioxin-induced changes in epididymal sperm count and spermatogenesis. Environ. Health Perspect. 118(4):458-464. Reprinted with permission in: Cien Saude Colet. 16(6):2893-905.
43. Morrison KM, Atkinson SA, Yusuf S, Bourgeois J, McDonald S, McQueen MJ, Persadie R, Hunter B, Pogue J, Teo K; FAMILY investigators. (Holloway A, **Foster W**, Steer P, Denburg J, Cyr M, Windsor S, Mohide P, Capes VS, Vaughn-Williams V, Gross J, Abdalla N, Sim C, Wright C, Sivaguranathan N, Singh P, Helden L, Beecroft ML.) (2009) The Family Atherosclerosis Monitoring In earLY life (FAMILY) study: rationale, design, and baseline data of a study examining the early determinants of atherosclerosis. Am. Heart J. 158(4):533-9.
44. **Foster WG**, Elias R, Faghih M, Dominguez MA, Elit L, Boutross-Tadross O. (2009) Immunohistochemical localization of tyrosine kinases A and B in endometriosis associated ovarian cancer. Histopathology. 54(7):907-912.
45. Tuttle AM, Stämpfli M, **Foster WG**. (2009) Cigarette smoke causes follicle loss in mice ovaries at concentrations representative of human exposure. Hum Reprod. 24(6):1452-1459.
46. Cameron HL and **Foster WG**. (2009) Developmental and lactational exposure to dieldrin alters mammary tumorigenesis in Her2/neu transgenic mice. PLoS One. 4(1):e4303.
47. Davis VL, Jayo MJ, Ho A, Kotlarczyk MP, Hardy ML, **Foster WG**, Hughes CL. (2008)

Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2. Cancer Res. 68(20):8377-8383.
48. Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B, **Foster WG**. (2008) Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ. Res. 108(1):56-62.
49. **Foster WG,** Mirshokraei P, Holloway AC, Zhang B. (2008) Developmental and lactational exposure to environmentally relevant concentrations of dieldrin does not alter pregnancy outcome and mammary gland morphology in BALB/c mice. Environ. Res. 108(1):21-27.
50. **Foster WG.** (2008) Environmental estrogens and endocrine disruption: importance of comparative endocrinology. Endocrinology. 149(9):4267-4268.
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52. **Foster WG.** (2008) Fetal and early postnatal environmental contaminant exposures and reproductive health effects in the female. Fertil. Steril. 89(2 Suppl):e53-54.
53. Phillips KP, **Foster WG**, Leiss W, Sahni V, Karyakina N, Turner MC, Kacew S, Krewski D. (2008) Assessing and managing risks arising from exposure to endocrine-active chemicals. J. Toxicol. Environ. Health B Crit. Rev. 11(3-4):351–372.
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58. Phillips KP and **Foster WG**. (2008) Endocrine toxicants with emphasis on human health risks. J. Toxicol. Environ. Health B Crit. Rev. 11(3-4):149–151.
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changes in aromatase activity in estrogen sensitive target tissues. J. Appl. Toxicol. 28(3):260-270.
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iv) **journal abstracts** – None

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NON-PEER REVIEWED PUBLICATIONS:

i) **journal articles** –

1. **Foster WG** and Moore E. (2008) Chemical Exposures and Infertility. J. Infertility Awareness Association of Canada.
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3. Zhang B and **Foster WG**. (2013) Brain derived neurotrophic factor and Trk B expression correlates with increased metastatic potential of breast cancer cell lines.
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UNPUBLISHED DOCUMENTS:

1. Provisional Patent No. 61889085: An assay for inflammatory disease progression and response to treatment.
2. Provisional Patent No. 796896: Method to predict pregnancy potential of an oocyte.
3. International PCT Application No. PCT/CA2007/002114: Trkβ: a diagnostic tool in endometriosis.

PAPERS GIVEN AT SCIENTIFIC MEETINGS:

i) **invited presentations** –

1. **Foster WG.** Publish or Perish: The pitfalls and tricks to getting your scientific article published. XIII Workshop da Pós-Graduação, Publicação, Pesquisa e Ensino, Salão Nobre da FMB, UNESP, Botucatu/SP, Brazil. June 4 – 7, 2014.
2. **Foster WG.** Endometriosis: Animal models and the role of toxicants. XIII Workshop da Pós-Graduação, Publicação, Pesquisa e Ensino, Salão Nobre da FMB, UNESP, Botucatu/SP, Brazil. June 4 – 7, 2014.
3. **Foster WG.** Por que meu artigo não é aceito? Os erros da escrita cientifica. XIII Workshop da Pós-Graduação, Publicação, Pesquisa e Ensino, Salão Nobre da FMB, UNESP,

Botucatu/SP, Brazil. June 4 – 7, 2014.

4. **Foster WG.** The ovarian effects of environmental toxicants: Clinical implications. The Society of Obstetricians and Gynaecologists of Canada, Ontario CME Program, Toronto, ON. November 28 - 30, 2013.
5. **Foster WG**. Characterization of a novel clinical marker of endometriosis. Grand Rounds, Department of Obstetrics & Gynecology, McMaster University, Hamilton, ON. September 4, 2013.
6. **Foster WG.** Exposure to environmental toxicants and ovarian dysfunction. International Workshop in Neuroendocrinology – Brazilian International Symposium on Integrative Neuroendocrinology. Dourado, Brazil. August 4 – 7, 2013.
7. **Foster WG.** Mechanisms of cigarette smoke induced ovarian follicle loss: The bumpy road to discovery. Graduate Program on General and Applied Biology, Institute of Biosciences of Botucatu, Universidade Estadual Paulista (unesp), Brazil. July 29 – August 2, 2013.
8. **Foster WG**. Clinical markers of endometriosis: what's new? Rounds, Department of Obstetrics & Gynecology, McMaster University. Hamilton, ON. May 29, 2013.
9. **Foster WG**. Strengths and limitations of *in vitro* test methods for reproductive toxicology. 52nd Annual Meeting of the Society of Toxicology. San Antonio, TX. March 10 – 14, 2013.
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14. **Foster WG.** Effects of endocrine disruption on reproductive function in the female. Center for Research in Biology of Reproduction (CRBR) Laval University, QC. December 15, 2011.
15. **Foster WG.** Mechanisms of cigarette smoke-induced sub-optimal ovarian follicle development and atresia. Department of Veterinary Medicine and Biomedical Sciences, Texas A&M University. September 30, 2011.
16. **Foster WG.** Windows of susceptibility: improving understanding of physiological and exposure differences. International Council of Chemical Associations Long-Range Research Initiative (ICCA-LRI) & Health Canada Workshop; Advancing Exposure Science to Improve Chemical Safety. Quebec City, QC. June 22 – 23, 2011.
17. **Foster WG**. Mechanisms of environmental toxicant induced ovarian follicle loss. Department of Reproductive Medicine, Seminars in Reproductive Science and Medicine, University of California San Diego. April 5, 2011.
18. **Foster WG.** The environment and its' implication to cancer and other diseases. The Kiwanis Club of Oakville, monthly meeting. Oakville, ON. November 15, 2010.
19. **Foster WG.** Regulating estrogen production and metabolism in estrogen-dependent diseases. Citywide Rounds. University of Toronto, Mount Sinai Hospital. Toronto, ON.

November 27, 2009.

20. **Foster WG.** Bisphenol A (BPA): science, policy options and risk communication. Improving the Public Communications of Chemical-related Health Risks Workshop. University of Ottawa, ON. September 30 – October 1, 2009.
21. **Foster WG**. Current and emerging issues in reproductive medicine and the placenta biology. 2009 Human Placenta Workshop, Opening Address. Queen's University. Kingston, ON. July 19, 2009.
22. **Foster WG.** Exposure to environmental toxicants and consequences for adverse health effects. Bay Area Restoration Council's 17th Annual Community Workshop – "Looking Beyond 2015". Parks Canada Discovery Centre. Hamilton, ON. April 25, 2009.
23. **Foster WG.** Effects of environmental contaminants on human reproductive health. Hamilton's 3rd Annual Health Research in the City. Hamilton, ON. February 11, 2009.
24. **Foster WG.** Breast Cancer and Environmental Toxicants: New Approaches to Animal Studies in Research, Environment & Health Seminar Series, Centre for Environment. University of Toronto, ON. January 29, 2009.
25. **Foster WG.** Impact of cigarette smoke and its constituents on ovarian function, Public Health Symposium on Infertility. Centers for Disease Control and Prevention. Atlanta, GA. September 15 – 17, 2008.
26. **Foster WG.** The animal evidence: Critical effects and dose-response. Dioxin 2008. 28th International Symposium in Halogenated Persistent Organic Pollutants (POPs). Birmingham, England, UK. August 17 – 22, 2008.
27. **Foster WG.** Bisphenol A: a reproductive hazard but what are the public health implications? Ontario Public Health Unit and Medical Officers of Health Webinar. June 24, 2008.
28. **Foster WG**. Hormone mimics and human health. The 5th PCB Workshop. New Knowledge Gained from Old Pollutants. Iowa City, IA. May 18 – 22, 2008.
29. **Foster WG.** Environmental hazards posed by chemicals and the problems associated with trying to understand the true risk. The Probus Club of Hamilton Mountain, meeting. Hamilton, ON. May 1, 2008.
30. **Foster WG**, Neal MS, Mulligan Tuttle A, Dominguez MA. Impact of environmental factors on ovarian function. Preconception Care Research: Improving Birth Outcomes and Reproductive Health Workshop. Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services. Potomac, MD. April 14 – 15, 2008.
31. **Foster WG.** Reproductive toxicity of environmental toxicants: state of the science and data gaps. CIHR Institute of Human Development and Child and Youth Health Workshop. Montreal, QC. February 11, 2008.
32. **Foster WG.** Reproductive toxicology: Potential hazards and risks to human reproductive health from environmental contaminants. San Diego Reproductive Endocrinology Society. San Diego, CA. November 15, 2007.
33. **Foster WG.** Reproductive toxicity of environmental contaminants: Potential hazards vs. risk to human reproductive health. Reproductive Medicine Grand Rounds. University of California. San Diego, CA. November 14, 2007.

34. **Foster WG.** Reproductive effects of endocrine disrupting compounds. Seminars in Reproductive Science and Medicine. University of California. San Diego, CA. November 14, 2007.
35. **Foster WG.** Cellular and molecular mechanisms of cigarette smoke-induced reproductive toxicity. 2nd Sino-Canada Workshop on Reproductive Medicine. Ottawa, ON. October 19 – 21, 2007.
36. **Foster WG.** Emerging issues in Reproductive Environmental Toxicant Research. UCSF-CHE Summit on Environmental Challenges to Reproductive Health and Fertility. University of California at San Francisco, CA. January 28 – 30, 2007.
37. **Foster WG**. Endocrine Disruption. National Policy Consultation Series on Children's Health and Environment. Ottawa, ON. January 23 – 24, 2007.
38. **Foster WG.** Resistance to Anoikis in estrogen dependent disease. National Institutes of Child Health and Human Development, Division of Epidemiology, Statistics, & Prevention Research. Rockville, MD. January 11, 2007.
39. **Foster WG.** Anoikis in estrogen sensitive target tissues and disease. Department of Anatomy and Physiology, Queen's University. Kingston, ON. December 7, 2006.
40. **Foster WG.** Reproductive effects of endocrine toxicants: From the lab to the clinic. 52nd Annual Meeting of the Canadian Fertility & Andrology Society. Ottawa, ON. November 15 – 18, 2006.
41. **Foster WG.** Environmental toxicants and ovarian function. American Society of Reproductive Immunology. Nashville, TN. June 15 – 17, 2006.
42. **Foster WG.** Ovarian cancer: Mechanisms of action for environmental toxicants and dietary chemicals. National Toxicology Program sponsored Hormonally-induced reproductive tumors: Relevance of rodent bioassays workshop. Raleigh, NC. May 22 – 24, 2006.
43. **Foster WG.** Reproductive effects of environmental endocrine toxicants. First Sino-Canada Bilateral Workshop on Reproductive Health Research. Beijing, China. November 15 – 18, 2005.
44. **Foster WG.** 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induced increase in endometrial aromatase activity is mediated through altered PGE2 metabolism. Institute of Gender and Health Annual Meeting. Vancouver, BC. November 8, 2005.
45. **Foster WG.** Endocrine toxicants and laboratory evidence. Endocrine Toxicants: Ecological and population health impacts. University of Ottawa. Ottawa, ON. October 28, 2005.
46. **Foster WG.** Relative effects of environmental toxicants on aromatase expression and activity in human endometrial stromal cell cultures. NIEHS sponsored workshop on Atrazine. Iowa City, IA. April 25 – 26, 2005.
47. **Foster WG.** Adverse effects of environmental toxicants on female reproduction. Society of Toxicology of Canada, 37th Annual Symposium. Montreal, QC. December 6 – 7, 2004.
48. **Foster WG**. Current context and need for basic research on environmental effects on reproduction. CIHR Workshop, 50th Annual Meeting of the Canadian Fertility & Andrology Society. Jasper, AB. November 24 – 28, 2004.
49. **Foster WG.** Endocrine disrupters and ovarian function. International Federation of Fertility Societies. Montreal, QC. May 23 – 28, 2004.
50. **Foster WG.** Environmental toxicants and breast cancer. Juravinski Cancer Centre.

Hamilton, ON. January 2004.

51. **Foster WG.** *In utero* exposure to endocrine toxicants and dietary phytoestrogens. Linus Pauling Institute, Oregon State University. Corvallis, OR. December 18, 2003.
52. **Foster WG.** Are dioxins involved in the pathogenesis of endometriosis? Department of Pharmacology & Toxicology, and the Department of Obstetrics & Gynecology, Queen's University. Kingston, ON. October 30, 2003.
53. **Foster WG**. Environmental toxicants: ovulation and endometriosis. World Congress on Endometriosis. San Diego, CA. February 24 – 27, 2002.
54. **Foster WG.** and YoungLai EV. Presence of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing *in vitro* fertilization. 28th Aquatic Toxicology Workshop. Winnipeg, MB. September 30 – October 3, 2001.
55. **Foster W.** Chan S. Platt L. and Hughes C. Human developmental exposure to endocrine active compounds. Key Note lecture, 5th International Symposium on Biological Monitoring. Banff, AB. September 18 – 21, 2001.
56. **Foster W.** Human exposure and potential health effects of endocrine disrupting compounds. Symposium # 2. Effects of Pollutants on Humans. Canadian Federation of Biological Societies, 44th Annual Meeting. Ottawa, ON. June 20 – 23, 2001.
57. **Foster WG** and Agarwal SK. Environmental contaminants and dietary factors in endometriosis. Endometriosis: Emerging Research and Intervention Strategies. National Institute of Child Health and Human Development. Bethesda, MD. April 9 – 10, 2001.
58. **Foster WG**. Effects of environmental contaminants on ectopic endometrium in animal models of endometriosis. University of Laval. Quebec City, QC. November 18, 2000.
59. **Foster WG**. Environmental contaminants - effects upon human reproductive physiology. Grand Rounds. Cedars-Sinai Medical Center. Los Angeles, CA. August 16, 2000.
60. **Foster WG**, Chan S, Platt L, Hughes CL. Detection of organochlorine compounds and phytoestrogens in second trimester human amniotic fluid. Int. Assoc. Great Lakes Res. Cornwall, ON. May 22 – 26, 2000.
61. **Foster WG**. Effects of environmental contaminants on ectopic endometrium in animal models of endometriosis. University of Western Ontario. London, ON. April 20, 2000.
62. **Foster WG**, Hughes CL. An overview of endocrine disruption and human health. Endocrine Disruption Workshop: Establishing a National Science Agenda on the scientific assessment of endocrine disrupting substances. Huntsville, ON. February 17 – 19, 2000.
63. **Foster WG**. Environmental contaminants and dietary factors: Consequence for human health. University of Ottawa. Ottawa, ON. November 18, 1999.
64. **Foster WG**, Hughes CL, Platt L, Chan S. Detection of Endocrine Disrupting Chemicals and Dietary Factors in Samples of Second Trimester Human Amniotic Fluid. Environmental Hormones: Past, Present, Future. Tulane University. New Orleans, LA. October 18 – 20, 1999.
65. **Foster WG**, EU/US Transatlantic Co-operation in Human Environmental Health; Expert Panel Meeting on Opportunities for Collaborative EU/US Research Programmes. Ispra, Italy. April 1999.
66. **Foster WG**. 1999 Special Meeting of the Toxicology Forum: Dose-Response Considerations for Potential Endocrine Active Substances. Washington, DC. April 1999.

67. **Foster WG**. Endocrine Disruptors and Human Health Effects: Health Canada Perspective. Southern Ontario Reproductive Biology Workshop. University of Waterloo. Waterloo, ON. May 8, 1998.
68. **Foster WG**. Endocrine Disruptors Panel Member. Health Conference. Montreal, QC. May 15 – 17, 1997.
69. **Foster WG**. Human health effects of endocrine modulating substances: fact or fiction? Grand Rounds, Department of Obstetrics & Gynaecology, McMaster University. Hamilton, ON. May 21, 1997.
70. **Foster WG**. Endocrine Disruptors: Potential Risks to Children. What on Earth Conference sponsored by the Canadian Institute of Child Health. Ottawa, ON. May 26 – 27, 1997.
71. **Foster WG**. White House expert committee on endocrine disrupters. Washington, DC. January 27, 1997.
72. **Foster WG**. Environmental Exposures and Human Reproduction: Women. Reproductive Health and The Environment Symposium. Toronto Department of Health. Toronto, ON. May 1996.
73. **Foster WG**. Endocrine Disruptors Chemicals: The Human Connection. DOE Workshop on Endocrine Disrupter Issue. Hull, QC. May 1996.
74. **Foster WG**. Endocrine Disruptors: Human Health Effects. Canadian Chemical Producers Association. Ottawa, ON. June 1996.
75. **Foster WG**. Animal models in reproductive biology and toxicology. Canadian Association for Laboratory Animal Science. Ottawa, ON. June 2, 1994.
76. **Foster WG**. Steroid actions on Endometriotic Tissue. Canadian Workshop on Human Reproduction and Reproductive Biology "From Bench to Bedside". Miami, FL. April 25 – 29, 1994.
77. **Foster WG**. Environmental contaminants and adverse reproductive health outcomes: Current status and future directions. University of Laval. Quebec City, QC. March 25, 1994.
78. **Foster WG**. Biomarkers in Reproduction: Effects in females. IPCS/Australian workshop on Biomarkers. Adelaide, Australia. October 11 – 15, 1993.
79. **Foster WG**, McMahon A, Rice D. The reproductive effects of chronic Lead exposure male cynomolgus monkey. Loebb Research Institute, Ottawa Civic Hospital, University of Ottawa. Ottawa, ON. January 1993.
80. **Foster WG**, McMahon A, Rice D. The reproductive effects of chronic Lead exposure male cynomolgus monkey. Canadian Wildlife Service. Hull, QC. January 1993.
81. **Foster WG**. Environmental Contaminants and Reproduction. Toxicology Research Division Seminar Series. Ottawa, ON. January 1993.
82. **Foster WG**. Session Moderator: Ovarian Function. 12th Annual Ottawa Reproductive Biology Workshop and 1993 Southern Ontario Reproductive Biology Meeting. May 25 – 26, 1993.
83. **Foster WG**. Environmental Contaminants and Reproduction. Ontario Farm Women's Association. Guelph, ON. June 1993.
84. **Foster WG**, McMahon A, Rice D. Reproductive toxicity of chronic Lead-exposure in the female and male cynomolgus monkey. Symposium On Lead In Adults. Durham, NC.

December 9 – 11, 1991.

ii) **contributions to peer reviewed presentations –**

1. Curren MS, Davis K, Liang CL, Adlard B, **Foster WG,** Donaldson SG, Kandola K, Brewster J, Potyrala M, Van Oostam J. Comparison of persistent pollutants (POPs) and metals in primiparous women from Canada and Mexico. 26th Annual Conference of the International Society for Environmental Epidemiology. Seattle, WA. August 24 – 28, 2014.
2. Agarwal SK and **Foster WG**. Medical shrinkage of endometriomas with aromatase inhibition and progestin add-back. 69th Annual Meeting of the American Society of Reproductive Medicine. Boston, MA. October 12 – 17, 2013.
3. Wessels JM, Leyland NA, Agarwal SK, Murji A, **Foster WG**. Can brain-derived neurotrophic factor be a clinical marker for endometriosis? 69th Annual Meeting of the American Society of Reproductive Medicine. Boston, MA. October 12 – 17, 2013.
4. Wessels J, Leyland N, **Foster WG**. The brain-uterus connection: Uterine expression of brain-derived neurotrophic factor (BDNF) and its receptor vary over the estrous cycle. 46th Annual Meeting of the Society for the Study of Reproduction. Palais des congress de Montréal. Montreal, QC. July 22 – 26, 2013.
5. Curren MS, Liang CL, Davis K, Thuppal V, Said F, Adlard B, Donaldson S, Kandola K, Brewster J, **Foster WG**, Van Oostdam J. Examination of contaminant exposures for populations from northern and southern Canada. Environmental Health 2013, Boston, MA. March, 2013.
6. Gannon AM, Stämpfli MR, **Foster WG**. Dysregulation of mitochondrial dynamics and activation of the autophagy cascade occur in a mouse model of cigarette smoke-induced ovarian follicle loss. 68th Annual Meeting of the American Society of Reproductive Medicine. San Diego, CA. October 20 – 24, 2012.
7. Sadeu JC and **Foster WG**. Mechanism of benzo[a]pyrene-induced inhibition of follicle growth and dysfunction. 68th Annual Meeting of the American Society of Reproductive Medicine. San Diego, CA. October 20 – 24, 2012.
8. Sadeu JC and **Foster WG**. In vitro exposure to benzo[a]pyrene alters the expression of factors controlling follicle growth. 58th Annual Meeting of the Canadian Fertility & Andrology Society. Ottawa, ON. September 6 – 9, 2012.
9. Gannon AM, Stämpfli MR, **Foster WG**. Cigarette smoke exposure triggers dysregulation of mitochondrial dynamics, leading to autophagy-mediated ovarian follicle loss in a mouse model. 45th Annual Meeting of the Society for the Study of Reproduction. Pennsylvania State University. State College, PA. August 12 – 15, 2012.
10. Wessels J and **Foster WG**. Uterine expression of brain-derived neurotrophic factor (BDNF) and its receptor during the estrous cycle and menstrual cycle. 45th Annual Meeting of the Society for the Study of Reproduction. Pennsylvania State University. State College, PA. August 12 – 15, 2012.
11. Sadeu JC, Doedée AM, Neal M, Hughes EG, **Foster WG**. Neurotrophins (BDNF and NGF) in ovarian follicular fluid of women with different infertility diagnoses. 57th Annual Meeting of the Canadian Fertility & Andrology Society. Toronto, ON. September 21 – September 24, 2011.

12. Gannon AM, Stämpfli MR, **Foster WG**. Cigarette smoke exposure triggers autophagy-mediated ovarian follicle loss in a mouse model. 44th Annual Meeting of the Society for the Study of Reproduction. Oregon Convention Center. Portland, OR. July 31 – August 4, 2011.
13. Sadeu JC, Doedée AM, **Foster WG**. Localization of ovarian neurotrophins (BDNF, NT-4/5 & NGF) and their receptors (Trk B & p^{75NTR}): Role in follicle growth. 2011 Annual Ottawa Reproductive Biology Workshop. Ottawa, ON. June 17, 2011.
14. Cameron H and **Foster WG.** Endocrine toxicants promote resistance to anoikis and invasiveness of breast cancer cells *in vitro.* 50th Anniversary Annual Meeting & ToxExpo, Society of Toxicology. Washington, DC. March 6 – 10, 2011.
15. Mulligan Tuttle AM, Stämpfli M, **Foster WG**. Cigarette smoke exposure results in significant follicle loss via an alternative ovarian cell death pathway. 50th Anniversary Annual Meeting & ToxExpo, Society of Toxicology. Washington, DC. March 6 – 10, 2011.
16. Sadeu JC and **Foster WG.** Cigarette smoke condensate inhibits follicular development, oocyte maturation and dysregulates steroids synthesis *in vitro*: Implications for human fecundity. 50th Anniversary Annual Meeting & ToxExpo, Society of Toxicology. Washington, DC. March 6 – 10, 2011.
17. Johnson NA, Meng WS, Witt-Enderby PA, **Foster WG,** Davis VL. Localized exposure to DDT congeners influence mammary gene expression. 50th Anniversary Annual Meeting & ToxExpo, Society of Toxicology. Washington, DC. March 6 – 10, 2011.
18. Sadeu JC and **Foster WG**. Cigarette smoke condensate (CSC) inhibits follicular development, oocyte nuclear maturation and disrupts progesterone synthesis *in vitro*: Implications for human fecundity. 56th Annual Meeting of the Canadian Fertility & Andrology Society. Vancouver, BC. September 29 – October 2, 2010.
19. Doedée A, Sadeu JC, **Foster W**G. The effects of bisphenol A (BPA) on the expression of neurotrophins (NTs) and neurotrophin receptors (NTRs) during *in vitro* follicle growth. 56th Annual Meeting of the Canadian Fertility & Andrology Society. Vancouver, BC. September 29 – October 2, 2010.
20. Mulligan Tuttle A and **Foster WG**. Cigarette smoke exposure results in significant follicle loss and decreased pro-survival expression in an *in vivo* mouse model. 56th Annual Meeting of the Canadian Fertility & Andrology Society. Vancouver, BC. September 29 – October 2, 2010.
21. Mallach G, Davidson A, Arbuckle T, Nethery E, Van Ryswk K, You H, Fisher M, **Foster W**, Moore E, Ripley D, Wheeler AJ. Assessing the Value of Including GPS in Personal Exposure Monitoring. ISES-ISEE 2010 Joint Conference of International Society of Exposure Science & International Society for Environmental Epidemiology. Seoul, Korea. August 28 – September 1, 2010.
22. Sadeu JC and **Foster WG.** Benzo[a]pyrene (B[a]P)-treatment at concentrations representative of human exposure attenuates ovarian follicle development and survival. 49th Annual Meeting of the Society of Toxicology. Salt Lake City, UT. March 7 – 11, 2010.
23. Lagunov A, Sadeu JC, Bruin JE, Woynillowicz AK, Anzar M, Khan MIR, Buhr M, Holloway AC, **Foster WG**. Effect of *in utero* and lactational nicotine exposure on the male reproductive tract in pubertal and adult rats. 55th Annual Meeting of the Canadian Fertility & Andrology Society. Montreal, QC. November 18 – 21, 2009.

24. Neal MS and **Foster WG**. Aryl hydrocarbon receptor (AhR) antagonists attenuates the deleterious effect of benzo[a]pyrene on isolated rat follicle growth *in vitro*. 54th Annual Meeting of the Canadian Fertility & Andrology Society. Calgary, AB. November 26 – 29, 2008.
25. Dominguez MA, Zhang B, **Foster WG**. BDNF and Trk B expression in the mouse ovary. 54th Annual Meeting of the Canadian Fertility & Andrology Society. Calgary, AB. November 26 – 29, 2008.
26. Mulligan Tuttle A, Stämpfli M, **Foster WG**. *In vivo* and *in vitro* follicle loss caused by cigarette smoke and benzo[a]pyrene exposure at physiologically relevant concentrations. 54th Annual Meeting of the Canadian Fertility & Andrology Society. Calgary, AB. November 26 – 29, 2008.
27. Boutross-Tadross O, Faghih M, Elias R, Elit L, **Foster WG**. Immunolocalization of tyrosine kinase receptor B (TrkB) expression in endometriosis associated ovarian cancer (EAOC) cells. 3rd Intercontinental Congress of Pathology. Barcelona, Spain. May 17 – 22, 2008.
28. Mulligan Tuttle A and **Foster WG**. Cigarette smoke and benzo[a]pyrene cause follicle loss *in vivo* and *in vitro* at physiologically relevant concentrations. 47Th Annual Meeting of the Society of Toxicology. Seattle, WA. March 16 – 20, 2008.
29. Monroy R, Bourgeois J, Shaw D, Morrison K, Atkinson S, Teo K, **Foster WG**. Effects of cigarette smoking in pregnancy on the placenta vasculosyncytial membrane thickness. 47th Annual Meeting of the Society of Toxicology. Seattle, WA. March 16 – 20, 2008.
30. Mulligan Tuttle A and **Foster WG.** Cigarette smoke causes follicle loss *in vivo* at physiologically relevant concentrations. 4th Annual Invitational Symposium for Research to Inform tobacco Control. A pre-conference symposium at the Society for Research on Nicotine and Tobacco Annual Conference. Portland, OR. February 2008.
31. Davis VL, Johnson NA, Jayo MJ, Hughes CL, **Foster WG**. Localized exposure to *p,p'* DDE accelerates mammary tumor development in MMTV-*neu* transgenic mice. Future Research on Endocrine Disruption: Translation of Basic and Animal Research to Understand Human Disease. Durham, NC. August 27 – 29, 2007.
32. Monroy R, Bourgeois J, Shaw D, Morrison K, Teo K, Atkinson S, **Foster WG**. Effects of maternal smoking on the placenta vasculosyncytial membrane thickness. 13th International Federation of Placenta Associations. Kingston, ON. August 17 – 22, 2007. Poster of Mention and Y. W. Loke New Investigator Award.
33. Cameron HL and **Foster WG.** The organochlorine pesticide dieldrin increases resistance to anoikis and invasiveness of breast cancer cells *in vitro.* American Association for Cancer Research Edward A. Smuckler Memorial Pathobiology of Cancer Workshop, Snowmass Village, CO. July 15 – 22, 2007.
34. Faghih M, Elias R, Boutross-Tadross O, Elit L, **Foster WG**. Immunolocalization of tyrosine kinase receptor B (TrkB) expression in endometriosis associated ovarian cancer (EAOC) cells. Society of Gynaecologists of Canada Annual Clinical Meeting. June 23, 2007.
35. Cameron HL and **Foster WG.** Developmental and lactational exposure to environmentally relevant concentrations of dieldrin in neu/ErB2 transgenic mice. American Association for Cancer Research special conference. Albuquerque, NM. May 30 – June 2, 2007.
36. Neal M, Holloway AC, **Foster WG**. Ovotoxicity of benzo[a]pyrene and the ovarian

protective effects of aryl hydrocarbon receptor antagonist. 52nd Annual Meeting of the Canadian Fertility & Andrology Society Meeting. Ottawa, ON. November 15 – 18, 2006. Organon Canada Ltd. Ontario Region Student/Resident Award.

37. **Foster WG**, Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C. Serum Levels of perfluorinated compounds in human maternal and umbilical cord blood samples. International Council of Chemical Associations. Minneapolis, MN. July 26 – 27, 2006.
38. Neal MS, Petrik J, **Foster WG**, Holloway AC. *In utero* and lactational exposure to nicotine: ovarian effects. Conjoint American Society for Reproductive Medicine and Canadian Fertility & Andrology Society Meeting. Montreal, QC. October 16 – 19, 2005. Best Basic Science Paper and Alpha Award.
39. Neal MS, Zhu J, **Foster WG**. Quantification of benzo-[*a*]-pyrene (B[*a*]P) in serum and follicular fluid and its effects on follicle growth in an isolated follicle culture assay. Conjoint American Society for Reproductive Medicine and Canadian Fertility & Andrology Society Meeting. Montreal, QC. October 16 – 19, 2005.
40. Stys KA, Zhang B, Holloway AC, **Foster WG**. Dioxin-induced changes in endometrial aromatase expression and activity. Society for the Study of Reproduction. Quebec City, QC. July 24 – 27, 2005.
41. Neal MS, Lim GE, YoungLai EV, Daya S, Holloway AC, **Foster WG**. Aromatase activity in granulosa cells as a predictor of pregnancy. International Federation of Fertility Societies. Montreal, QC. May 23 – 28, 2004.
42. **Foster WG**, Agarwal SK, Holloway AC. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induced increased endometrial aromatase activity is mediated through altered PGE_2 metabolism. 51st Annual Meeting of the Society for Gynecologic Investigation. Huston, TX. March 24 – 27, 2004.
43. Edmunds KE, Holloway AC, Beecroft ML, Daya SH, Crankshaw DJ, **Foster WG**. The effects of dietary phytoestrogens on aromatase activity in endometrial stromal cell cultures. 51st Annual Meeting of the Society for Gynecologic Investigation. Houston TX. March 24 – 27, 2004.
44. Lim GE, Stals SI, **Foster WG**, Petrik JJ, Holloway AC. Fetal exposure to water disinfection byproducts alters postnatal growth and glucose homeostasis. 51st Annual Meeting of the Society for Gynecologic Investigation. Houston TX. March 24 – 27, 2004.
45. **Foster WG**, Wade MG, Hughes CL, YoungLai EV. Developmental exposure to a complex mixture of environmental toxicants interacts with postnatal genistein to induce changes in reproductive development of female Sprague Dawley rats. 43rd Annual Meeting of the Society of Toxicology. Baltimore, MD. March 21 – 25, 2004.
46. YoungLai E, Holloway A, Lim G, Neal M, **Foster W.** Synergistic effects of FSH & DDE on human granulosa cell aromatase. 49th Annual Meeting of the Canadian Fertility & Andrology Society. Victoria, BC. November 5 – 8, 2003.
47. YoungLai E, Kakuda N, Neal M, **Foster W**, Buhr M. Additive effects of progesterone & DDE on calcium flux in human sperm. 49th Annual Meeting of the Canadian Fertility & Andrology Society. Victoria, BC. November 5 – 8, 2003.
48. Neal M, Holloway A, Hughes E, **Foster W**. Effect of sidestream and mainstream smoking on IVF outcomes. 49th Annual Meeting of the Canadian Fertility & Andrology Society.

Victoria, BC. November 5 – 8, 2003.

49. Chomej A, Holloway A, **Foster W**. Effects of Bisphenol A on tissue remodeling enzymes in human luteinized granulosa cells *in vitro*. 49th Annual Meeting of the Canadian Fertility & Andrology Society. Victoria, BC. November 5 – 8, 2003.
50. Miller M, Holloway AC, **Foster WG**. Benzo-a-pyrene alters invasion in human breast cancer cell lines BT-474 and MDA-MB-231 through altered prostaglandin E_2 (PGE_2) metabolism. 2nd Annual AACR International Conference, Frontiers in Cancer Prevention Research. Phoenix, AZ. October 26 – 30, 2003.
51. Holloway A, Beecroft ML, Sinasac S, YoungLai E, Daya S, Edmunds K, **Foster WG**. Environmental Toxicant Induced Changes in Aromatase Activity in Estrogen Sensitive Target Tissues. Society for the Study of Reproduction, 36th Annual Meeting. Cincinnati, OH. July 19 – 22, 2003.
52. WWW.EMCOM.CA - A risk communication vehicle about endocrine disruption. Phillips KP, Aronson KJ, Brunet P, **Foster WG**, Kacew S, Leiss W, Mehta M, Poirier R, Salem T, Van Der Kraak G, Wade MG, Walker M, Wigle D, Krewski D. Society for the Study of Reproduction, 36th Annual Meeting. Cincinnati, OH. July 19 – 22, 2003.
53. Davis VL, Jayo MJ, Hardy ML, Ho A, Shaikh F, Lee H, **Foster WG**, Hughes CL. Effects of black cohosh on mammary tumor development and progression in MMTV-*neu* transgenic mice. American Association of Cancer Researchers. Washington, DC. July 11 – 14, 2003.
54. Davis VL, **Foster W**, Jayo M, Ho A, Shaikh F, Lee H, Hughes C. Influence of Locally Stored DDT Metabolites on Mammary Cancer Development induced by the *neu* proto-oncogene. American Association of Cancer Researchers. Washington, DC. July 11 – 14, 2003.
55. Hughes CL, Davis V, Shaikh F, Villegas M, Ho A, **Foster WG.** The effects of *in utero* and Lactational Exposure to Genistein or Daidzein on reproductive development in FVB/N mice and occurrence of mammary tumors in MMTV-*neu* transgenic mice. US-EPA Sponsored Endocrine Disruptors Workshop. Research Triangle Park, NC. October 29 – 31, 2002.
56. **Foster W**, Sinasac S, Holloway A. Histopathological changes in endometrial stroma and epithelium of 2,3,7,8-tettachlorodibenzo-*p*-dioxin (TCDD) treated monkeys. 48th Annual Meeting of the Canadian Fertility & Andrology Society. Charlevoix, QC. September 25 – 28, 2002.
57. **Foster WG**, Daya SH, Holloway AC. Inappropriate estrogen production induced by environmental toxicants. 48th Annual Meeting of the Canadian Fertility & Andrology Society. Charlevoix, QC. September 25 – 28, 2002.
58. Davis VL, Villegas M, Shaikh F, Ho A, **Foster WG**, Hughes CL. The Effects of *in Utero* and Lactational Exposure to the Soy Isoflavones, Genistein and Daidzein, on Reproductive Development of Male and Female Mice. Society for Gynecologic Investigation. Los Angeles, CA. March 20 – 24, 2002.
59. Helliwell J, Agarwal SK, **Foster WG**. Endometriosis and rheumatological disease: An observational study using diagnostic criteria from the American Board or Rheumatology. Society of Gynecologic Investigation. Los Angeles, CA. March 20 – 24, 2002.
60. Rodriquez S, Estrada S, **Foster W,** Agarwal SK. What motivates women to take part in clinical and basic science endometriosis research? World Congress on Endometriosis. San

Diego, CA. February 24 – 27, 2002.

61. Agarwal SK, Estrada S, **Foster WG**. Pilot study evaluating the efficacy of delorelin with add-back low-dose sex steroids for the treatment of pelvic pain secondary to laparoscopically confirmed endometriosis. World Congress on Endometriosis. San Diego, CA. February 24 – 27, 2002.
62. **Foster WG**. Yang JZ. Fournier M. Immunological effects of 2,3,7,8-tetrachlorodiebnzo-p-dioxin (TCDD) in monkeys with endometriosis. 47th Annual Meeting of the Canadian Fertility & Andrology Society. Whistler, BC. October 3 – 6, 2001.
63. YoungLai EV. Wade MG. **Foster WG**, Hughes CL. Endocrine disrupting effects of a mixture of environmentally relevant pollutants in the pregnant female. 47th Annual Meeting of the Canadian Fertility & Andrology Society. Whistler, BC. October 3 – 6, 2001.
64. Wade MG, **Foster WG**, YoungLai EV, Desaulniers D, Hughes CL. Thyroid and reproductive effects of *in utero*/lactational exposure to a mixture of persistent environmental contaminants. Canadian Federation of Biological Societies, 44th Annual Meeting. Ottawa, ON, June 20 – 23, 2001.
65. Agarwal SK, Surrey MW, **Foster WG**, Harris R. The occurrence of and screening for appendiceal disease in women with endometriosis and right lower quadrant pain. 49th Annual Meeting of the Pacific Coast Reproductive Society. Rancho Mirage, CA. April 2001.
66. **Foster WG**, Chan S, Platt L, Hughes C. Detection of phytoestrogens in samples of second trimester human amniotic fluid. 46th Annual Meeting of the Canadian Fertility & Andrology Society. St. John's, NL. September 13 – 16, 2000.
67. Liu G, Blas-Machado U, Duong Q, Lee H, **Foster WG**, Davis VL, Magoffin DA, Hughes CL. Long-term exposure to high lactose diet fails to induce ovarian dysfunction in Long Evans rats. Society for the Study of Reproduction. Madison, WI. July 15 – 18, 2000.
68. Shridhar S, Farley A, Reid RL, **Foster W**, Van Vugt DA. Tetrachlorodibenzo-p-dioxin (TCDD) on gene expression of Corticotropin Releasing Hormone, Arginine Vasopressin, and Pro-opiomelanocortin in the hypothalamus of non-human primates. 82nd Annual Meeting of the Endocrine Society. Toronto, ON. June 21 – 24, 2000.
69. YoungLai EV, **Foster WG**, Wade MG, Hughes CL. Effect of a mixture of environmental contaminants on the male rat. American Society of Andrology. Boston, MA. April 7 – 11, 2000.
70. Hughes C, **Foster W**, Platt L, Chan S, Thompson S, Hubbard S, DuBose A, Tyrey L. Midgestation intrauterine exposure of the human fetus to dietary isoflavones in North America: How does this exposure compare to animal studies in late gestation and lactation that alter developmental endpoints. Third International Symposium on The Role of Soy in Preventing and Treating Chronic Disease. Washington, DC. October 31 – November 3, 1999.
71. **Foster WG**, Chan S, Platt L, Hughes C. *In utero* exposure of the human fetus to xenobiotics endocrine disrupting chemicals: Detection of organochlorine compounds in samples of second trimester human amniotic fluid. 81st Endocrine Society Annual Meeting. San Diego, CA. June 12 – 15, 1999.
72. Douglas GR, Gingerich JD, Soper LM, McMahon A, **Foster WG**. Gene mutations in

follicular granulosa cells of super-ovulated lacZ transgenic mice. Environmental Mutagen Society Meeting. Washington, DC. March 27 – April 1, 1999.

73. Desaulniers D, Leingartner K, Cooke GM, Wade M, Yang J, Yagminas A, **Foster WG**. Effects of a "Human-milk PCB-DDT-DDE" mixture on MCF-7 cell proliferation *in vitro* and on nitrosomethylurea-induced mammary tumours in the rat. Society of Toxicology of Canada. Montreal, QC. December 2 – 3, 1998.
74. Ruka MP, Gareau PJ, Janzen EG, **Foster WG**. Use of MRI T1/T2 weighted images to evaluate the lesions in surgically induced endometriosis in a mouse model. Royal College of Physicians and Surgeons Annual Meeting. Toronto, ON. September 24 – 27, 1998.
75. Desaulniers D, Leingartner K, Fintelman E, Wade M, Yagminas A, **Foster WG**. Relative sensitivity of several endocrine biomarkers following acute exposure to PCB-126 and 153 in adult Sprague Dawley male rats. Health Conference '97. Montreal, QC. May 12 – 15, 1997.
76. Buttar HS, Moffatt JH, McMahon A, **Foster WG**. Sperm motility analysis, sperm chromatin strucutre assay and serum hormone assessment in alph-chlorohydrin treated rats. Society of Teratology. Palm Beach, FL. June 21 – 27, 1997.
77. Van Vugt DA, Kizemian A, Roy BN, **Foster W**, Lundahl S, Marcus S, Reid RL. Photodynamic endometrial ablation in non-human primates. 42nd Annual Meeting of the Canadian Fertility & Andrology Society. Lake Louise, AB. November 20 – 23, 1996.
78. Yang JZ, **Foster WG**. Repeated exposure to TCDD inhibits growth of surgically induced endometriosis in the mouse. Society for the Study of Reproduction. London ON. 1996.
79. Van Vugt DA, Kizemian A, Roy BN, **Foster W**, Lundahl S, Marcus S, Reid RL. Photodynamic endometrial ablation in rhesus monkeys: 22nd Annual Meeting of the Society of Obstetrics & Gynaecology Canada. 1996.
80. **Foster WG**, Desaulniers D, Chu I, Poon R. Reproductive effects of tris (4-chlorophenyl) methanol in the male rat. 41st Annual Meeting of the Canadian Fertility & Andrology Society. Montebello, QC. September 19 – 23, 1995.
81. Jarrell JF, Gocmen A, **Foster WG**. A long-term review of the human reproductive outcomes of inadvertent exposure to hexachlorobenzene. 41st Annual Meeting of the Canadian Fertility & Andrology Society. Montebello, QC. September 19 – 23, 1995.
82. Yang JZ, Van Vugt DA, Reid RL, **Foster WG**. Intrauterine 5-aminolevulinic acid induces selective endometrial photosensitization in the Rhesus and Cynomolgus monkeys. 41st Annual Meeting of the Canadian Fertility & Andrology Society. Montebello, QC. September 19 – 23, 1995.
83. YoungLai EV, **Foster WG**, Jarrell JF. Relationship between environmental contaminants in human reproductive fluids and results of *in vitro* fertilization. 41st Annual Meeting of the Canadian Fertility & Andrology Society. Montebello, QC. September 19 – 23, 1995.
84. Ruka MP, McCutcheon JL, Gareau PJ, **Foster WG**, Janzen EG. Surgically-induced model of endometriosis in B6C3F1 mice. Royal College of Physicians & Surgeons of Canada, 64th Annual Meeting. Montreal QC, September 13 - 17, 1995.
85. Ruka MP, McCutcheon JL, Gareau PJ, **Foster WG**, Janzen EG. Evaluation of estrogen/progesterone treatment on the functional integrity of the endometrium temporally exposed to warm ischemia prior to its auto-transplantation. Royal College of Physicians & Surgeons of Canada, 64th Annual Meeting. Montreal, QC. September 13 – 17, 1995.

86. **Foster WG**, Rice DC, McMahon A, Reed BL. Altered semen quality in Cynomolgus monkeys with occupationally relevant circulating concentrations of lead. Society for the Study of Reproduction. Davis, CA. July 9 – 12, 1995.
87. Desaulniers DM, Leingartner K, Stoddart K, **Foster WG**. Development of an *in vitro* bioassay to assess the estrogenic potential of xenobiotics using cloned and wild types MCF-7 cells. Society for the Study of Reproduction. Davis, CA. July 9 – 12, 1995.
88. Desaulniers D, Leingartner K, **Foster WG**. Comparison of proliferation indices derived from 3H-thymidine incorporation and the metabolic reduction of alamar blue (Tm) in estradiol-stimulated human breast cancer cells. 14th Annual Ottawa Reproductive Biology Workshop. Ottawa, ON. June 2 – 3, 1995.
89. **Foster WG**, Jarrell JF, YoungLai EV. Preliminary results of a survey of contaminants present in serum and follicular fluid of women participating in fertility clinics in six Canadian cities. Southern Ontario Reproductive Biology Workshop. Kingston, ON. May 5, 1995.
90. **Foster WG**, McMahon A, Reed BL, Rice DC. Flow cytometric and conventional analysis of semen from chronically lead exposed Cynomolgus monkeys (Macaca fasicularis). Southern Ontario Reproductive Biology Workshop. Kingston, ON. May 5, 1995.
91. YoungLai EV, Baillie J, Yie S-M, Hughes EG, Collins JA, **Foster WG**. Acrosin activity in frozen sperm samples does not correlate with *in vitro* fertilization of human oocytes. International Federation of Gynaecology & Obstetrics (FIGO). Montreal, QC. September 24 – 30, 1994.
92. **Foster WG**, Rice DC, McMahon A. Suppression of luteal function in the chronically lead exposed cynomolgus monkey (*Macaca fascicularis*). 40th Annual Meeting of the Canadian Fertility & Andrology Society. St. John, NB. September 7 – 10, 1994.
93. **Foster WG**, Yagminas A, McMahon A. Reverse phase HPLC demonstration of cortisol, corticosterone, progesterone, and 17 a-hydroxyprogesterone in rat serum. 40th Annual Meeting of the Canadian Fertility & Andrology Society. St. John, NB. September 7 – 10, 1994.
94. YoungLai EV, Yie S-M, Hughes EG, Collins JA, **Foster WG**. Seasonal variation in hormones in human follicular fluid and granulosa cell steroidogenesis. 40th Annual Meeting of the Canadian Fertility & Andrology Society. St. John, NB. September 7 – 10, 1994.
95. **Foster WG**, McMahon A, YoungLai EV, Hughes EG. Ovarian toxicity of hexachlorobenzene in the cynomolgus monkey (*Macaca fascicularis*). Society for the Study of Reproduction, 27th Annual Meeting. Ann Arbor, MI. August 24 – 27, 1994.
96. **Foster WG**. Alterations in ovarian function following exposure to hexachlorobenzene (HCB) in the rodent and primate model. 13th Annual Ottawa Reproductive Biology Workshop. Ottawa, ON. June 8, 1994.
97. **Foster WG**, Rice DC, McMahon A. Adverse effects of low circulating lead levels on menstrual cycle characteristics in the monkey. Southern Ontario Reproductive Biology Workshop (SORB), Hamilton, ON. May 6, 1994.
98. **Foster WG**. Steroid actions on endometriotic tissue. The Canadian Workshop on Human Reproduction and Reproductive Biology. Miami, FL. April 25 – 29, 1994.
99. Singh A, Bourque A, Lakhanpal N, McMahon A, **Foster WG**. Electron microscopy of

ovary from the monkey administered hexachlorobenzne. Society of Toxicology. Dallas, TX. March 12 – 18, 1994.

100. Bourque A, Singh A, Dykeman A, McMahon A, **Foster W**. Hexachlorobenzene at low doses produces lesions in nonhuman primate ovary. 26th Annual Meeting of the USGEB/USSBE. University of Bern, Switzerland. March 17 – 18, 1994.
101. **Foster WG**, McMahon A, YoungLai EV, Hughes EG. Ovarian toxicity of hexachlorobenzene in the cynomolgus monkey (*Macaca fascicularis*). Montreal area Reproductive and Developmental Biologists First Annual Research Day. Montreal, QC. November 15, 1993.
102. **Foster WG**. Biomarkers in Reproduction - Effects in females. IPCS/Australian Workshop on Biomarkers. Adelaide, Australia. October 11 – 15, 1993.
103. Cullen C, Singh A, **Foster WG**. Electron microscopy of monkey seminal vesicle. 159th National Meeting of the American Association for the Advancement of Science. Boston, MA. February 11 – 16, 1993.
104. **Foster WG**, McMahon A. Effects of organochlorine contaminants on steroidogenesis in the rat. 12th Annual Ottawa Reproductive Biology Workshop and 1993 Southern Ontario Reproductive Biology Meeting (SORB). May 25 – 26, 1993.
105. Singh A, Dykeman A, Rice D, **Foster WG**. Electron microscopy of testis from the monkey fed Lead: A 9-year study. American Association of Veterinary Anatomists. July 15 – 18, 1993.
106. **Foster WG**, McMahon A, YoungLai EV, Hughes EG, Rice DC. Reproductive endocrine effects of chronic Lead exposure in the male cynomolgus monkey (*Macaca fascicularis*). 38th Annual Meeting of the Canadian Fertility & Andrology Society. November 27, 1992.
107. Todoroff EC, Sevcik M, Brännstrom M, Janson PO, **Foster WG**, Villeneuve DC, Jarrell JF. The effect of photomirex on the *in vitro* perfused ovary of the rat. 38th Annual Meeting of the Canadian Fertility & Andrology Society. November 27, 1992.
108. Reid RL, Kennedy JC, Van Vugt DA, Yang JZ, Fletcher A, **Foster W**. Evidence in the human and the non human primate for aminolevulinic acid (ALA) induced selective endometrial photosensitization: A potential agent for photodynamic ablation of the endometrium. Society for Gynecologic Investigation. March 31 – April 3, 1993.
109. Singh A, **Foster WG**, Dykeman A, Villeneuve DC. Hexachlorobenzene toxicity in the rat ovary II. Ultrastructure induced by medium (10 mg/kg) dose exposure. Proceedings of the 50th Annual Meeting, Electron Microscopy Society of America. August 16 – 21, 1992.
110. Singh A, **Foster WG**, Arendz J. Chronic Lead exposure induces ultrastructural alterations in the monkey seminal vesicle. C.V.M.A. July 5 – 8, 1992.
111. Singh A, **Foster W**, McMahon A, Villeneuve DC. Lead-induced alterations in the testis of monkeys: An ultrastructural study. Annual Meeting, Society of Toxicology. February 23 – 27, 1992.
112. Singh A, **Foster WG**, McMahon A, Rice DC, Villeneuve DC. Electron microscopy of seminal vesicles from monkeys exposed to Lead: A 9-year study. 24th Annual Meeting, USGEB/USSBE. March 19 – 20, 1992.
113. Singh A, **Foster W**, Villeneuve D. Hexachlorobenzene-induced alterations in the ovary of rats. 105th Annual Meeting, American Association of Veterinary Anatomists. March 1992.

114. **Foster WG**, McMahon A, Pentick JA. Hexachlorobenzene (HCB) augments circulating progesterone concentration in the female rat. 34th Annual Meeting Canadian Federation of Biological Societies. (Abstract) p. 95. 1991.
115. McMahon A, **Foster WG**, Pentick JA, Lecavalier PR. Tissue distribution and ovarian subcellular localization of Hexachlorobenzene (HCB) in the female rat. 34th Annual Meeting Canadian Federation of Biological Societies. (Abstract) p. 95. 1991.
116. **Foster WG**, McMahon A, Villeneuve DC, Jarrell JF. Hexachlorobenzene (HCB) suppresses progesterone secretion during the luteal phase in the female cynomolgus monkey. 73rd Annual Meeting of The Endocrine Society. (Abstract) P. 118. 1991.
117. **Foster WG**, Jarrell JF, Younglai EV. Sexual maturation in the female rabbit: Effect of Tamoxifen and Pregnant Mare Serum. 32nd Annual Meeting Canadian Federation of Biological Societies. (Abstract) p. 35. 1989.
118. **Foster WG**, Jarrell JF, Younglai EV. Light and ultrastructural characterisation of gonadotropin hormone-releasing hormone (GnRH) neurones in the rabbit. 31st Annual Meeting Canadian Federation of Biological Societies. (Abstract) p. 114. 1988.
119. **Foster WG**, Jarrell JF, Dolovich J, Younglai EV. IgE mediated hypersensitivity in response to chronic treatment with Gonadorelin-HC_l (Factrel) in a female patient. 44th Annual Meeting Society of Obstetrics & Gynecology Canada. (Abstract) p. 105. 1988.

ADMINISTRATIVE RESPONSIBILITIES:

i) **Local** – McMaster University/Hamilton Health Sciences

1. Member, Tenure & Promotion Committee, Department of Obstetrics & Gynecology, 2008 – present.
2. Member, Animal Advisory Committee, Faculty of Health Sciences, 2007 – present.
3. Member, Graduate Curriculum Committee, Faculty of Health Sciences, 2006 – present.
4. Member, Undergraduate Hearing Committee, Faculty of Health Sciences, 2005 – present.
5. Member, Finance Management Committee, Department of Obstetrics & Gynecology, 2004 – present.
6. Member, Search Committee for Chair, Department of Obstetrics & Gynecology, 2009 – 2010.
7. Member, Reproductive Endocrinology and Infertility Fellowship Committee, Department of Obstetrics & Gynecology, 2008 – 2010.
8. Member, Undergraduate Student Appeals Committee, Faculty of Health Sciences, 2005 – 2010.
9. Co-theme Team Leader, Environment & Health, Collaborations for Health, 2005 – 2010.
10. Member, Postgraduate Education Committee, Department of Obstetrics & Gynecology, 2003 – 2010.
11. Director, Reproductive Biology Division, Department of Obstetrics & Gynecology, 2002 – 2010.
12. Coordinator, Resident Research Program, Department of Obstetrics & Gynecology, 2002 – 2010.

13. Member, Research Advisory Committee, Hamilton Health Sciences, 2006 – 2009.
14. Member, Program Evaluation Committee, Department of Obstetrics & Gynecology, 2003 – 2009.
15. Member, Maternal Medicine Fellowship Committee, Department of Obstetrics & Gynecology, 2003 – 2009.
16. Member, Search Committee for Associate Dean, Graduate Studies, 2007 – 2008.
17. Medical Director, Centre for Reproductive Care, Hamilton Health Sciences, 2005 – 2008.
18. Member, BioSafety Committee, Faculty of Health Sciences, 2003 – 2005.

ii) **National -**

1. Member, Grants Review Committee, Canadian Breast Cancer Fund, 2014 – present.
2. Member, Catalyst Grant Committee, Genes and Chronic Disease, CIHR, 2013 – present.
3. Member and Mentor, CIHR Training Program in Reproduction, Early Development, and the Impact on Health (REDIH), University of Ottawa, 2009 – present.
4. Affiliate, R. Samuel McLaughlin Centre for Population Health Risk Assessment, 2008 – present.
5. Mentor, CIHR Strategic Training Program in Tobacco Research (CIHR-STPTR), University of Waterloo, 2005 – present.
6. Member of Expert Registry, US-National Toxicology Program, Center for the Evaluation of Risk to Human Reproduction, 2005 – present.
7. Panel Member, Integrating Emerging Technologies into Chemical Safety Assessment, Council of Canadian Academies, 2010 – 2012.
8. Expert Panel Member, Integrated Testing of Pesticides, Council of Canadian Academies, 2009 – 2011.
9. Mentor, Strategic Training in Research in Reproductive Health Sciences (STIRRHS), University of Montréal, 2006 – 2011.
10. Expert Panel Member, Assisted Human Reproduction Canada, The Environment and Reproductive Health: A Scientific Roundtable Steering Committee, Health Canada, 2010.
11. Organizing Committee Member, Assisted Human Reproduction Canada, The Environment and Reproductive Health: A Scientific Roundtable Steering Committee, Health Canada, 2010.
12. Member, Obstetrics & Gynecology Task Force - In vitro Fertilization, College of Physicians and Surgeons of Ontario, 2008 – 2010.
13. Member, Grants Review Committee, Canadian Breast Cancer Fund, 2007 – 2010.
14. Member, Clinical Investigation 'A' Peer Review Panel, CIHR, 2006 – 2010.
15. Member, Scientific Program Committee, Canadian Fertility and Andrology Society, 2006 – 2010.
16. Invited Participant, Health Canada and CIHR Sponsored Workshop of Child Health, Ottawa, ON, February 10 – 11, 2009.
17. Member, Science Committee, Association of Professors of Obstetrics & Gynaecology, 2003 – 2009.
18. Member, Assisted Human Reproduction Canada/CIHR Sponsored Workshop Scientific Organizing Committee, 2008.

19. President, Canadian Fertility and Andrology Society, 2007 – 2008.
20. Chair, Scientific Program Committee, Canadian Fertility and Andrology Society, 2007 – 2008.
21. Member, Research Committee, The Society of Obstetricians and Gynaecologists of Canada (SOGC), 2003 – 2008.
22. Chair, Science Panel, EM-COM web site, www.EMCOM.ca, 2002 – April 2005.
23. Member, Board of Directors, Infertility Awareness Association of Canada, 1998 – 2004.
24. Toxic Substances Research Initiative, Healthy Environments and Consumer Safety Branch, Health Canada, 1999 – 2003.
25. Chairman, Endocrine Disrupters Technical Review Committee, 1999 – 2000.
26. Vice-president, President-elect, Society of Toxicology of Canada, 1998 – 1999.
27. Co-chair, Interdepartmental Research Committee on Endocrine Disruptors, Health Canada,1998 – 1999.
28. Member, Endocrine Disruptor Committee, Organisation for Economic Co-operation and Development (OECD), Health Canada, 1997 – 1999.
29. Chairperson, Committee on Endocrine Disruptors, Health Protection Branch, Health Canada, 1994 – 1999.
30. Member, Animal Care Committee, Health Protection Branch, Health Canada, 1993 – 1998.

iii) **International -**

1. Member, Advisory Board, Endometriosis Association, 2014 – present.
2. President, Lake Ontario Regional Chapter, Society of Toxicology, 2012 – present.
3. Scientific Advisor, Development and Reproductive Toxicology (DART) Technical Committee, ILSI Health and Environmental Sciences Institute (HESI), 2012 – present.
4. Member, Center for Scientific Review (CSR), US Department of Health & Human Services, National Institutes of Health (NIH), 2010 – present.
5. Ad hoc Member, FIFRA Scientific Advisory Panel, US-Environmental Protection Agency (EPA), 1999 – present.
6. Invited participant, Expert Workshop: Improving the Risk Assessment of persistent, bioaccumulative and toxic (PBT) chemicals in breast milk, October 24 – 26, 2012.
7. Expert Panel Member, site visit, Division of Epidemiology, Statistics & Prevention Research, National Institute of Child Health and Human Development (NICHD), October 22 – 24, 2012.
8. Secretary Treasurer, Reproductive Developmental Toxicology Specialty Section, Society of Toxicology, 2010 – 2012.
9. Chair, Core Committee, Society for the Study of Reproduction, 2010 – 2012.
10. Committee on Reproduction and the Environment, Society for the Study of Reproduction, 2008 – 2012.
11. Expert Panel Member, Reproductive & developmental effects of soy products and genistein, National Institutes of Health/National Institute of Environmental Health Sciences – National Toxicology Program (NIH/NIEHS-NTP), 2009 – 2010.
12. Invited Participant, Mammary Gland Evaluation and Risk Assessment Round Robin Workshop, Oakland, CA, November 16 – 17, 2009.

13. Member, NIH Study Section, Integrative and Clinical Endocrinology and Reproduction Study Section, October 5 – 6, 2009.
14. Team Member, NICHD site visit, September 24 – 26, 2008.
15. Member, WHO/IPCS Steering Group on Endocrine Disrupters, 1998 – 2002.
    - Global Inventory of Endocrine Disrupter Research.
    - International Assessment of the State of Knowledge on Endocrine Disrupters.
16. Expert Panel Member, Joint US/EU Endocrine Disruptor Research, 1999.
17. Member, Organisation for Economic Co-operation and Development (OECD), Working Group on Endocrine Disrupter Testing and Assessment, 1997 – 1999.
    - National Co-ordinator, Test Guideline Program – OECD, 1997 – 1998.
18. Member, National Sanitation Foundation - International, Health Effects Task Group, 1996 – 1998.

MARY E. (BETTE) MEEK

Summary: ***Experience in management of teams to deliver time-limited regulatory mandates to set priorities for and assess health risks of chemical contaminants. Development of process, content and methodology for assessment of chemical contaminants, internationally.***

Citizenship: ***Canadian***

Address: ***1 Stewart Street, Suite 309***
Ottawa, Ont. K1N 6N5
Telephone (613) 562-5800 x2105
Fax (613) 562-5380
e-mail: bmeek@uottawa.ca

Education: ***Ph.D., Risk Assessment Sciences***
Faculty of Veterinary Medicine
University of Utrecht
Utrecht, the Netherlands
October, 2009

M.Sc. Toxicology (with Distinction)
University of Surrey
Guildford, Surrey, U.K.
September, 1981

B.Sc. (Honours, Biology)
Queen's University
Kingston, Ontario
May, 1976

Experience: ***July, 2007 to November, 2010(on Interchange from Health Canada); November, 2010 to Present***

Associate Director
Chemical Risk Assessment
McLaughlin Centre for Population Health
University of Ottawa

Responsibilities:

Identify and develop opportunities for mutually beneficial interactions involving the federal government, the academic community and agencies such as the World Health Organization regarding health risk assessment, risk management and risk communications, including:

sharing of priority setting and assessment tools developed for categorization of the Domestic Substances List under the Canadian Environmental Protection Act

contributing to harmonization initiatives of the International Programme on Chemical Safety on risk assessment including physiologically based pharmacokinetic modeling, mode of action analyses, approaches for mixtures and chemical specific adjustment factors

increasing capacity of academic institutions to support chemicals assessment, management and communications functions of the Government of Canada.

April, 1999 to July, 2007
Acting Chief/Manager, Environmental/Existing Substances Division
Bureau of Chemical Hazards
Environmental Health Directorate/Safe Environments Programme
Health Canada

Responsibilities:

Develop organizational structure for the Existing Substances Division to address expanded responsibilities under CEPA 99; develop and implement plan for classification and staffing. Manage a budget of approx. 4M$ in salary/operating resources annually to address priorities for HC regarding requirements under CEPA 99 relating to the Priority Substances Lists (PSL) and the Domestic Substances List (DSL). Efficiently manage a staff of approximately 40 professionals and administrative support staff; develop training plans and advise on career development

Manage interface at program level with relevant groups within HC, partner Department (Environment Canada), other Government Departments, stakeholder groups, other national/international agencies, research organizations and outside technical experts to address methodology and priorities for HC for Existing Substances under CEPA 99.

Develop and refine methodology and process for preparation, review and finalization of priority setting and assessments of Existing Substances conducted under CEPA 99, including consideration of all 23, 000 substances on the Domestic Substances List within mandated timeframes. Lead and contribute to development of methodology and training materials internationally including predictive exposure and hazard tools, issue identifications and screening assessments to meet the regulatory mandate.

Schedule completion of, review and revise priority setting for health assessments of significant numbers of Existing Substances under CEPA 99. Develop communications plan and materials, input to renewal of the legislation and prepare and publish manuscripts on risk assessment methodology and assessments

September, 1989 to April, 1999;
Head, Priority Substances Section
Bureau of Chemical Hazards
Environmental Health Directorate
Health Canada

Responsibilities:

supervision of approximately 10 professional staff in the preparation of assessments on complex datasets for chemical contaminants in the general environment under the Canadian Environmental Protection Act, including administration of a contract budget of approximately $500,000 annually and development of tailored introductory and advanced training programs

development of the process for finalization of assessments of Priority Substances within legislated time frames (approx. 50 in a 5 year period), including identification of research gaps and conduct of studies, acquisition of appropriate expert (including written and panel meeting reviews) and public input and scheduling in conjunction with a partner Department

development and modification of the approach to risk assessment for Priority Substances, including introduction of novel methodology for multimedia exposure estimation, data-derived uncertainty factors for non-neoplastic effects, mode of action frameworks, measures of potency for carcinogens and models of peer review

review of Supporting Documentation and finalization of risk assessments on Priority Substances

presentation and defence of methodology for and assessments of Priority Substances at various scientific, technical and public fora and contribution to international harmonization of both methodology and assessments of individual substances

initiation of development of process and approach for categorization and screening of the 23,000 substances included on the Domestic Substances List

November, 1981- September, 1989
Senior Evaluator and Acting Section Head
Environmental Criteria Section
Bureau of Chemical Hazards
Environmental Health Directorate
Health Canada

Responsibilities:

staffing and supervision of evaluators involved in preparation of critical reviews on chemical contaminants in the general environment

advising on the need for and developing suitable approaches for use by the Bureau in deriving guidelines or standards for chemical contaminants in air (ambient and indoor) and drinking water

developing recommendations for exposure in various media to a wide range of chemical contaminants including formaldehyde, man-made mineral fibres, trihalomethanes, chlorobenzenes, nitrogen dioxide, ozone, sulphur oxides, benzene, nitrate and arsenic

critically reviewing and revising supporting documentation and recommendations for exposure limits for a wide range of chemical contaminants prepared by evaluators within the Bureau

presenting and defending critical reviews and recommendations for exposure limits at various scientific, technical and public fora, preparing documentation for, and participating in deliberations of international organizations

May, 1976 - September, 1980
Biologist/Evaluator
Bureau of Chemical Hazards
Environmental Health Directorate
Health Canada

Responsibilities:

evaluation of published and unpublished toxicological and related data to prepare critical reviews to make recommendations for exposure limits for chemical contaminants in the occupational and general environments. (e.g. arsenic, chromium, manganese, several pesticides, selenium, the fuel additive MMT and HCB)

preparation of reports on toxicological and related data to make recommendations concerning the use of chemical formulations in potable water supplies. (e.g. chlorine compounds, flocculating agents and coatings for distribution systems)

advising on the need for and supervising research studies conducted under contract by outside consultants. (e.g. health hazard assessments for the environmental pollutants CO, NO2 and chlorinated benzenes)

Appointments: ***Temporary Advisor and/or reviewer for various international agencies and organizations on health risk assessment for chemical contaminants including (See Appendix 1):***

International Programme on Chemical Safety (IPCS, World Health Organization)
World Health Organization Regional Office for Europe
International Labour Organization
Organization for Economic Cooperation and Development
International Life Sciences Institute (ILSI) Research Sciences Institute (RSI)
ILSI Health and Environmental Sciences Institute (HESI)
U.S. Environmental Protection Agency (US EPA)
U.S. National Academy of Sciences (US NAS)
Australian Department of Health and Ageing
Agence Nationale de Securité Sanitaire Alimentation Environnement Travail (ANSES)
Joint Research Centre, European Union
Chulabhorn Research Institute, Thailand
Health Canada

Recent and Ongoing Examples:

Member, Advisory Committee, EU Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information
Chair, US EPA Peer Review Group on Mutagenic Mode of Action
External Advisor, Office of Chemical Safety, Australian Department of Health and Ageing
Member, Groupe du travail des "Valeurs toxicologiques de référence" I,II Agence Nationale de Securité Sanitaire Alimentation Environnement Travail (ANSES)
Ad Hoc Member, U.S. Federal Insecticide, Fungicide and Rodenticide Scientific Advisory Panel

Chair, IPCS Harmonization Planning Group on Physiologically based Pharmacokinetic Modelling
Chair, IPCS Harmonization Planning Group on Risk Assessment of Combined Exposures
Chair, Alliance for Risk Assessment Science Panel
Member, IPCS Harmonization Training Group
Member, Council of International Society of Regulatory Toxicology and Pharmacology
Chair, IPCS Drafting Group on Mode of Action
Member, WHO Steering Committee on Mode of Action
Member, Organizing Committees for several International Conferences
Reviewer for Journals and Research Grants Organizations
Peer Reviewer, Toxicology Excellence for Risk Assessment

Professional Affiliations:

Member, Society of Toxicology
Member, Society of Toxicology of Canada
Member, Society for Risk Analysis
Member, International Society of Regulatory Toxicology and Pharmacology
Past Member, British Toxicology Society
Past Member, New York Academy of Sciences

Additional Training

Second Language:
Various courses and training to meet and retain French linguistic profile of CBC (Canadian Government)

Management:
Various courses on team leadership, project planning, coaching practices, financial and contract administration, staffing

Technical:
Epidemiology 5341 (postgraduate), University of Ottawa, 1985
Epidemiology 5340 (postgraduate), University of Ottawa, 1982
Environmental Epidemiology, University of Ottawa, 1982
Law of Environmental Quality, Carleton University, 1978

Publications:

More than 175 scientific articles on risk assessment methodology, process and content published in the peer reviewed scientific literature (See attached list).
More than 75 publications of the Government of Canada

Presentations:

More than 275 external presentations (See attached list)

Awards Include:

Deputy Minister and Public Service Awards for Team Excellence, 1998 and 2007, Arnold J. Lehman Award, Society of Toxicology, 2011

Appendix 1: M.E. (Bette) Meek
Appointments

Development of Methodology/Training for Risk Assessment

Member, Cumulative Risk Assessment Expert Panel to the US EPA Science Adviser, June 24th, 2013.

Member, OECD Advisory Group on Molecular Screening and Toxicogenomics, May, 2013 – Present.

Member of the Selection Committee for the ECVAM Scientific Advisory Committee, February – April, 2013.

Member of the FIFRA Science Advisory Panel on Scientific issues associated with Prioritizing the Universe of Endocrine Disruptor Screening Program (EDSP) Chemicals using Computational Toxicology Tools. Arlington, January 29th – February 1st, 2013.

Chair, World Health Organization Meeting on the Regulation of Mixtures of Chemicals in Drinking-water, Dubendorf, Switzerland, March 22nd.

Chair, Session on Mode of Action Analysis, SRA Annual Meeting, San Francisco, December 10th, 2012.

Rapporteur, Break-out Group II, ECHA/Cefic LRI Workshop on Read-across, October 3rd, 2012.

Member, Dose-Response Subgroup, ILSI Risk 21, August, 2009 to Present.

Chair, Breakout Group on Exposure and Risk Assessment – Human Health, ECETOC Workshop: Combined Exposure to Chemicals, July 10th-11th, 2011.

Member, FIFRA Scientific Advisory Panel Meeting on Integrated Approaches to Testing and Assessment Strategy: Use of New Computational and Molecular Tools, Arlington, May 24 – 26th, 2011.

Chair, WHO/International Programme on Chemical Safety (IPCS) Drafting Group on Mode of Action in Evolving Toxicity Testing Strategies, October, 2010 to Present.

Member, WHO/International Programme on Chemical Safety (IPCS) Steering Committee on Mode of Action in Evolving Toxicity Testing Strategies, October, 2010 to Present.

Chair, Expert Panel, Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment. Alliance for Risk Assessment, October, 2010 to Present.

Chair, Session A, WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals, Paris, February 15th – 16th, 2011.

Rapporteur, Workshop on Combined Exposures and Synergistic Effects, Global Risk Assessment Dialogue 2nd International Conference on Risk Assessment, Brussels, January 25th – 28th, 2011.

Chair, Syndicate 2 - Link from in vitro / in vivo and extrapolation across species: Mammal to Humans, daphnia to fish, ECETOC Workshop on Omics in (Eco)toxicology: Case Studies and Risk Assessment, Malaga (Spain), February22nd-23rd, 2010.

Chair, Break-out Group, on Toxicological Mode of Action: are we prepared to use it in the current regulatory framework? ECETOC-ILSI Workshop on Using Mode of Action Information to improve Regulatory Decision Making, London, November 2nd-3rd, 2009.

Member, Steering Committee, ECETOC-ILSI Workshop on Using Mode of Action Information to improve Regulatory Decision Making, January - November, 2009.

Appendix 1: M.E. (Bette) Meek
Appointments

Member, Advisory Committee, A Framework for the Development and Application of Environmental Biological Monitoring Guidance Values, Cranfield University, U.K., October, 2008 to June, 2009.

Ad hoc member, U.S. EPA Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP), September, 2008 to Present.

Membre, Groupe du travail des "Valeurs toxicologiques de référence", Agence Française de Sécurité Sanitaire de l'Environnement et du travail (AFSSET), August, 2008 to Present.

Member, Advisory Committee, EU Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information, January, 2008 to September, 2011.

Member, International Programme on Chemical Safety (IPCS) Training Group on Harmonization of Risk Assessment Methodology, July, 2008 to June, 2010.

Chair, External Peer Review Panel for US EPA Draft Framework for Determining a Mutagenic Mode of Action for Carcinogens, April, 2008.

Member, International Programme on Chemical Safety (IPCS) Steering Group on Harmonization of Risk Assessment Methodology, September, 2002 to Present

Chair, IPCS Harmonization Workgroup on Physiologically-Based Pharmacokinetic (PBPK) Modelling, April, 2005 to January, 2013.

Chair, IPCS Harmonization Workgroup on Aggregate/Cumulative Risk Assessment, March, 2005 to January, 2011.

Member, Planning Committee, International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) Planning Committee on Approaches to Weight of Evidence Evaluation in Risk Assessment, 2005 to 2009.

Member, IPCS Harmonization Workgroup on Uncertainty in Exposure Assessment, April, 2005 to 2008

Member, IPCS Harmonization Workgroup on a Framework for Human Relevance of Animal Modes of Action in Addressing Non-Cancer Risk, March, 2006 to January, 2007

Member, IPCS Harmonization Workgroup on a Framework for Human Relevance of Animal Modes of Action in Addressing Cancer Risk, March, 2004 to June, 2006

Member, Steering Group, International Life Sciences Institute Risk Sciences Institute (RSI) Project to Develop better predictive hazard tools for developmental toxicity, March, 2003 to 2006

Member, ILSI Research Sciences Institute Project to Develop a Human Relevance Framework for Animal Modes of Action (Non-Cancer), April, 2003 to June, 2004

Chair of the Framework Development Subgroup, ILSI RSI Project to Develop a Human Relevance Framework for Animal Modes of Action (Cancer), August, 2000 to December, 2002

Chair, IPCS Planning Workgroup on Uncertainty and Variability in Risk Assessment (IPCS Harmonization Project on Chemical Specific Adjustment Factors), December, 1996 to March, 2001; December, 2004

Member, IPCS Harmonization Planning Workgroup on Development of a Conceptual Framework for Cancer Risk Assessment, March, 1997 to February, 1999

Appendix 1: M.E. (Bette) Meek
Appointments

Author, Drafting Group on IPCS Monograph on Scientific Principles for Risk Assessment, February, 1996 to September, 1997

Chair, Development of Methodology for Derivation of Guidance Values in IPCS Environmental Health Criteria Documents, January, 1992 to June, 1993

Process/Priorities/Workplanning for Assessments

External Advisor to the Office of Chemical Safety, Department of Health and Ageing, Canberra Australia, April, 2008.

Member, Steering Group, Alliance for Risk Assessment, Toxicology Excellence for Risk Assessment (TERA), January, 2007 to Present

Member, International Programme on Chemical Safety (IPCS) Steering Group on Risk Assessment, September 1999 to Present

Member, Final Review Board on Concise International Chemical Assessment Documents, September 1996 to October, 2005

Member, IPCS Programme Advisory Committee, 2001 to 2002

Member, Steering Group on Concise International Chemical Assessment Documents, May 1995 to October, 1998

Member, Inter-organization Programme for the Sound Management of Chemicals (IOMC) Coordinating Group on the Assessment of Existing Industrial Chemicals and Pollutants, September 1999 to 2005

Member, Organization for Economic Cooperation and Development (OECD) Task Force on Existing Chemicals, May 1999 to Present

Health Canada representative to the Organization for Economic Cooperation and Development Program on High Production Volume Chemicals (Initial Assessments), April, 1990 to June, 2001

Author, IPCS/OECD Consultation on Priority Setting and Related Matters, December, 1993 to February, 1995

Peer Review

Reviewer for several scientific journals including Critical Reviews in Toxicology, Regulatory Toxicology and Pharmacology, Toxicological Sciences Environmental Health Perspectives, Journal of Applied Toxicology and Risk Analysis.

Reviewer for "Port Hedland Health Risk Assessment Methodology. Prepared by ToxConsult for the Western Australia Department of Health, Draft dated May 20th, 2013.

Scientific Peer-Review of the Carcinogenic Section (Section 4.2) of the Hexavalent Chromium Development Support Document to derive health-protective Effects Screening Levels (ESLs) and Reference Values (ReV) for hexavalent chromium (CrVI). Texas Commission on Environmental Quality, Final Draft dated March, 2013.

Prepared Review Comments on "Tetrachloroethylene in Drinking Water", Prepared by the Federal-Provincial-Territorial Committee on Drinking Water Draft for Peer Review. Draft dated November, 2012.

Appendix 1: M.E. (Bette) Meek
Appointments

Prepared Review Comments on Memorandum RE: Provisional tolerableDailyIntake (TDI) for Perfluorooctane Sulfonate (PFOS) in Support of a Soil Quality Guideline for the Protection of Human Health (SQG_{HH}) dated October 2012 prepared by the Contaminated Sites Division of Health Canada. Draft dated October, 2012.

Assessment of the Mode of Action Underlying Development of Rodent Small Intestinal Tumors Following Oral Exposure to Hexavalent Chromium and Relevance to Humans, C Thompson et al. Draft Manuscript dated 8-17-12, Toxicology Excellence for Risk Assessment..

FIFRA Scientific Advisory Panel (FIFRA SAP) for the April 10-13, 2012 US Environmental Protection Agency FIFRA SAP Meeting: Chlorpyrifos Health Effects (IATA), April 10^{th} – 13^{th}, 2012.

Peer Reviewer, Green Chemistry Hazard Traits Regulation and Initial Statement of Reasons. State of California, April, 2011.

FIFRA Scientific Advisory Panel Meeting on Reevaluation of the Human Health Effects of Atrazine: Review of Non-cancer Effects and Drinking Water Monitoring Frequency, Arlington, Sept. 14^{th} – 17^{th}, 2010.

FIFRA Scientific Advisory Panel Meeting on the "Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment", Arlington, February 2^{nd} – 5^{th}, 2010

FIFRA Scientific Advisory Panel Meeting on A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:The Use of Structure Activity Relationships of Estrogen Binding Affinity to Support Prioritization of Pesticide Inert Ingredients and Antimicrobial Pesticides for Screening and Testing, Arlington, August 25-26, 2009

Science Advisory Board on Research Framework for Evaluating the Potential Mode(s) of Action Underlying the Carcinogenicity of Hexavalent Chromium Following Exposure in Drinking Water , Toxicology Excellence for Risk Assessment, Chapel Hill, July 28^{th}-29^{th}, 2009

External Peer Reviewer for draft assessment on Tertiary-Butyl Acetate (TBAC), Toxicology Excellence for Risk Assessment, Cincinnati, January 4-5, 2009

Ad Hoc Member of the U.S. Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel to Consider and Review the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos, September 16^{th} to 19^{th}, 2008

External Peer Reviewer for draft ATSDR profile on formaldehyde, July, 2008

Member, U.S. National Academy of Sciences (NAS) External Peer Review Panel for Draft Assessment on Tetrachloroethylene prepared by the U.S. Environmental Protection Agency, November, 2006 to August, 2009

External Peer Reviewer for the Review of Harmonization in Interspecies Extrapolation: Use of Body Weight 3/4 as Default Method in Derivation of the Oral RFD for the U.S. EPA, May, 2006

Referee, Proposals for the Strategic Research Program for the National Institute for Public Health and the Environment in the Netherlands, July 2006 to Present

Chair, Toxicology Excellence for Risk Assessment Peer Consultation on the Scientific Rationale for Deriving Database and Toxicodynamic Uncertainty Factors for Reproductive and Developmental Toxicants, September, 2005

Appendix 1: M.E. (Bette) Meek
Appointments

U.S. National Academy of Sciences Subcommittee on Acute Exposure Guideline Levels, July, 2002

Member, Pan American Health Organisation Advisory Committee on Epidemiological Study on Copper in Drinking Water in Chile, October, 2000

Author, Background Paper, International Programme on Chemical Safety (IPCS) Consultation on Process for Peer Review of Risk Assessments, October, 1998

Peer Reviewer, Toxicology Excellence for Risk Assessment, 1995 to Present

Reviewer, Human & Ecological Risk Assessment, July 1995 to Present

Reviewer, BC Health Research Foundation (research proposals), 1991 to Present

Reviewer, Canadian Journal of Public Health, July, 1984 to Present

Preparation of Assessments

Member, International Life Sciences Institute (Health and Environmental Sciences Institute) Expert Panel to Evaluate Chloroform and Dichloroacetate as Case Studies for the Application of EPAs Proposed Guidelines for Carcinogen Risk Assessment, September, 1996 to September, 1997

International Programme on Chemical Safety (IPCS) Task Groups on Environmental Health Criteria Documents:

- ***July 2nd to 5th, 1996 (Chrysotile, Chairman)***
- ***June 24th to 28th, 1996 (Copper)***
- ***October 30th to November 3rd, 1995 (Dibutyl Phthalate, Coauthor & Rapporteur)***
- ***April 24th to 28th, 1995 (Aluminum)***
- ***March 20th to 24th, 1995 (Chlorinated Paraffins, Chairman)***
- ***December 6th to 10th, 1993 (Acetaldehyde, Chairman)***
- ***November 16th to 20th, 1993 (Chloroform, Chairman)***
- ***September 28th to October 2nd, 1992 (Selected Synthetic Mineral Fibres, Author)***
- ***June 24th to 29th, 1990 (Chlorobenzenes other than Hexachlorobenzene, Author)***
- ***September 14-18, 1987 (Man-made Mineral Fibres, Author)***
- ***July 15-22, 1985 (Asbestos, Rapporteur)***

IPCS Working Group on Environmental Reduction of Asbestos (Rapporteur), December, 1988

Consultant, Organization for Economic Cooperation and Development Environment Committee Air Management Policy Group (Contributing Author on Assessment on Asbestos), April, 1984

Development of Guidelines

Appendix 1: M.E. (Bette) Meek
Appointments

Chair, Working Group on Chemical Substances in Drinking Water (revision of the WHO Guidelines for Drinking Water Quality), April 21st to 26th, 1997

Member of the Review Group, Revision of the WHO Guidelines for Drinking Water Quality
May 19th to 22nd, 1992 (Rapporteur)
October 14th to 18th, 1991
June 10th to 14th, 1991
March 18th to 22nd, 1991
November 6th to 10th, 1990

Subgroup Chair, Final Consultation on World Health Organization/European Office (WHO/Euro) Air Quality Guidelines for Europe, October 28th to November 1st, 1996

Subgroup Chair, Update and Revision of the WHO/Euro Air Quality Guidelines for Europe, Meeting of the Working Group on Volatile Organic Compounds, October 2nd to 6th, 1995

Working Group on Indoor Air Quality: Inorganic Fibres and Other Particulate Matter for revision of the WHO /Euro Air Quality Guidelines for Europe, July 24th to 28th, 1990

Working Group on Indoor Air Quality: Combustion Products for revision of the WHO /Euro Air Quality Guidelines for Europe, October 31st to November 4th, 1989

Author, Working Group on Indoor Air Quality – Radon and Formaldehyde for revision of the WHO/Euro Air Quality Guidelines for Europe, August 26-30, 1985

Member, Federal Provincial Subcommittee on National Ambient Air Quality Objectives, February, 1985, to September, 1990.

Member, Secretariat of the Federal Provincial Subcommittee on Drinking Water Quality, June, 1983 to September, 1990.

Member, Federal Provincial Working Group on the Development of Guidelines to Control Risks for Women in Industry, December, 1981 to March, 1985.

Member, Secretariat, Federal Provincial Working Group on Indoor Air Quality, December, 1981 to September, 1985.

Member, Secretariat, Federal Provincial Working Group on Drinking Water, May, 1976 to 1978.

Scientific/Technical Councils and Organizing Committees

Member, Organizing Committee, American Chemistry Council ExpoDat2012: Advancing Exposure-Informed Chemical Safety Assessment, October, 2012 – Present.

Member, Organizing Committee, WHO/IPCS Organizing Committee for Workshop on Mode of Action: Recent Developments, Regulatory Applications and Future Work held in Vienna, February 21st-22nd, 2013, May, 2012 – June, 2013

Member, Planning Group, Second WHO Meeting on Global Collaboration in Chemical Risk Assessment, held in Bonn, Germany, March 28th – 30th, 2012, August, 2011 – March, 2012.

Member, Organizing Committee of the 2011 International Society of Exposure Science Annual Meeting, January to October, 2011.

Appendix 1: M.E. (Bette) Meek
Appointments

Member, Council, International Society for Regulatory Toxicology and Pharmacology, December, 2006 to Present

Member of the Organizing Committee, Second International Conference on the Safety of Water Disinfection, Miami, November 15th to 17th, 1999.

Member of the Organizing Committee, Benzene State of the Science Workshop, Ottawa, December 16th to 17th, 1998.

Member of the Organizing Committee, International Workshop on Risk Assessment of Metals and their Inorganic Compounds, Angers, France, November 12th to 15th, 1996.

Co-chairman and Editor of the Proceedings, Symposium on Fibres in Friction Materials and Health, International Brake Colloquium, Atlantic City, October 7-8, 1987.

Rapporteur, Disinfection and Disinfection By-Products in Drinking Water, Safety of Water Disinfection: Balancing Chemical and Microbial Risks, Washington, D.C., September, 1992.

Rapporteur, Workshop on Approaches to Evaluating the Toxicity and Carcinogenicity of Man-Made Fibers, Chemical Industry Institute of Toxicology, R.T.P., North Carolina, November 11th to 13th, 1991.

Other

Member, Canadian General Standards Board Committee on Asbestos Cement Products, January, 1984 to 1990.

Appendix 2: M.E. (Bette) Meek
Publications

M.E. Meek, C. Palermo, C. North and R.J. Lewis (submitted). Mode of Action Human Relevance (MOA/HR) Framework– Evolution of the Bradford Hill Considerations and Comparative Analysis of Weight of Evidence. Toxicology and Applied Pharmacology.

M.E. Meek, A. Boobis, I. Cote, V. Dellarco, G.Fotakis, S. Munn, J. Seed, and C. Vickers (submitted). New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. Toxicology and Applied Pharmacology.

R S. Thomas, M.A. Philbert, S. S. Auerbach, B.A. Wetmore, M.J. Devito, I. Cote, J. C.Rowlands, M.P. Whelan, Sean M Hays, M.E. Andersen, M.E. Meek, L.W. Reiter, J.C.Lambert**, H.J. Clewell III, Martin L. Stephens, Q. J. Zhao, S.C.Wesselkamper**, L.Flowers, E.W. Carney, T.P. Pastoor, D.D. Petersen, C.L. Yauk, and A. Nong (submitted). Incorporating New Technologies into Toxicity Testing and Risk Assessment: Moving from 21st Century Vision to a Data-Driven Framework. Toxicological Sciences.

M.E. Meek, M. Bolger, J.S. Bus, J.Christopher, R.B. Conolly, R.J. Lewis, G. M. Paolini, R. Schoeny, L. T. Haber, A. B. Rosenstein and M. Dourson (2013) A framework for fit-for-purpose dose response assessment. Regulatory Toxicology and Pharmacology 66 (2013) 116–129.

M.E. Meek, H.A. Barton, J.G. Bessems, J.C. Lipscomb and K. Krishnan (2013) Case Study Illustrating the WHO IPCS Guidance On Characterization and Application Of Physiologically Based Pharmacokinetic Models In Risk Assessment. Regulatory Toxicology and Pharmacology 66:116-129.

Meek, M.E. (2012) International Experience in Addressing Combined Exposures: Increasing the Efficiency of Assessment. Toxicology2012.09.015. http://www.ncbi.nlm.nih.gov/pubmed/23146753

Meek, M.E., Boobis, A. R., Crofton, K.R., Heinemeyer, G., Van Raaij, C. and Vickers, C. (2011). Risk Assessment of Combined Exposures to Multiple Chemicals: A WHO/IPCS Framework. Reg. Toxicol. Pharmacol. 60: S1–S14.

Meek, M.E. (2011), Annex A. Screening level risk assessment of mixtures – An Example – Polybrominated diphenyl ethers (PBDEs), A WHO/IPCS Framework. Reg. Toxicol. Pharmacol. 60: S7–S10.

Rhomberg, L, Goodman, J., Haber, L. T., Dourson, M., Andersen, M., Klaunig, J., Meek, M.E., Price, P., MClellan, R. and Cohen, S. (2011). Linear Low-Dose Extrapolation for Non-Cancer Heath Effects is the Exception, Not the Rule. Critical Reviews in Toxicology 41(1): 1–19.

Fruijtier-Pölloth, C., Bausen, M., Boobis, A.R., Carmichael, N., Cohen, S.M., Doe, J., Embry, M., Greim, H., Lewis, R., Meek, M.E., Mellor, H. and Vickers, C. (2011). Using Mode of Action Information to Improve Regulatory Decision-Making: An ECETOC Workshop Overview. Critical Reviews in Toxicology 41(3):175-185.

Chambers, A., Krewski, D., Birkett, N., Plunkett, L., Hertzberg, R., Danzeisen, R., Aggett, P., Starr, T., Baker, S., Dourson, M., Jones, P., Keen, C., Meek, B., Schoeny, R., and Slob, W. (2011) An Exposure-Response Curve for Copper Excess and Deficiency. Journal of Toxicology and Environmental Health, Part B, http://dx.doi.org/10.1080/10937404.2010.538657

Meek, B. and Dourson M. (2010) Integrating Cancer and Non-Cancer Dose Response Assessment Approaches to Risk Assessment: The Role of Mode of Action. Risk Policy Report 17(39):28.

Appendix 2: M.E. (Bette) Meek
Publications

Meek, M.E. and Klaunig, J. (2010) Interpreting available data and identifying critical data gaps for benzene risk assessment. Evolution and Contribution of the IPCS/ILSI framework for "Mode of Action/Human Relevance". Chemico-Biological Interactions 184: 279–285.

Meek, M.E., Experimental Animal Studies for Carcinogenicity (2010) Cancer Risk Assessment: Chemical Carcinogenesis. From Biology to Standards Quantification, Hsu, G. and Stedeford, T. John Wiley & Sons, Inc., N. Y.

Meek, M.E., Levy , L., Beck, B.D., Danzeisen, R., Donohue, J.M., Arnold, I.M.F. and Krewski, D. (2010) The Path Forward: Risk assessment practice for essential metals. Journal of Toxicology and Environmental Health Journal of Toxicology and Environmental Health, Part A, 73: 2, 253 — 260.

Meek, M.E, McArdle, H. and Bedard, D. (2010) Preface. Special Issue: Health Risk Assessment of Essential Metals. Journal of Toxicology and Environmental Health 73: Part A, 2, 93 — 95.

Hughes, K., Paterson, J. and Meek, M.E. (2009) Tools for the prioritization of substances on the Domestic Substances List in Canada on the basis of hazard. Reg. Toxicol. Pharm. 55:382-393.

Meek, B. and Doull, J. (2009) Pragmatic Challenges for the Vision of Toxicity Testing in the 21st Century in a Regulatory Context: Another Ames Test? . . .or a New Edition of ''the Red Book''? Toxicological Sciences 108:19–21.

Meek, M.E. (2009) Letter to the Editor in Response to Forristal et al.: Improving the Quality of Risk Assessments in Canada Using a Principle-Based Approach, Regulatory Toxicology and Pharmacology 53: 156–157

Meek, M.E., Berry, C., Boobis, A.R., Cohen, S.M., Hartley, M., Munn, S., Olin, S., Schlatter, V. and Vickers, C (2008). Letter to the Editor Re: Guyton, Kathryn Z., Barone, Stanley, Jr., Brown, Rebecca C., Euling, Susan Y., Jinot, Jennifer, Makris, Susan (2008). Mode of Action Frameworks: A Critical Analysis. Journal of Toxicology and Environmental Health, Part B, 11:681–685.

Meek, B., Boobis, A., Crofton, K., Heinemeyer, G., Kleiner, J., Lund, B., Olin, S., Pavitrannon,S., van Raaij,M., Vickers, C., and Waight-Sharma, N.(2009) Assessment of Combined Exposures to Multiple Chemicals. Report of a WHO/IPCS International Workshop on Aggregate/Cumulative Risk Assessment, http://www.who.int/ipcs/methods/harmonization/areas/workshopreportdocument7.pdf.

Embry, M.R., Barrow, C., Dearfield, K., Devlin, D.J., Hale Henry, C., Meek, B., Murphy, S., Satchwill, T., Schreider, J., Sette, W., Solomon, K.R. and Weed, D.L. (In press) Approaches to Weight of Evidence evaluation in Risk Assessment: An ILSI-HESI Initiative. Risk Analysis.

Meek, M.E., Sonawane, B. and Becker, R.A. (2008) Foreword, Biomonitoring Equivalents Special Issue. Regulatory Toxicology and Pharmacology 51(3): 53.

Meek, M.E. (2008) Recent Developments in Frameworks to Consider Human Relevance of Hypothesized Modes of Action for Tumours in Animals. Environmental and Molecular Mutagenesis 49:(2) 110-116.

Boobis, A.R., Doe. J.E., Heinrich-Hirsche, B., Meek, M.E., Munn, S., Ruchirawat,M., Schlatter,J., Seed,J. and Vickers, C. (2008) IPCS Framework for analysing the relevance of a non-cancer mode of action for humans. Crit. Rev. Toxicol. 38:87-96.

Meek, M.E., Patterson, J., Strawson, J. and Liteplo, R. (2007) Engaging expert peers in the development of risk

assessments. Risk Analysis 28(1):1609-1621.

Meek, M.E. and Armstrong, V.C. (2007) The assessment and management of industrial chemicals in Canada, Risk Assessment of Chemicals, Van Leeuwen, K. and Vermeire, T. Kluwer Academic Publishers, Dordrecht, the Netherlands.

***Stern, BR, Solioz, M, Krewski, D., Aggett, P., Aw, T.C., ...Meek, B., et al. (2007) Copper and Human Health: Biochemistry, Genetics and Strategies for modeling Dose-Response Relationships. J Toxicol Environ Health B Crit Rev*. 10(3): 157-222.**

Zenie, A. and Meek, M.E. (2007) Qualitative Methods for Characterizing Uncertainty in Exposure Assessment, Abstract for the International Society of Exposure Analysis, Durham, RTP, October

Meek, M.E. (2007) Developments in Risk Assessment: Priority Setting and Mode of Action Frameworks, Abstract for the 11th International Congress of Toxicology, Montreal, Quebec, July 15th – 19th.

Meek, M.E. (2007) Regulatory Systems – Are they Working? Considering Dermal Exposure in Evolving Mandates for Existing Substances, Abstract for Occupational and Environmental Exposure of Skin to Chemicals, Golden, Colo., June 20th.

Meek, M.E., Paterson, J. and Hughes, J. (2007) Development and Use of Predictive Hazard Modeling in the Categorization and Screening of Existing Substances at Health Canada, Abstract for U.S. EPA International Science Forum on Computational Toxicology, Research Triangle Park, North Carolina, May 22nd.

Boobis, A.R., Cohen, S.M., Dellarco, V., McGregor, D., Meek, M.E., Vickers, C., Willcocks, D., and Farland, W. (2006) IPCS framework for analysing the relevance of a cancer mode of action for humans. Crit. Rev. Toxicol. 36 (10): 781-92.

Cohen, S.M., Boobis, A.R., Meek, B., Preston, R.J., and McGregor, D.B. (2006) 4-aminobiphenyl and DNA reactivity: Case study within the context of the 2006 IPCS human relevance framework for analysis of a cancer mode of action for humans. Crit. Rev. Toxicol. 36 (10): 803-819.

Meek, M.E. (2006) Application of a framework for mode of action and human relevance analysis of observed tumours in animals (Abstract). Experimental and Molecular Mutagenesis 47(6 401).

Meek, M.E. (2006) A framework for human relevance analysis of information on carcinogenic modes of action. Abstract for U.S. Toxicology and Risk Assessment Conference, April 26th, Cincinnati.

Meek, B. and Renwick, A. (2006) Guidance for the development of chemical specific adjustment factors - Integration with mode of action frameworks. Toxicokinetics and Risk Assessment, Ed. Lipscomb, J.C. and Ohanian,E.V., Informa Healthcare, New York, N.Y.

Meek, M.E. and Liteplo, R. (2006) Peer engagement in the health assessment of Existing Substances under the Canadian Environmental Protection Act (CEPA), Abstract for the Society of Risk Analysis Annual Meeting.

Naumann, B., Meek, B., Dourson, M.L. and Ohanian, E. (2005) The future of chemical specific adjustment factors in risk assessment. Risk Policy Report, August 8.

Meek, M.E. (2005) Chemical-Specific Adjustment Factors (CSAF). Encyclopedia of Toxicology, Elsevier.

Appendix 2: M.E. (Bette) Meek
Publications

Corley, R. Meek, B. and Carney, E. (2005). Mode of Action: Oxalate crystal-induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis-renal and developmental effects of ethylene glycol. Critical Reviews in Toxicology 35 (8-9): 691-702.

Seed, J., Carney, E., Corley, R., Crofton, K., DeSesso, J., Foster, P., Kavlock, R., Kimmel, G., Klaunig, J., Meek, M.E., et al. (2005) Overview: Using mode of action and life stage information to evaluate the human relevance of animal toxicity data. Critical Reviews in Toxicology 35 (8-9):664-672.

Sutcliffe, R., and Meek, M.E. (2005). Consumer Exposure Scenarios in the Health Canada Existing Substances Program, Extended abstract for the EU Workshop on Scenarios Development, Verbania, Italy, June 25th.

Meek, M.E. (2005) Consumer Exposure in the Health Canada Existing Substances Program, Abstract for the IPCS Workshop on the Use of Human Data in Consumer Risk Assessment, Federal Institute for Risk Assessment, Berlin, May 8th.

Meek, M.E. (2005) Developments, Challenges and Opportunities in Risk Assessment of Existing Substances Abstract for the SEP Science and Risk Assessment Committee, Ottawa, April 18th.

Meek, M.E. (2005) Assessing Weight of Evidence for Existing Substances, Abstract for the Society of Risk Analysis Annual Meeting, Orlando, Fla., December 4th – 7th.

Meek, M.E., Liteplo,R., D'Amour, M. and Long, G. (2005) The Identification, Prioritization and Health Risk Assessment of Existing Chemicals in Canada: Addressing Children's Health, Abstract for the 38th Annual Symposium of the Canadian Society of Toxicolog, Montreal, Que., December 6th.

Meek, M.E. (2005) Update on International Initiatives on Guidance for CSAF and PBPK Models in Risk Assessment, Abstract for the Society of Risk Analysis Specialty Group on Dose Response Teleseminar, March 1st.

Meek, M.E. (2004) Human Exposure Assessment for Existing Substances under CEPA 1999, Abstract for Annual Meeting, Society for Risk Analysis, Palm Springs, December 8th.

Meek, M.E. (2004) Risk Assessment of Existing Substances under CEPA, Abstract for CIRTOX 2004, Montreal, May 20th.

Ohanian, E., Dourson, M., Lewis, S., Meek, M.E. et al (2004) A national and international debate on default or Chemical-Specific Adjustment Factors for Precursor and Toxicological Endpoints. Human and Ecological Risk Assessment 10:167-178.

Cohen, S.M., Klaunig, J., Meek, M.E. et al. (2004) Evaluating the human relevance of chemically induced animal tumors. Toxiocological Sciences 78(2): 181-186.

Lipscomb, J.C., Meek, M.E., Krishnan, K., Kedderis, G.L.,Clewell, H. & Haber, L. (2004) Incorporation of pharmacokinetic and pharmacodynamic data into risk assessments. Toxicology Mechanisms and Methods 14: 145-158.

Meek, M.E. (2004) Toxicological Highlight - Biologically motivated computational modelling: Contribution to risk assessment. Toxicological Sciences 82(1): 1-2.

Julien, E., Wilhite, C.C., Richard, A.M., DeSesso, J.M., Brown, N.S., Donohue, J.M., Foster, P.M.D., Hunter, E.S., Meek, M.E. et al. (2004) Challenges in constructing statistically based structure-activity relationship models

for developmental toxicity. Birth Defects Research (Part A) 70: 902-911.

Watts, P., Long, G. and Meek, M.E. (2004) Concise International Chemical Assessment Document 58 on chloroform. World Health Organization, Geneva

Meek, M. E., Bucher, J. R., Cohen, S. M., Dellarco, V., Hill, R. N., Lehman-McKeeman, L. D., Longfellow, D. G., Pastoor, T., Seed, J., Patton, D. E. (2003) A framework for human relevance analysis of information on carcinogenic modes of action. Critical Reviews in Toxicology, 33(6): 591-653.

Cohen, S.M., Meek, M.E., Klaunig, J.E., Patton, D.E., Fenner-Crisp, P.A. (2003) The human relevance of information on carcinogenic modes of action: overview. Crit. Rev. Toxicol. 33(6):581-9.

Meek, M.E., et al. (2003) Practical application of kinetic data in risk assessment. An IPCS initiative. Tox. Letters 138: 151-160.

Meek, M.E. (2003) Risk Assessment of Existing Substances. Poster and Handouts for the Health Canada Science Forum, October 20th.

Kirman, C.R., Sweeney, L.M., Meek, M.E. and Gargas, M.L. (2003) Assessing the dose-dependency of allometric scaling using physiologically based pharmacokinetic modelling. Regul. Toxicol. Pharmacol. 38(3): 345-67.

Liteplo, R.G. and Meek, M.E. (2003) Inhaled formaldehyde: Exposure estimation, hazard characterization and exposure-response analysis. J. Toxicol. Environ. Health, B6(1), 85в114.

Hughes, K., Meek, M.E., Walker, M. and Beauchamp, R. (2003) 1,3-Butadiene: exposure estimation, hazard characterization and exposure-response analysis. J. Toxicol. Environ. Health Part B Crit Rev. 6(1):55-83.

Newhook, R., Hirtle, H., Byrne, K. and Meek, M.E. (2003) Releases from copper smelters and refineries and zinc plants in Canada: human health exposure and risk characterization. Sci. Total Environ. 301: 23-41.

Liteplo, R., Meek, M.E. and Lewis, M. (2003) Concise International Chemical Assessment Document 54 on ethylene oxide. World Health Organization, Geneva

Meek, M E. (2003) IPCS Harmonization Initiative - Approaches to Assessment of Risk. Abstract for Pest Management Regulatory Agency Seminar Series, Ottawa, Jan. 13th.

Meek, M.E., Renwick, A., Ohanian, E., Dourson, M., Lake, B., Naumann, B.D. and Vu, V. (2002) Guidelines for application of chemical-specific adjustment factors in dose/concentration-response assessment, Toxicology December 27th 181-182: 115 – 120.

Meek, M .E. and Renwick, A. (2002) Addressing Variability in Risk Assessment – Recent Developments, Abstract for the Society of Toxicology of Canada – 35th Annual Symposium, Montreal, PQ. December 5-6th.

Meek, M.E. (2002) Refinements – Mode of Action Analysis for Animal-Human Concordance Analysis. Abstract for Annual Meeting of the Society of Risk Analysis, New Orleans, December.

Meek, M.E., Beauchamp, R., Long, G., Moir, D., Turner, L. and Walker, W. (2002) Chloroform: exposure estimation, hazard characterization, and exposure-response analysis, J. Toxicol. Environ. Health B, 5(3): 283-334.

Meek B., Renwick, A., Ohanian, E. and Sonich-Mullin, C. (2002) Guidance for derivation of chemical-specific

Appendix 2: M.E. (Bette) Meek
Publications

adjustment factors (CSAF). Development and implementation, Human Ecol. Risk Assess, 8: 769.

Newhook, R. and Meek, M.E. (2002) Concise International Chemical Assessment Document 46 on carbon disulphide. World Health Organization, Geneva

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Presentations

Meek, M.E. (2013) Recent International Developments in Mode of Action/Adverse Outcome Pathway Analysis. ARA Workshop, Beyond Science & Decisions: Workshop VI, Arlington, May 29th.

Meek, M.E. (2013) Update – WHO International Steering Group on Mode of Action, OECD Advisory Group on Molecular Screening and Toxicogenomics, Paris, May 14th-15th, 2013

Meek, M.E. (2013) Recent Developments in Adverse Outcome Pathway/Mode of Action Analysis. US EPA Arsenic Webinar Series, April 24th.

Meek, M.E. (2013) Integration of Genomic Data in Regulatory Risk Assessment. An International Initiative for Toxicogenomics, Health Canada GRDI Workshop, April 23rd.

Meek, M.E. (2013) Recent International Developments 1) Combined Exposure to Multiple Chemicals and 2) Update of the WHO/IPCS Mode of Action Framework. American Chemistry Council Webinar, April 17th.

Meek, M.E. (2013) Update of the WHO/IPCS Mode of Action Framework. Health Canada Genomics Working Group, April 9th.

Meek, M.E. (2013) International Experience in Addressing Combined Exposures. World Health Organization Meeting on the Regulation of Mixtures of Chemicals in Drinking-water, March 22nd.

Meek, M.E. (2013) Risk Characterization. CE Course - Human Health Risk Assessment, Society of Toxicology Annual Meeting, March 10th.

Meek, M.E. (2013) Revised "Position Paper on Human Health Risk Assessment for Short-term Exposures to Chemicals (Noncancer Endpoints)" Health Canada Peer Consultation, March 1st.

Meek, M.E. (2013) Purpose Oriented Integration of Genomic Data in Regulatory Risk Assessment. ECETOC Workshop on 'Omics and Risk Assessment Science, Malaga, February 25th.

Meek, M.E. (2013) Update of the WHO/IPCS Mode of Action Framework. ECETOC/WHO/IPCS Mode of Action Workshop, Vienna, February 21st.

Meek, M.E. (2012) International Experience in Addressing Combined Exposures. Annual Meeting of the Society of Risk Analysis, San Francisco, December 12th.

Meek, M.E. (2012) Evolution of the ARA Framework on Problem Formulation to Dose-Response. Annual Meeting of the Society of Risk Analysis, San Francisco, December 11th.

Meek, M.E. (2012) Mapping of Risk Assessment Methodologies. Presentation to the WHO Risk Assessment Network, December 7th.

Meek, M.E. (2012) Peer Consultation on "Position Paper on Human Health Risk Assessment for Short-term Exposures to Chemicals (Noncancer Endpoints)" Presentation to Health Canada Risk Assessment Programs, Ottawa, December 5th.

Meek, M.E. (2012) Considering Risks and Uncertainties Related to Combined Exposures. Challenging Boundaries in Risk Assessment - Sharing Experiences, 10th Anniversary of EFSA, Parma, Italy, November 8th.

Meek, M.E. (2012) Opportunities and Obstacles for Populating the Data Landscape. Expodat Symposium, ISES

Appendix 3: M.E. (Bette) Meek
Presentations

2012, Seattle, October 13th.

Meek, M.E. (2012) Improving Current Practice Through Problem Formulation and Mode of Action. SOT CCT FutureTox, Arlington, October 19th.

Meek, M.E. (2012) The Canadian Prioritization Progam & Beyond: Implications for Impact. NICNAS IMAP Launch and Forum, Sydney, Australia, July 19th.

Meek, M.E. (2012) International Developments in Consideration of Combined Exposures to Multiple Chemicals. World Congress of the Society of Risk Analysis, Sydney Australia, July 18th.

Meek, M.E. (2012) Implications of Early Canadian Experience in Considering All Existing Chemicals.. World Congress of the Society of Risk Analysis, Sydney Australia, July 18th.

Meek, M.E. (2012) Introduction and Tutorial on WHO IPCS Framework on Combined Exposure to Multiple Chemicals. ACTRA Workshop, Canberra, July 17th.

Meek, M.E. (2012) Tutorial on WHO IPCS Framework on Combined Exposure to Multiple Chemicals. Continuing Education Course at Eurotox, Stockholm, June 17th.

Meek, M.E. (2012) What Else Can We Do? Exposure Determinants for High-Throughput Exposure Assessment. Expodat 2012, Budapest, June 15th.

Meek, M.E. (2012) WHO IPCS Framework, Combined Exposure to Multiple Chemicals, Beyond Science & Decisions: Workshop IV, Austin, Texas, May 24th.

Meek, M.E. (2012) Uptake and Implementation of International Risk Assessment Methodologies Second WHO Meeting on Global Collaboration in Chemical Risk Assessment – Strengthening Capacity Building and Networking, Bonn, March 29th

Meek, M.E. (2012) WHO IPCS Framework. Combined Exposure to Multiple Chemicals. Second WHO Meeting on Global Collaboration in Chemical Risk Assessment – Strengthening Capacity Building and Networking, Bonn, March 29th.

Meek, M.E. (2012) Perspective from an International Project on Combined Exposures to Multiple Chemicals: Evolution of the WHO IPCS Framework, Society of Toxicology Annual Meeting, San Francisco, March 14th.

Meek, M.E. (2012) Experience and Perspective from an International Project on Combined Exposures. Stakeholder Conference on the Acropolis Research Project, Brussels, February 1st.

Meek, M.E. (2012) Data Synthesis Across Studies & Evaluation/Application. Panel Presentation, American Chemistry Council (ACC) Center for Advancing Risk Assessment Science and Policy's (ARASP) Weight of Evidence Workshop, Washington, December 4th .

Meek, M.E. (2012) Relevance of Biomonitoring Equivalents to Health Canada Risk Assessment Programs. Presentation to Health Canada Risk Assessment Programs, Ottawa, April, 2012.

Meek, M.E. (2012) Problem Formulation to Dose-Response: Advances via the ARA Beyond Science and Decisions Workshops 37th Annual Meeting of the Winter Toxicology Forum, Washington, January 30th, 2012.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2011) Considering Combined Exposures to Environmental Chemicals. Uncertainty, Sensitivity, Communication. International Symposium - Cancers and Environmental Exposures, The French Agency for Food, Environmental and Occupational Health & Safety (ANSES), the French National Cancer Institute (InCa) and the French National Alliance for Life Sciences and Health (AVIESAN), Paris, December 12th.

Meek, M.E. (2011) The Importance of Mode of Action in "Fit for Purpose" Assessment. Society for Risk Analysis Annual Meeting, Charleston, S.C., December 6th.

Meek, M.E. (2011) Recent International Developments in Coordinated Priority Setting and Tiered Assessment, International Society for Exposure Sciences, Baltimore, October 24th.

Meek, M.E. (2011) Evolution of the WHO IPCS Framework on Combined Exposures to Multiple Chemicals, International Toxicology of Mixtures Conference 2011, Arlington, October 21st – 23rd.

Meek, M.E. (2011) Addressing Key Data Gaps and Issues. Minimal Dataset. Exposure-Based Chemical Prioritization Workshop II: US EPA, RTP, NC, September 26th.

Meek, M.E. (2011) Session III: Pathway Based Methods for Toxicity Testing. Implications for Chemical Risk Assessment. Toxicity Pathways Workshop, Ispra, Italy, September 29th.

Meek, M.E. (2011) The WHO IPCS Framework on Combined Exposures to Multiple Chemicals, ECETOC Workshop on Combined Exposure to Chemicals, Berlin, Germany, 11-12 July.

Meek, M.E. (2011) Critical Questions on Napthalene. Naphthalene Research Committee Science Team 2011 Naphthalene Research Meeting, American Chemistry Council, Ottawa, June 29 – 30.

Meek, M.E. (2011) WHO IPCS Framework on Risk Assessment of Combined Exposures to Multiple Chemicals, ICCA-LRI and Health Canada Workshop – Advancing Exposure Science to Improve Chemical Safety, Quebec City, June 22nd-23rd.

Meek, M.E. (2011) "Fit for Purpose" MOA/Human Relevance Analysis, Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Alliance for Risk Assessment Workshop III, Arlington, May 4th – 6th.

Meek, M.E. (2011) More Efficiently Addressing Combined Exposures to Multiple Chemicals, Health Canada Contaminated Sites Workshop on Mode of Action/Human Relevance Analysis, Mutagenic Modes of Action and Combined Exposures, University of Ottawa, March 23rd.

Meek, M.E. (2011) Overview Presentation, Health Canada Contaminated Sites Workshop on Mode of Action/Human Relevance Analysis, Mutagenic Modes of Action and Combined Exposures, University of Ottawa, March 23rd.

Meek, M.E. (2011) Problem Formulation and Risk Assessment Needs, Annual Meeting of the Society of Toxicology, Washington, D.C., March 10th.

Meek, M.E. (2011) WHO IPCS Combined Exposures Framework. Illustrative Case Study, WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals, Paris, February 15th.

Meek, M.E. and A. Kortenkamp (2011) Thought Starter on Combined Exposures to Multiple Chemicals, Global

Appendix 3: M.E. (Bette) Meek
Presentations

Risk Assessment Dialogue, Second International Conference on Risk Assessment, Brussels, January 27th.

Meek, M.E. and A. Kortenkamp (2011) Report of Workgroup 5: Second International Conference on Risk Assessment, Brussels, January 28th.

Meek, M.E. (2010) International Developments – More Efficiently Addressing Combined Exposures to Multiple Chemicals, Society of Risk Analysis Annual Meeting, Salt Lake City, December 8th.

Meek, M.E. (2010) Ensuring Efficiency in Assessment to Meet Identified Needs: the Importance of Problem Formulation/Issue Identification, Society of Risk Analysis Annual Meeting, Salt Lake City, December 7th.

Meek, M.E. (2010) Enhancing the uptake of PBPK models by the Regulatory Community. The WHO/IPCS Project on Good PBPK Modelling Practice, Society of Risk Analysis Annual Meeting Salt Lake City, December 6th

Meek, M.E. (2010) Scoping of Priorities in Mode of Action/Human Relevance Analysis, WHO IPCS Planning Meeting on Mode of Action, London, October 14th.

Meek, M.E. (2010) Mode of Action/Human Relevance Analysis, Nuclear Receptor Workshop, Research Triangle Park, N.C. September 27th.

Meek, M.E. (2010) Considering Combined Exposures in Risk Assessment: Recent Developments, Opportunities & Challenges, XII International Congress of Toxicology (ICT XII), Barcelona, July 23rd.

Meek, M.E. (2010) Mode of Action/Human Relevance Analysis: Napthalene. Annual Meeting of the Toxicology Forum, Aspen, July 15th.

Meek, M.E. (2010) Developments and Good Practice in Mode of Action / Human Relevance Analysis. Society of Toxicology Risk Assessment Specialty Section (RASS) Seminar Series, June 30th.

Meek, M.E. (2010) Developments & Good Practice in Mode of Action/Human Relevance Analysis. Risk 21 Dose Response Subteam Meeting, ILSI HESI, Washington, June 28th.

Meek, M.E. (2010) Integrated Tools for the Next Generation of Risk Assessment – Challenges and Possibilities. Integrating New Advances in Exposure Science and Toxicity Testing: Next Steps, Stresa, June 16th.

Meek, M.E. (2010) The Evolution of Chemical Risk Assessment. Default to Data-Informed. The Derivation of a Derived No Effect Level using PBPK & Benchmark Dose Response Modelling, UK Health and Safety Laboratory, Buxton, U.K., June 15th.

Meek, M.E. (2010) Enhancing the Uptake of Predictive Models by the Regulatory Community, QSAR 2010, Montreal, May 27th.

Meek, M.E. (2010) "Benchmarking" Exposure Priority Setting Tools. Exposure-Based Chemical Prioritization Workshop: Exploring Opportunities for Collaboration, Research Triangle Park, North Carolina, April 6th.

Meek, M.E. (2010) The Evolution of Chemical Risk Assessment. Quantitative Modelling. Annual Meeting of the British Toxicology Society, Edinburgh, March 30th.

Meek, M.E. (2010) Directions in the Science of Chemical Risk Assessment, WHO/IPCS Meeting on

Appendix 3: M.E. (Bette) Meek
Presentations

Strengthening Global Collaboration in Chemical Risk Assessment, March 22nd.

Meek, M.E. (2010) Developing risk assessment. Beyond Science and Decisions. Beyond Science and Decisions: From Problem Formulation to Dose-Response, Texas Commission on Environmental Quality, Austin, March 16th.

Meek, M.E. (2010) Potential options in characterizing risks above guidelines. Workshop on current state-of knowledge in health risk assessment approaches for drinking water chemicals, Health Canada, Ottawa, February 1st.

Meek, M.E. (2010) Tools for Priority Setting, Presentation to the Council of Canadian Academies on the Integrated Testing of Pesticides, January 14th.

Meek, M.E. (2009) Risk assessment of combined exposures to multiple chemicals: a WHO/IPCS framework, Annual Symposium of the Canadian Society of Toxicology, Montreal, December 1st.

Meek, M.E. (2009) Transitioning to Mode of Action Based Testing: Frameworks for Human Relevance Analysis of Modes of Action & Predictive Methodologies, European Chemicals Agency, Helsinki, November 5th.

Meek, M.E. (2009) The IPCS human relevance framework and examples of its use. ECETOC, ILSI-HESI, and ILSI Research Foundation workshop on using mode of action information to improve regulatory decision making, November 2nd.

Meek, M.E. (2009) Principles of characterizing and applying physiologically based pharmacokinetic models – an Introduction. Symposium 6: Best practice in biologically based toxicokinetic modeling for risk assessment. Eurotox, Dresden, September 15th.

Meek, M.E. (2009) Interpreting Available Data & Identifying Critical Data Gaps for Benzene Risk Assessment. Role of MOA/HR Frameworks, Benzene 2009, Munich, September 8th

Meek, M.E. (2009) Overview of the Project. WHO/IPCS International Workshop on Principles of Characterizing and Applying PBPK Models in Chemical Risk Assessment, Berlin, July 6th.

Meek, M.E. (2009) Current State of the Science in Chemical Risk Assessment, Workshop on International Implications of the U.S. National Research Council Report on Toxicity Testing in the 21st Century: Challenges and Opportunities in Implementation, University of Ottawa, June 29th,

Meek, M.E. (2009) Testing the Framework, Workshop on A Framework for the Development and Application of Environmental Biological Monitoring Guidance Value, Woburn, U.K., June 18th.

Meek, M.E. (2009) The Mode of Action/Human Relevance Framework & Transition to Mode of Action Based Testing, Exxon Mobil, Inc., Newark, N.J., May 20th.

Meek, M.E. (2009) Le Cadre de Travail pour Évaluer la Pertinence Humaine des Modes D'Action, Séance du Groupe du travail des "Valeurs toxicologiques de référence", Agence Française de Sécurité Sanitaire de l'Environnement et du travail (AFSSET), Paris, April 10th.

Meek, M.E. (2009) Overview of the Mode of Action/Human Relevance Framework. Implications for Dose-Response, Society of Toxicology Annual Meeting, March 16th.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2009) Promoting Understanding, Use and Best Practice for PBPK Modelling, An IPCS Initiative, Society of Toxicology Annual Meeting, March 18th

Meek, M.E. (2009) Developments in Chemical Risk Assessment, NCEA, US EPA, Cincinnati, January 6th.

Meek, M.E. (2008) Developments in Chemical Risk Assessment, RIVM, Utrecht, the Netherlands, November 20th.

Meek, M.E. (2008) Opponent Comments: Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information, Second OSIRIS Stakeholder Workshop Human and environmental toxicity and exposure: results and critical points of the OSIRIS framework, November 17th.

Meek, M.E. (2008) Prioritizing Chemicals for Safety Assessment, Safety Workshop, Emerging Science of Safety, Personal Care Products Council, Newark, October 22nd.

Meek, M.E. (2008) Weight of Evidence for Dose-Response: Considerations and Framework Development, Session on Methodological Advances in the Use of Weight of Evidence in Risk Assessment, Recent Initiatives, Eurotox, Rhodes, October 7th.

Meek, M.E. (2008) Next Steps in Evolution of the ILSI/IPCS Mode of Action (MOA)/Human Relevance (HR) Framework, 34th Annual Summer Meeting of the Toxicology Forum, Aspen, July 7th – 10th.

Meek, M.E. (2008) Considering Exposure in Priority Setting. Categorization of the Domestic Substances List under the Canadian Environmental Protection Act (CEPA), U.S. EPA Exposure Prioritization Community of Practice Teleconference, July 8th.

Meek, M.E. (2008) The Path to Integration of Advanced Technologies in Risk Assessment:Developments, Opportunities and Challenges ICCA –LRI Workshop on Twenty-first Century Approaches to Toxicity Testing, Bimonitoring and Risk Assessment, Amsterdam, June 16th–17th.

Meek, M.E. (2008) The Framework for Human Relevance (HR) of Mode of Action (MOA) A California Mode of Action Workshop: Characterizing Dose Response & Hazard, Sacramento, May 20th.

Meek, M.E. (2008) International Advancements in Risk Assessment Methodology: Increasing Transparency, Reducing Uncertainty and Improving Efficiency. Office of Chemical Safety, Department of Health and Ageing, Canberra, April15th , Office of the National Industrial Chemicals Notification Scheme (NICNAS), Sydney, April 17th, Department of Health and Ageing, Canberra, April 21st and the Advisory Group on Chemical Safety, Canberra, April 23rd.

Meek, M.E. (2008) The Health Canada Existing Substances Programme/Categorization of 23, 000 Substances on the Domestic Substances List, Office of Chemical Safety, Department of Health and Ageing, Canberra, April15th , Office of the National Industrial Chemicals Notification Scheme (NICNAS), Sydney, April 17th, the Advisory Group on Chemical Safety, Canberra, April 22nd and meeting of industrial representatives, Sydney, April 30th..

Meek, M.E. (2008) The Framework for Human Relevance (HR) of Mode of Action (MOA), Office of Chemical Safety, Department of Health and Ageing, Canberra, April 15th , and Office of the National Industrial Chemicals Notification Scheme (NICNAS), Sydney, April 18th and the Advisory Group on Chemical Safety, Canberra, April 23rd.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2008) Evaluating the Human Relevance of Modes of Action in Animals, A Course for the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Canberra, April 29th.

Meek, M.E. (2008) Chemical Specific Adjustment Factors(CSAF). Guidance of the International Programme on Chemical Safety (IPCS), Office of the National Industrial Chemicals Notification Scheme (NICNAS), Sydney, April 18th and Office of Chemical Safety, Department of Health and Ageing, Canberra, April 23rd.

Meek, M.E. (2008) Chemical Specific Adjustment Factors (CSAF). Guidance of the International Programme on Chemical Safety (IPCS), IPCS Training Course, Bradford, U.K., March 26th-27th.

Meek, M.E. (2008) Chemical Specific Adjustment Factors (CSAF). Guidance of the International Programme on Chemical Safety, Society of Toxicology Continuing Education Course, Annual Meeting, Seattle, Washington, March 16th.

Meek, M.E. (2008) Issue Identification . Experience in the Health Canada Existing Substances Programme, International Programme on Chemical Safety (IPCS) Risk Assessment Tookit Meeting , Montreux, March 6th to 7th.

Meek, M.E. (2008) The Health Canada Existing Chemicals Programme, Tools for Priority Setting, International Programme on Chemical Safety (IPCS) Risk Assessment Tookit Meeting , Montreux, March 6th to 7th.

Meek, M.E. and Hughes, K. (2008) Problem Formulation/Issue Identification . Experience in the Health Canada Existing Substances Programme, ILSI Risk Sciences Institute Meeting on Problem Formulation, Washington, D.C., February 27th – 28th.

Meek, M.E. (2008) The Framework for Human Relevance (HR) of Mode of Action (MOA), 33rd Annual Winter Meeting of the Toxicology Forum, Washington, D.C., January 29th to 31st.

Dearfield, K. and Meek, M.E. (2007), Regulatory Perspectives on the Use of Weight of Evidence, Annual Meeting of the Society for Risk Analysis, San Antonio, December 9th to 12t.h.

Meek (2007) Considering Mechanistic Data to Assess Human Relevance, International Training Course on Health/Environmental Risk and Impact, Chulabhorn Research Institute, Bangkok, December 6th.

Meek, M.E. (2007) The Health Canada Existing Chemicals Programme, Meeting of Experts on Formaldehyde, French Agency for Environmental and Occupational Health, Paris, November 19th – 20th.

Meek, M.E. (2007) Priority Substances Assessment on Formaldehyde, Meeting of Experts on Formaldehyde, French Agency for Environmental and Occupational Health, Paris, November 19th – 20th.

Meek, M.E. (2007) The Framework for Human Relevance (HR) of Mode of Action (MOA), National Research Council Workshop on Mouse Liver Tumours, Washington, D.C. Nov. 8th to 9th.

Meek, M.E. (2007) Considering Consumer Exposure to Existing Substances, ISP/PPP/AAPS Workshop, Trailblazing the Skin Frontier: Evidence Base. Opportunities and Training, George Washington University, Washington, August 12th.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2007) Developments in Risk Assessment. Priority Setting and Mode of Action Frameworks, 11th International Congress of Toxicology Montreal, Quebec, July 17th.

Meek, M.E. (2007) The International Programme on Chemical Safety and Risk Sciences Institute Human Relevance Frameworks, 33rd Annual Summer Meeting of the Toxicology Forum, Aspen, Colo., July 12th.

Meek, M.E. (2007) Regulatory Systems – Are they Working? Considering Dermal Exposure in Evolving Mandates for Existing Substances, Occupational and Environmental Exposure of Skin to Chemicals, Golden, Colo., June 20th.

Benz, R.D., Collins, T.FX., DeSesso, J.M., Foster, P.M.D., Gu, Y., Hew K.W., Matthews, E. J., Meek, M.E., Mirkes, P.E., Richard, A.M., Seed, J., Shackelford, M., Stump D.G., .Willhite, C.C.. Wise, L.D., Yang, C., Van Landingham, C. and Julien, E. (2007) A Robust Developmental Toxicity Database, Live Prototype Demonstration, Teratology Society 47th Annual Meeting, Pittsburgh, June 24th.

Meek, M.E. (2007) Development and Use of Predictive Hazard Modeling in the Categorization and Screening of Existing Substances at Health Canada, U.S. EPA International Science Forum on Computational Toxicology, Research Triangle Park, North Carolina, May 22nd.

Benz, R.D., Collins, T.FX., DeSesso, J.M., Foster, P.M.D., Gu, Y., Hew K.W., Matthews, E. J., Meek, M.E., Mirkes, P.E., Richard, A.M., Seed, J., Shackelford, M., Stump D.G., .Willhite,C.C.. Wise, L.D., Yang,C., Van Landingham, C. and Julien, E. (2007) Towards Refined Use of Toxicity Data in Statistically Based SAR Models for Developmental Toxicity, U.S. EPA International Science Forum on Computational Toxicology, Research Triangle Park, North Carolina, May 21st.

Patterson, J., Strawson, J., Meek, M.E., and Liteplo, R. (2007) Expanding the Role of Expert Peer Involvement in Risk Assessment: A Comprehensive Process, 46th Annual Meeting of the Society of Toxicology, Charlotte, North Carolina, March 25th – 29th.

Meek, M.E., Liteplo, R., Patterson, J. and Strawson, J (2007) Expanding the Role of Expert Peer Involvement in Risk Assessment: Use of Experts in the CEPA Existing Substances Programme, 46th Annual Meeting of the Society of Toxicology, Charlotte, North Carolina, March 25th – 29th.

Dellarco, V., Fenner-Crisp, P., Meek, M.E., Olin, S. and Patton, D. (2007) Evaluating the Human Relevance of Animal Modes of Action, ILSI Research Foundation Workshop Course, ILSI, Washington, April 16th.

Meek, M.E. (2007) Physiologically-Based Pharmacokinetic Modelling: the Needs of Risk Assessors, An International Workshop on the Development of Good Modelling Practice for PBPK Models, Chania, Crete, April 27th to 29th.

Meek, M.E. (2007) Screening level risk assessment of mixtures – An Example – Polybrominated diphenyl ethers (PBDEs). Abstract for the International Programme on Chemical Safety Workshop on Aggregate/Cumulative Risk Assessment, Washington, D.C., March 19th.

Meek, M.E. (2007) Improving linkages between the IPCS CICADs and Harmonization Programs, Presentation to the 14th Final Review Board meeting for Concise International Chemical Assessment Documents, Helsinki, March 26th to 29th.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2006) Weight of Evidence. Some Thoughts from an Existing Substances Perspective, Panel Discussion – International Life Sciences Institute (ILSI) Workshop on Approaches to Weight of the Evidence Evaluation, Baltimore, December 7th.

Meek, M.E. and Liteplo, R. (2006) Peer Engagement in the Health Assessment of Existing Substances under the Canadian Environmental Protection Act (CEPA), Society of Risk Analysis (SRA) Annual Meeting, Baltimore, December 6th.

Dellarco, V., Fenner-Crisp, P., Meek, M.E., Olin, S. and Patton, D. (2006) Evaluating the Human Relevance of Animal Modes of Action, ILSI Research Foundation Society for Risk Analysis Continuing Education Course, Baltimore, December 3rd.

Haber, L., Lipscomb, J. and Meek, M.E. (2006) Chemical Specific Adjustment Factors, Society for Risk Analysis Continuing Education Course, Baltimore, December 3rd.

Meek, M.E. (2006) Application of a Framework for Mode of Action and Human Relevance Analysis of Observed Tumours in Animals, 37th Annual Environmental Mutagen Society Meeting, Vancouver, B.C., September 17th.

Meek, M.E. et al. (2006) Consumer Exposure Scenarios in the Health Canada Existing Substances Program International Society for Exposure Analysis Annual Meeting, Paris, France, September 5th.

Meek, M.E. (2006) Biomonitoring for Risk Assessment and Policy, International Council of Chemical Associations Biomonitoring Science Meeting, Minneapolis, Minnesota, July 26th.

Meek, M.E. (2006) Case Study of A Cancer Risk Assessment: Ethylene Oxide - Some Observations. 35th Annual Summer Meeting of the Toxicology Forum, Aspen, July 13th.

Meek, M.E. (2006) Cumulative Risk Assessment - Challenges for Assessment of Existing Chemicals, 35th Annual Summer Meeting of the Toxicology Forum, Aspen, July 12th.

Meek, M.E. (2006) Existing Substances Science and Research Agenda, Presentation to Research-Assessment Workshop, Ottawa, June 29th.

Liteplo, R. and Meek, M.E. (2006) Health-Related Categorization - Process, Multi-Stakeholder Technical Briefing on Categorization and PostBCategorization, Ottawa, June 12th.

Meek, M.E. and Liteplo, R. (2006) Health-Related Categorization – Results, Multi-Stakeholder Technical Briefing on Categorization and PostBCategorization, Ottawa, June 12th.

Meek, M.E. (2006) Guidance for Chemical-Specific Adjustment Factors, U.S. EPA Risk Assessment Forum Teleconference, May 09th.

Meek, M.E. (2006) Application of Quantitative Structure Activity Response [(Q)SAR] Modelling to the Prioritization and Assessment of Existing Substances at Health Canada, Leadscope Consortium Meeting, Bethesda, April 27-28th.

Meek, M.E. (2006) A Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action, 2006 Toxicology and Risk Assessment Conference, Cincinnati, April 26th.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2006) Human Relevance. Renal and Developmental Toxicity of Ethylene Glycol, International Programme on Chemical Safety (IPCS) Workshop on Human Relevance, Extension to Non-Cancer, Geneva, March 30th-31st.

Meek, M.E. (2006) Categorization of the Domestic Substances List (DSL), Environment Canada (EC)-Health Canada (HC) Technical Briefing, Ottawa, March 9th.

Meek, M.E. (2006) Priority Setting and Screening of Existing Substances – Health Aspects, Meeting with U.S. Environmental Protection Agency (U.S. EPA), Washington, D.C., March 1st – 2nd.

Meek, M.E. (2006) State of the Science Reports, Industry Coordinating Group Meeting, Toronto, February 14th.

Meek, M.E. (2005) The Mandate for Priority Setting and Assessment of Existing Substances in Canada in the Context of Children, 38th Annual Symposium of the Society of Toxicology of Canada, Montreal, December 6th.

Meek, M.E. (2005) Assessing Weight of Evidence for Existing Substances, Society of Risk Analysis Annual Meeting, Orlando, December 5th.

Haber, L., Meek, M.E. and Lipscomb, J. (2005) Chemical Specific Adjustment Factors, Society for Risk Analysis Continuing Education Course, Orlando, December 4th.

Meek, M.E. (2005) Canadian Experience - Priority Setting and Screening of All Existing Substances under the Canadian Environmental Protection Act (CEPA), International Society of Regulatory Toxicology and Pharmacology Workshop on Progress and Barriers to incorporating Alternative Toxicological Methods in the U.S., Baltimore, MD, November 18th.

Meek, M.E. (2005) Mode of Action Analysis in Risk Assessment, Panel Discussion, ILSI Workshop on Framework Approaches to Risk Assessment, Nice, France, November 15th.

Meek, M.E. (2005) HC Categorization Package. Relevant Documentation, HC/EC meeting with the Industry Coordinating Group (ICG)/Environmental Non-Governmental Organizations (ENGOs), Hull, November 22nd.

Meek, M.E. and Liteplo, R. (2005) HC Domestic Substances List (DSL) Results, Meeting of HC with ENGOs, Ottawa, October 28th.

Meek, M.E. (2005) Focus on the Margins of Exposure, Meeting of HC with ENGOs, Ottawa, October 28th.

Meek, M.E. (2005) Priority Setting and Screening of All Existing Substances in Canada, Meeting of the U.S. National Academy of Sciences Committee on Toxicity Testing & Assessment of Environmental Agents, Washington, D.C., October 20th.

Meek, M.E. (2005) IPCS Harmonization Initiative on Guidance for PBPK Models in Risk Assessment, ECVAM Workshop on PBPK Modelling, October 10th.

Meek, M.E. (2005) Update on Health Canada=s Activities for Categorization and Screening of the DSL, Industry Coordinating Group Update Conference, Toronto, October 7th.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2005) (Q)SAR Weight of Evidence in Priority Setting and Assessment of Existing Substances at Health Canada, Consultation Meeting on Consensus Modelling and Battery Approaches in QSAR, European Chemicals Bureau, Joint Research Centre, Ispra, September 26th.

Meek, M.E. (2005) Update on DSL Priority Setting/Screening to the Industry Coordinating Group/Environmental Non-Governmental Organizations, Meeting of EC/HC with ICG/ENGOS, Ottawa, September 8th.

Meek, M.E. (2005) Update on DSL Priority Setting/Screening to the Environmental Non-Governmental Organizations, Meeting of HC with ENGOS, Ottawa, September 7th.

Paterson, J., Meek, M.E., Albert, M. and Shaw, M. (2005) (Q)SAR Developments in Priority Setting and Assessment of Existing Substances at Health Canada, Meeting with the European Chemicals Bureau/Denmark/the Netherlands, Ottawa, August 17th.

Meek, M.E. (2005) Context – Scoping the Analogues Project, Meeting with the European Chemicals Bureau/Denmark/the Netherlands, August 15th.

Meek, M.E. (2005) Meeting the Expanded CEPA Mandate for Existing Substance, Focus on Priorities Process/Content/Results/Next Steps, Meeting with Toxicology Advice and Consulting, Ottawa, July 28th.

Sutcliffe, R. and Meek, M.E. (2005) Exposure Modeling for Consumer Products in the Health Canada Existing Substances Program, Verbania, June 24th.

Meek, M.E. (2005) Update on DSL Categorization & Screening - Health, EC Meeting with ICG/ENGOs, Ottawa, June 1st.

Meek, M.E. (2005) Consumer Exposure in the Health Canada Existing Substances Program, IPCS Workshop on the Use of Human Data in Consumer Risk Assessment, Federal Institute for Risk Assessment, Berlin, May 9.

Meek, M.E. (2005) (Q)SAR Developments in Priority Setting and Assessment of Existing Substances at Health Canada, ECB Consultation Meeting on the Development of an International QSAR Decision Support System, Milan, April 28th.

Meek, M.E. (2005) An IPCS Integrated Framework for Weight of Evidence/Human Relevance of Mode of Action, IPCS Cancer Framework Workshop, Bradford, U.K., April 21-23.

Paterson, J. and Meek, M.E. (2005) Complex Hazard Tool (ComHaz) Weight of Evidence Component - TERA Peer Consultation Teleconference, Ottawa, April 19th.

Meek, M.E. (2005) Developments, Challenges and Opportunities in Risk Assessment of Existing Substances, Seminar for Health Canada, SEP Science and Risk Assessment Committee, Ottawa, April 18th.

Glover, P. and Meek, M.E. (2005) DSL Categorization/Screening – Human Health. Update for the U.S. Safe Management of Chemicals Meeting, Chicago, April 18th.

Meek, M.E. (2005) Possible International Initiative on Guidance for Physiologically Based Pharmacokinetic (PBPK) Models in Risk Assessment, IPCS Harmonization Teleconference, Ottawa, April 15th.

Meek, M.E. (2005) DSL Categorization/Screening – Human Health. The Need for Robust (Q)SAR Models, ILSI

Appendix 3: M.E. (Bette) Meek
Presentations

Meeting of the Developmental Toxicity Structure Activity Working Group, March 30-31st.

Meek, M.E. (2005) DSL Categorization/Screening – Human Health, Briefing for EU Reach Implementation Project 3.3, Brussels, March 15th.

Meek, M.E. (2005) Update on International Initiatives on Guidance for Chemical Specific Adjustment Factors and Physiologically Based Pharmacokinetic (PBPK) Models in Risk Assessment, SRA Specialty Group on Dose Response Teleseminar, March 1st.

Meek, M.E. (2004) Where Does the Complex Exposure Tool (ComET) Fit? Objectives of the Meeting, Meeting with the Lifeline Group and the Canadian Environmental Modeling Centre, Toronto, December 14th-15th.

Clarkson, S. and Meek, M.E. (2004) Role of Assessment of Existing Substances under CEPA 1999, Society of Toxicology of Canada 37th Annual Symposium, Montreal, Dec. 10th.

Meek, M.E. (2004) World Health Organization (WHO) Drinking Water Guideline on Vinyl Chloride, Panel Session, Annual Meeting, Society for Risk Analysis, Palm Springs, Dec. 8th.

Meek, M.E. and Sutcliffe, R. (2004) Human Exposure Assessment for Existing Substances under CEPA 1999, Annual Meeting, Society for Risk Analysis, Palm Springs, December 8th.

Meek , M.E. (2004) Health Risk Assessment for Existing Substances under CEPA 1999, Presentation to Canadian Consultants, Toronto, November 23rd.

Meek, M.E. (2004) Health Related Components of DSL Categorization under CEPA 1999, Update on Screening/What we have Learned/Path forward, Existing Substances Information Session for Stakeholders, Toronto, November 22nd.

Meek, M.E. (2004) Health Related Components of DSL Categorization under CEPA 1999 - The Integrated Framework, Existing Substances Information Session for Stakeholders, Toronto, November 22nd.

Meek, M.E. (2004) Objectives, Existing Substances Information Session for Stakeholders, Toronto, November 22nd.

Meek, M.E. (2004) Path Forward, Complex Exposure Tool Peer Input Meeting, Cincinnati, Ohio, Nov.8th.

Meek, M.E. (2004) Context & Objectives, Complex Exposure Tool Peer Input Meeting, Cincinnati, Ohio, Nov.8th.

Meek, M.E. (2004) Guidance for PBPK Models in Risk Assessment, 7th Meeting of IPCS Harmonization Steering Committee, Cincinnati, Ohio, Oct. 24th – 25th.

Meek, M.E. (2004) Development of the Complex Exposure Tool under the Canadian Environmental Protection Act - Context/Relevance to REACH, European Consumer Exposure Modelling Workshop, October 25th.

Meek, M.E. (2004) Chemical Risk Assessment - Application to Risk Management, IPCS Workshop on Chemical Safety, Hanoi, Sept. 17th.

Meek, M.E. (2004) Update on Health Aspects of Categorization, CEPA Industry Coordinating Group Meeting, Ottawa, July 14th.

Appendix 3: M.E. (Bette) Meek
Presentations

Meek, M.E. (2004) CEPA Assessment for Human Health for Existing Substances, The Path to 2006 & Beyond, Binational Toxics Strategy Integration Workshop, Toronto, June 16th.

Meek, M.E. (2004) CEPA Assessment for Human Health, The Path to 2006 & Beyond, Plenary Session, Industry Coordinating Group Update Conference, Toronto June 3rd.

Meek, M.E. and Sutcliffe, R. (2004) Health Assessment of Existing Chemicals under CEPA, Workshop, ICG Update Conference, Toronto, June 1st.

Meek, M.E. (2004) Categorization & Screening for Human Health. The Path to 2006 & Beyond, Meeting with U.S. Environmental Protection Agency, Washington, DC, May 25th.

Meek, M.E. (2004) Risk Assessment of Existing Substances under CEPA, Developments in Methodology, Plenary Lecture, CIRTOX 2004, University of Quebec, Montreal, May 20th.

Meek, M.E. (2004) Where to From Here – The Complex Exposure Tool, Update to the CEPA Industry Coordinating Group, Ottawa, May 17th.

Meek, M.E. (2004) Health Components of DSL Categorization- Substances of Unknown and Variable Composition and Biologicals (UVCBs) and Polymers. What Do We Need? CEPA Industry Coordinating Group, Toronto, April 19th.

Meek, M.E. (2004) Assessment of Existing Chemicals under CEPA – Update to Canadian Chemical Specialty Producers Association Interface, Toronto, April 5th.

Meek, M.E. (2004) Process - Health Assessment of Existing Chemicals under CEPA, Proctor & Gamble, Toronto, April 1st.

Meek, M.E. (2004) Objectives, Information Briefing – Health Assessment of Existing Chemicals, Information Briefing for Stakeholders, Toronto, March 8th.

Meek, M.E. (2004) Objectives, Overview - Health Assessment of Existing Chemicals under CEPA, Information Briefing for Stakeholders, Toronto, March 8th.

Meek, M.E. (2004) Path Forward - Health Assessment of Existing Chemicals under CEPA, Information Briefing for Stakeholders, Toronto, March 8th.

Meek, ME. (2004) Health Canada Perspective: Categorization and screening of the Domestic Substances List, Annual Canadian Chemicals Specialty Producers Association/Federal Government Interface, Ottawa, February 4th.

Snellings, W. and Meek, M.E. (2004) Case Study: Ethylene Glycols Category, Relationships in Structural, Physicochemical, Environmental Fate/Effects and Toxicological Properties, OECD High Production Volume Chemicals Workshop on Categories, January 29th to 30th.

Meek, M.E. (2004) An update on priority setting and screening of Existing Chemicals, CEPA Imdustry Coordinating Group (ICG) Meeting, December 10th.

Meek, M.E. (2003) Priority Setting and Assessment of Health Effects of Existing Chemicals in Canada, EU

Appendix 3: M.E. (Bette) Meek
Presentations

Chemicals Control Workshop, Ispra, December 1st.

Meek, M.E. (2003) Proposal for Greatest Potential for Human Exposure – Categorization and an Update on Screening, CEPA Industry Coordinating Group, October 1st.

Meek, M.E. and Liteplo, R. (2003) Priority Setting and Assessment – Research Priorities, Presentation to the Chief Scientist of HC, September 24th.

Beauvais, J. and Meek, M.E. CEPA '99 Existing Substances, Presentation to Officials of DG Enterprise, DG Environment and the Joint Research Centre of the European Union, Brussels, July 4th.

Meek, M.E. (2003) Chemical Specific Adjustment Factors, Guidance for Adequacy of Data, Mini Symposium on Risk Methods Harmonization, 2003 World Congress on Risk, Brussels, June 25th.

Meek, M.E. (2003) Update on DSL to the Danish Environmental Protection Agency, Copenhagen, June 11th.

Meek, M.E. (2003) Update on DSL to Toxicology Advice and Consulting, Sutton, U.K., May 7th.

Meek, M E. (2003) Priority Setting/Assessment DSL - Health Canada (HC). DSL Briefing to the CEPA Industry Coordinating Group, Ottawa, April 23rd.

Meek, M.E. (2003) Update on DSL. Presentation to the Environment Canada/Health Canada Risk Assessment Risk Management Workshop, Ottawa, April 11th.

Meek, M E.(2003) Process/Focus - Priority Substances Assessment - 2-BE – Briefing to the American Chemistry Council, Ottawa, April 10th.

Meek, M.E. (2003) Implications of Mandate for Existing Substances under CEPA for Research on Foods, Presentation to Research Scientists in the Food Directorate, HC, Ottawa, April 4th.

Meek, M .E. (2003) Background and Objectives – Suspension of the PSL 2 Assessment on Aluminum Salts, Meeting of the Expert Steering Committee on Neurotoxicity of Aluminum, Ottawa, March 27th – 28th.

Meek, M. E. and Myres, A. W. (2003) Developments in Risk Assessment – Children's Health, CEC North American Workshop on Risk Assessment and Children's Environmental Health, Mexico, February 19th – 21s.

Meek, M E. (2003) Priority Setting/Assessment DSL - Health Canada (HC), DSL Briefing to the CEPA Industry Coordinating Group, Ottawa, February 20th.

Meek, M E. (2003) Priority Setting/Assessment DSL - Health Canada (HC), Update to the Canadian Chemical Producers Association. Ottawa, February 19th.

Meek, M E. (2003) Priority Setting/Assessment DSL - Health Canada (HC). Annual Government Interface Session of the Canadian Chemical Specialties Producers Association, Ottawa, February 5th.

Meek, M E. (2003) IPCS Harmonization Initiative - Approaches to Assessment of Risk. Pest Management Regulatory Agency Seminar Series, Ottawa, Jan. 13th.

Meek, M E. (2002) Refinements - Mode of Action Analysis for Animals-Human Concordance Analysis. Society for Risk Analysis Annual Meeting, New Orleans, Louisiana, December 10th.

M.E. (Bette) Meek
Presentations

Meek, M E. (2002) The Continuum – Default to Data – Informed. Roundtable on A Data-Informed Framework for the Development of Uncertainty Factors, Annual Meeting of the Society for Risk Analysis, New Orleans, Louisiana, December 10th.

Meek, M .E. and Renwick, A. (2002) Addressing Variability in Risk Assessment – Recent Developments, Society of Toxicology of Canada – 35th Annual Symposium, Montreal, PQ. December 5-6th.

Meek, M.E. (2002) Case Study Preview, ILSI Workshop on the Human Relevance of Animal Tumours, Washington, December 4th.

Meek, M.E. (2002) Update on categorization and screening to the CEPA Industry Coordinating Group, Hull, November 22nd.

Meek, M.E. (2002) Priority Setting/Assessing DSL at Health Canada, Presentation to industry representatives and ENGOs, Ottawa, Nov. 21st.

Meek, M.E. (2002) Introduction, Context and Objectives, Discussion of Hazard Profiling for Categorization, Presentation to industry representatives and ENGOs, Ottawa, Nov. 21st.

Meek, M E. (2002) Debate: Precursor or End Stage Lesion: Same or Different Uncertainty Factors?, Sixth Annual Meeting on Chemical Specific Adjustment Factors in Health Risk Assessment. Newark, N.J., November 15th.

Meek, M.E. (2002) Objectives and Charge - Consultation with Industrial Stakeholders on Consideration of DSL Use Codes in Characterizing Potential for Exposure for DSL categorization, Ottawa, October 18th.

Meek, M.E. (2002) Priority Setting/Assessing Substances on the Domestic Substances List, CEPA Industry Coordinating Group Update Conference on Existing/New Chemicals, Toronto, October 10th.

Meek, M.E. (2002) CEPA Existing Substances Program with Emphasis on Priority Setting, U.S. National Academy of Sciences Subcommittee on Acute Exposure Guideline Levels, Washington, September 2nd.

Meek, M.E. (2002) Categorization and Screening of the Domestic Substances List in Canada – HC Component, Potential Relevance to Scheduling of the Food and Drugs Act under CEPA, Presentation to HC EC CEPA programs, June 17th.

Meek, M.E. (2002) Context and Charge, Consultation with TNO/BIBRA to consider approach to priority setting for "inherent toxicity" under CEPA, May 21st.

Meek, M E. (2002) Dose Response - Cancer Vs. Non-cancer Dose-Response Assessment, National Capital Area Society of Toxicology Spring Symposium, Bethesda, Maryland, May 16th.

Meek, M.E. (2002) Priorities for Research – Priority Setting and Assessment of Existing Substances, Presentation to the Safe Environment Programme Research Scientists, May 8th.

Meek, M.E. (2002) Process and Approach – Health Components of DSL Categorization and Screening, CEPA Industry Coordinating Group Meeting, Ottawa, April 30th.

Meek, M E. (2002) Chemical Specific Adjustment Factors (CSAF) in Dose/Concentration Response Assessment -

M.E. (Bette) Meek
Presentations

Guidance for Adequacy of Data. Continuing Education Session, Annual Meeting of Society of Toxicology, Nashville, March 17th.

Hammond, G. and Meek, M.E. (2002) Application of (Q)SAR in the Assessment of New and Existing Substances in Canada, Workshop on Regulatory Acceptance of (Q)SARs for Human Health and Environmental Endpoints, Setubal, March 4th.

Meek, M.E. (2002) Objectives and Charge, Peer Consultation for Review of Draft Framework for Estimation of Dermal Exposure in Assessments of Existing Substances, Ottawa, March 7th.

Meek, M.E. (2002) Objectives and Charge, Peer Consultation on Genotoxicity Components of Priority Setting and Screening in Assessments of Existing Substance, Ottawa, March 14th.

Meek, M.E. (2002) Compound Specific Adjustment Factors - Guidance for Adequacy of Kinetic and Dynamic Data – Dose-Response, Human Health Risk Assessment for Copper, U. of Ottawa Institute of Population Health Risk Assessment and International Copper Association, Hilton Head, February 14th.

Meek, M.E. (2002) Categorization and Screening of the Domestic Substances List in Canada – HC Component, CEPA Industry Coordinating Group meeting, January 17th.

Meek, M.E. (2001) Guidance on Compound Specific Adjustment Factors - Interspecies Differences and Human Variability, Criteria for the Use of Compound Specific Adjustment Factors, Annual Meeting of the Society of Risk Analysis, Seattle, December 4th.

Meek, M.E., Renwick, A. and Sonich-Mullin, C. (2001) Practical application of kinetic data in risk assessment – An IPCS initiative. International Workshop on the Application of Physiological-Toxicokinetic Modcling to Health Hazard Assessment of Chemical Substances, Munich, October 11th-12th.

Meek, M.E. (2001) Use of Case Reports in Risk Assessment with Reference to Ethylene Glycol (2001) International Programme on Chemical Safety Consultation on Bridging the Gap between Clinical and Regulatory Toxicology, Edinburgh, September 20th.

Meek, M.E. (2001) Categorization and Screening of the Domestic Substances List in Canada – HC Component, Presentation to U.S. EPA, Cincinnati, September 18th.

Meek, M.E. and Vu, V. (2001) Mode of Action and Relevance to Humans, ILSI Health and Environmental Sciences Institute Workgroup on Relevance to Humans Framework, Washington, August 15th.

Meek, M.E. (2001) Guidance for Application of Chemical Specific Adjustment Factors (CSAF), Symposium 5: Scientific and Societal Issues in Risk Assessment, Continuing Education Session of the International Congress on Toxicology IX, Brisbane, July 10th.

Meek, M.E. (2001) Chemical Specific Adjustment Factors (CSAF) - A framework for incorporating kinetic/dynamic data in dose-response assessment, New Issues in Risk Assessment Methodology, International Congress on Toxicology IX, Brisbane, July 8th.

Meek, M.E. (2001) Panel Presentation, Priority Substances Assessment on Ethylene Glycol, Toxicology Forum, Aspen, Colo., July 10th.

Meek, M.E. (2001) PSL/DSL - Implications for Risk Management, Joint EC-HC Workshop for Risk Managers,

M.E. (Bette) Meek
Presentations

Ottawa, June 20th.

Meek, M.E. (2001) Guidance for derivation of chemical specific adjustment factors – development and implementation. Fifth Annual Workshop on Evaluation of Default Safety Factors in Health Risk Assessment, Newark, N.J., June 1st.

Meek, M.E. (2001) Debate. Does the use of data-derived uncertainty factors allow risk assessors to describe uncertainty more accurately? Fifth Annual Workshop on Evaluation of Default Safety Factors in Health Risk Assessment, Newark, N.J., June 1st.

Meek, M.E. and Chenier, R. (2001) Potential interface of the CEPA Domestic Substances List programme with the International Council of Chemical Associations (ICCA) high production chemicals testing initiative, Presentation to the Business and Industry Advisory Council to the Chemicals Programme of the Organization of Economic Cooperation and Development, Paris, April 24th.

Meek, M.E. (2001) Compound Specific Adjustment Factors - An International Initiative, Presentation to the Dose-Response Specialty Subgroup of the Society for Risk Analysis, Teleconference, April 3rd.

Meek, M.E. (2001) Informing Risk Assessment. Dinner Presentation to the Nickel International Development Institute, Museum of Civilization, Hull, March 28th.

Meek, M.E. (2001) A Proposal to Develop Nominations for the International Council of Chemical Associations testing initiative based on the HC Stream of the DSL Categorization and Screening Program, CEPA Industry Coordinating Group meeting, Toronto, March 26th.

Meek, M.E. (2001). The Use of GenomicData in Risk Assessment - Panel Presentation, International Council of Chemical Associations Genomics Workshop, Orlando, March 7th.

Meek, M.E. (2001) Dose-Response in Cancer Risk Assessment, Risk Sciences Institute Scientific Session on Dose-Response, International Life Sciences Institute Annual Meeting, Montego Bay, January 22nd.

Meek, M.E. (2001) Status of Development of HC Responsibilities for the DSL Categorization and Screening Program, CEPA Industry Coordinating Group meeting, Ottawa, November 24th.

Meek, M.E. (2000) Introductory Presentation on the Use of Kinetic and Dynamic Data in Developing Compound Specific Adjustment Factors, IPCS Workshop on Uncertainty and Variability in Risk Assessment, Berlin, May 9th to 11th.

Meek, M.E. (2000) Case Study B, IPCS Workshop on Uncertainty and Variability in Risk Assessment, Berlin, May 9th to 11th.

Meek, M.E. (2000) Categorical Defaults. Database Uncertainties, Fourth Annual Workshop on Evaluation of Default Safety Factors in Health Risk Assessment, Newark, May 3rd.

Meek, M.E. (2000) Health Assessments - Priority Substances and Domestic Substances Lists, Interface 2000, Canadian Manufacturing Chemical Specialties Association Federal Government Annual Interface, Ottawa, Feb. 11th.

Meek, M.E. (1999) Risk Assessment Methodologies: Trends and Needs - An International Perspective. Session V - Disinfection Byproducts: Toxicology and Risk Assessment. The Safety of Water Disinfection: Balancing

M.E. (Bette) Meek
Presentations

Chemical and Microbial Risks. Second International Conference, Miami Beach, November 15 – 17th.

Meek, M.E. (1999) IPCS Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals. Cancer. ILSI/IPCS Harmonization Briefing/Mechanistic Data in Risk Assessment Meeting, Washington, D.C., August 6th.

Meek, M.E. (1999) Carcinogenesis case study. Acrylonitrile. IPCS Workshop on a Conceptual Framework for Cancer Risk Assessment, Lyon, France, February 16th – 18th.

Meek, M.E. (1999) Carcinogenesis case study. Ethylene Dibromide. IPCS Workshop on a Conceptual Framework for Cancer Risk Assessment, Lyon, France, February 16th – 18th.

Meek, M.E. (1999) Integration of Epidemiological andToxicological Data on Disinfection Byproducts. Panel Discussion on Characterization of Cancer Risks. Health Effects Stakeholder Meeting for the Stage 2 Disinfection Byproducts Rule, Washington, February 10th – 12th.

Meek, M.E. (1998) Priority Substances Program. Benzene. Observations for risk assessment. Benzene State of the Science Workshop, Ottawa, December 16th – 18th.

Meek, M.E. (1998) Experience in the Priority Substances Program - Implications for definition of reference or tolerable dose/concentration. Symposium on ATowards a Quantitative Definition of Reference Dose at Annual Meeting of the Society for Risk Analysis, Phoenix, December 6th – 9th.

Meek, M.E. (1998) Application of uncertainty factors in the Priority Substances Program and international harmonization. Third Annual Workshop on Evaluation of Default Safety Factors in Health Risk Assessment, Newark, November 11th.

Meek, M.E. (1998) Assessments of Priority Substances under CEPA. Consumer exposure. IPCS Workshop on Methodological Aspects of Characterization of Risks to Consumers of Chemical Substances, Lyon, September 8th-9th.

Meek, M.E. (1998) Assessments of Priority Substances under CEPA. Carcinogenic potency. Awareness Session, Canadian Petroleum Products Institute, Ottawa, September 1st.

Meek, M.E. (1998) IPCS harmonization of risk assessment. Assessment of non-cancer endpoints. International Congress of Toxicology VIII, Paris, July 5th-8th.

Meek, M.E. (1998) Historical overview and objectives of workshop. U.S. EPA/Health Canada External Peer Review Workshop on Dose-Response Analyses for Formaldehyde, March 18th-20th.

Meek, M.E. (1998) Approach to and status of completion of assessment on acrylonitrile. 23rd Annual Winter Toxicology Forum, Washington, February 2nd-5th.

Meek, M.E. (1998) Case study. Diethylhexyl Phthalate. IPCS Workshop on Harmonization of Cancer Risk Assessment, Hanover, Germany, January 27th – 30th.

Meek, M.E. (1998) Case study. Formaldehyde. IPCS Workshop on Harmonization of Cancer Risk Assessment, Hanover, Germany, January 27th – 30th.

Meek, M.E. (1998) Experience of the planning committee in comparison and contrast of assessments of

carcinogens in various countries. IPCS Workshop on Harmonization of Cancer Risk Assessment, Hanover, Germany, January 27th – 30th.

Meek, M.E. (1997) Approach to health risk assessment for releases from zinc and copper smelters and refineries. Environmental Resource Group for the Priority Substances assessment on Releases from Copper and Zinc Smelters and Refineries, September 3rd-5th.

Long, G. and Meek, M.E. (1997) Priority Substances List and CEPA. Workshop on Air Quality and the Health of our Ecosystem, Vancouver, June 16th - 17th.

Meek, M.E. (1997) Approach to health risk assessment for substances on the second Priority Substances List. Annual Workshop of the SRA/SETAC, Laurentian and Saint-Laurent Chapters, Montreal, May 30th-31st.

Meek, M.E. (1997) Approach to assessment of PSL 2 compounds. Annual Meeting of the Canadian Chemical Specialty Manufacturers= Association, Toronto, May 29th.

Meek, M.E. (1996) Health risk assessment for Priority Substances under the Canadian Environmental Protection Act, non-neoplastic effects. IPCS Workshop on Identification of Issues related to Harmonization of Quantitative Risk Assessment Methods for Non-Cancer Endpoints, New Orleans, LA, December 12th – 14th.

Meek, M.E. (1996) Extemporaneous summary. Incorporating human data in quantitative risk assessment: issues, status and future. 1996 Annual Meeting, Society for Risk Analysis and International Society for Exposure Analysis, New Orleans, LA, December 8th – 12th.

Meek, M.E. (1996) Developing uncertainty distributions for Tolerable Intakes: a staged approach. 1996 Annual Meeting, Society for Risk Analysis and International Society for Exposure Analysis, New Orleans, LA, December 8th – 12th.

Meek, M.E. (1996) Charge to the break-out groups. International Workshop on Risk Assessment of Metals and their Inorganic Compounds, Angers, France, November 13th – 15th.

Krewski, D., Meek, M.E., Hughes, K., Farland, W. and Gibb, H. (1996) Assessments of metals and their compounds under the Canadian Environmental Protection Act. International Workshop on Risk Assessment of Metals and their Inorganic Compounds, Angers, France, November 13th – 15th.

Meek, M.E. (1996) Summary of data reviewed for assessment of risk in the general environment associated with chloroform. ILSI Expert Panel to Evaluate EPA=s Proposed Guidelines for Carcinogen Risk Assessment using Chloroform and Dichloroacetate as Case Studies, Washington, September 10th – 12th.

Meek, M.E. and Hughes, K. (1996) Approach to risk assessment for Priority Substances in Canada: Novel aspects, harmonization of State/Federal approaches to environmental risk, Harmonization of State/Federal Approaches to Environmental Risk, Fort Lansing, MI, May 20th-21st.

Meek, M.E. (1996) Assessment of nickel and its compounds under the Canadian Environmental Protection Act. Identification of priorities for reseearch. 1996 Nickel Resource Workshop, Rockville, MD, June 3rd – 6th.

Krewski, D., Meek, M.E. and Armstrong, V.C. (1996) Managing environmental risks under the Canadian Environmental Protection Act. Technical Workshop on the Technical Feasibility of Predicting the Deposition Pattern and Distinguishing Characteristics of Canadian Base Smelter Emissions, Ottawa, Ont., May 2nd – 3rd.

M.E. (Bette) Meek
Presentations

Meek, M.E. (1995) Health risk assessment for Priority Substances under the Canadian Environmental Protection Act. Developing guidance in an international arena. Annual Meeting of the Society for Risk Analysis, Honolulu, Hawaii, December 3rd – 6th.

Meek, M.E. (1995) Health Canada activities on respirable fibrous materials. Workshop on Chrysotile Asbestos: International Scientific Regulatory Update, Montreal, October 23rd.

Meek, M.E., Hughes, K., Newhook, R. and Chan, P.K.L. (1995) Health assessments of metals and their compounds under CEPA. 5th COMTOX Symposium on Toxicology and Clinical Chemistry of Metals, Vancouver, July 10th – 13th.

Meek, M.E. (1995) Assessment of Priority Substances under CEPA - variation in exposure and response. World Health Organization Meeting on Variability in Toxic Response - Human and Environmental, Southampton, U.K., March 8th – 10th.

Meek, M.E. and Hughes, K. (1995) Is ingested inorganic arsenic a threshold carcinogen? A Canadian perspective. Roundtable at Annual Meeting of Society of Toxicology, Baltimore, March 9th.

Meek, M.E. (1995) International assessments of Existing Chemicals: Coordination and Facilitation of Preparation. IPCS/OECD Joint Consultation on Priority Chemicals and Related Issues, Research Triangle Park, North Carolina, January 30th - February 3rd.

Meek, M.E. (1994) Approach to health risk determination under CEPA. Canadian Chemical Producers Association Health Committee, Ottawa, September 23rd.

Meek, M.E. and Hughes, K. (1994) Approach to health risk determination for metals and their compounds under the Canadian Environmental Protection Act. 5th Nordic Symposium on "Trace Elements in Human Health and Disease", Loen, Norway, June.

Hughes, K., Meek, M.E., Newhook, R. and Chan, P.K.L. (1994) Speciation in health assessments of elements under the Canadian Environmental Protection Act. 5th Nordic Symposium on "Trace Elements in Human Health and Disease", Loen, Norway, June.

Meek, M.E. (1994) Assessment of man made vitreous fibres under CEPA. International Labour Organization (ILO) Seminar on Measures of Prevention and Control in the Use of Mineral and Synthetic Fibres, Sao Paulo, Brazil, May 2nd – 6th.

Meek. M.E. (1994) Approach to assessment of "toxic" for Priority Substances under CEPA and assessment of "nickel and its compounds". Health Committee, Mining Association of Canada, Toronto, February 4th.

Hughes, K, and Meek, M.E. (1993) Assessment of arsenic and its compounds under CEPA. International Conference on Arsenic Exposure and Health Effects, New Orleans, July 28th-30th.

Meek, M.E. (1993) Approach to assessment of health risks for Priority Substances under the Canadian Environmental Protection Act. Seminar for Staff of the Department of the Environment, Hull, June 7th.

Meek, M.E. (1993) Approach to assessment of health risks for Priority Substances under the Canadian Environmental Protection Act. Meeting of the Industry Coordinating Group, Canadian Chemical Producers' Association, Toronto, April 5th.

M.E. (Bette) Meek
Presentations

Meek, M.E. (1993) Approach to assessment of health risks for Priority Substances under the Canadian Environmental Protection Act with emphasis on multimedia exposure. Meeting of the International Programme on Chemical Safety Working Group on Derivation of Guidance Values, Langen, Germany, January 19th-22nd.

Meek, M.E., Newhook, R., Liteplo, R.G. and Armstrong, V. Hazard and risk assessment for inhaled pollutants. International Symposium on Respiratory Toxicology and Risk Assessment, Hanover, Germany, October 6th – 9th.

Meek, M.E. (1991) Update on health effects assessment for man-made mineral fibres. Annual General Meeting of Canadian Man-Made Mineral Fibre Manufacturers, January 31st.

Meek, M.E. (1991) Approach to assessment of "toxic" to human health for CEPA Priority Substances. CEPA Priority Substances List Task Group Leaders Workshop, Montebello, Quebec, December 3-5th,.

Meek, M.E. (1990) Asbestos - Health risks in the occupational and general environments. Course on Environmental Carcinogenesis, Environmental Resources Studies Program, Trent University, November 27th.

Meek, M.E. (1990) Asbestos in buildings - Health risks. University of Toronto Public Seminar on Asbestos in Buildings - What Should We Do?, Toronto, November 24th.

Gilman, A.P., Harrison, J. and Meek, M.E. (1991) PCB's, dioxins, aluminum, asbestos:proven poisons or pointless panic. Ontario College of Family Physicians, Toronto, November 22nd.

Meek, M.E. (1990) Health risks associated with exposure to man-made mineral fibres and implications for occupational health. International Trade Union Seminar, Montreal, September 20-21st.

Meek, M.E. (1990) Risks associated with exposure to low levels of asbestos. Canadian Centre for Occupational Health and Safety Workshop on Asbestos in Buildings, Montreal, September 11-12th.

Meek, M.E. (1990) Assessment of the health effects of man-made mineral fibres: implications for occupational health. McGill University School of Occupational Health, Montreal, February 27th.

Meek, M.E. (1989) Revision of the Guidelines for Canadian drinking water quality. Technical Conference, Municipal Expo '89, Calgary, Alta., May 3rd-4th.

Meek, M.E., Armstrong, V.C. and and Toft, P. (1988) Revision of the Canadian drinking water guidelines. Forty First Annual Conference of the Atlantic Canada Section of the American Water Works Association, Charlottetown, September 18-20th.

Meek, M.E. (1988) Review of epidemiological evidence. Man-made mineral fibres and cancer. VIIth International Conference on the Pneumoconioses, Pittsburgh, August 23-26th.

Meek, M.E. (1988) Respirable fibous materials. Evaluation of potential health risks. VIIth International Conference on the Pneumoconioses, Pittsburgh, August 23-26th.

Meek, M.E. (1988) Arsenic in drinking water. Canadian activities. National Science Council, Taipei, Taiwan, June 17th.

Meek, M.E. (1988) Department of National Health and Welfare programme on drinking water. 1988 Joint Conference of the Ontario Section of the American Water Works Association and the Ontario Municipal Water

M.E. (Bette) Meek
Presentations

Association, London, May 1st-4th.

Meek M.E. (1986) Fibrous substitute material for asbestos. Health aspects. Air Pollution Control Association International Specialty Conference on Asbestos, Atlantic City, N.J., November 4th-7th.

Meek, M.E. (1986) Asbestos in the general environment. Health aspects. National Congress of Electrical and Mechanical Engineering and the Industry, Panama City, October 20th-24th.

Meek, M.E. (1986) Asbestos in drinking water and indoor air. Risks to the general population. Lecture for a course for South American health officials, Asbestos Institute, Montreal, September 15th-26th.

Meek, M.E. (1986). Ingested asbestos. A review. Scientific Program for the Anniversary of the Ecuador Institute for Sanitary Works, Quito, Ecuador, May 5th-9th.

Meek, M.E. (1986) Asbestos in drinking water. Seminar at the Centro Panamericano de Ecologia Humana Y Salud (PAHO), Lima, Peru, May 6th.

Meek, M.E. (1986) Asbestos in drinking water and ambient air. Health aspects. International Seminar on Asbestos Exposure, Environmental and Occupational Aspects, Sao Paulo, Brazil, April 22-24th.

Meek, M.E. (1986) Asbestos in drinking water. Health risks. Presentation to the Executive Policy Committee, City of Winnipeg, Winnipeg, February 12th.

Meek, M.E. (1985) Formaldehyde in indoor air. Establishing a guideline. Workshop on Risk Assessment and Risk Management. Bureau of Chemical Hazards, Environmental Health Centre, Ottawa, November 22nd.

Meek, M.E. (1985) Asbestos and public health. Lecture for a Continuing Education Course, Canadian Institute of Public Health Inspectors, Saskatoon, May 8th.

Meek, M.E. (1984) Ingested asbestos. A review. Can-Am Chemical Congress, Montreal, June 3rd-6th.

Meek, M.E. (1984) Asbestos in drinking water. Thirtieth Annual Manitoba Water and Waste Seminar, Winnipeg, March 12th-14th.

Meek, M.E. (1982) Asbestos - historical perspective and health effects assessment. Lecture for a course in Environmental Epidemiology, University of Ottawa, November.

Meek, M.E. (1982) Transmigration of ingested asbestos. U.S. Environmental Protection Agency Summary Workshop on Ingested Asbestos, Cincinnati, October.

Meek, M.E. (1981) Pathological effects of ingested asbestos in the rat. BP Research Centre, Sunbury on Thames, U.K., September.

Meek, M.E. (1980) Indoor concentrations of nitrogen dioxide and implications for exposure studies. Canadian Public Health Association 71st Annual Meeting, Ottawa, June.

CURRICULUM VITAE

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Education:

1982 – Ph.D., Epidemiology, University of North Carolina

1980 – M.P.H., Epidemiology, University of North Carolina

1977 – M.D., The Ohio State University

1974 – B.Sc., Engineering, *summa cum laude*, The Ohio State University

Experience:

Dr. Weed is an independent scientific consultant. He is a physician-epidemiologist with 30 years of experience in epidemiological research and research training. Dr. Weed is an internationally recognized scholar and educator in causation, causal inference, and the ethics of epidemiology. He has extensive experience in the methods of general causation, cancer causation, systematic reviews, and weight-of-evidence methods. He holds an academic appointment—adjunct full professor—at the University of Utah School of Medicine. He co-chaired the National Academy of Sciences Committee on the *Daubert* decision and was a Visiting Scholar at the Federal Judicial Center (Washington, DC). He maintains an active research program in scientific methods, nutritional epidemiology, occupational epidemiology, and the ethics of research. Recent invited lectures include: American Association for the Advancement of Science, at the World Congress of Epidemiology, and at the National Cancer Institute's Summer Course in Cancer Prevention and Control. Dr. Weed is the Reviews Editor for the Journal of the National Cancer Institute and formerly an Associate Editor at the American Journal of Epidemiology.

Dr. Weed is the founder of DLW Consulting Services, LLC. This scientific consulting company provides expertise in disease causation, the methods of causal inference, weight of evidence methods, epidemiological and clinical research methods, and the ethics of epidemiology and public health. DLW Consulting Services, LLC specializes in providing expert advice and guidance on problems at the interface of science, law, commerce, and public policy. Typical projects include expert testimony and consultation in toxic tort litigation, assessments of health risks from exposure to chemicals, metals, infectious agents, pharmaceuticals, and medical devices, as well as assessments of key methodological and ethical problems facing stakeholders. Examples of such problems include: scientific uncertainty, conflicts of interest, and methods used in legal and regulatory contexts to determine general and specific causation.

Employment:

2008- present	Managing Member, DLW Consulting Services, LLC.
2007-2008	Vice President for Epidemiology and Biostatistics, The Weinberg Group, Washington DC
1990-2007	Chief, Office of Preventive Oncology, National Cancer Institute Director, Cancer Prevention Fellowship Program, Bethesda MD
1982-1989	Senior Staff Fellow, Biometry Branch, National Cancer Institute
1978-1982	Public Health Service Trainee, Department of Epidemiology, University of North Carolina, Chapel Hill, NC.
1978	Research Associate, Environmental Protection Agency, Chapel Hill, NC.
1977	Medical Intern, N. Carolina Memorial Hospital, Chapel Hill, NC.

Professional and Scientific Organizations:

American College of Epidemiology (Fellow)
International Epidemiological Association (Member)
Kennedy Institute of Ethics (Member)
Society for Epidemiologic Research (Member)

Elected Positions:

Board of Directors, American College of Epidemiology, 1998-2001
Executive Committee, Society for Epidemiologic Research, 1996-1999

Editorial Positions:

Associate Editor, Journal of the National Cancer Institute, 1994-present
Reviews Editor, Journal of the National Cancer Institute, 1995-present
Associate Editor, American Journal of Epidemiology, 1997-2013
Editor-in-Chief, NCI Division of Cancer Prevention Newsletter, 1999-2002

Reviewer:

American Family Physician
American Journal of Clinical Nutrition
American Journal of Epidemiology
American Journal of Industrial Medicine
American Journal of Preventive Medicine
American Journal of Public Health

Annals of Epidemiology
Cancer
Clinical Trials
Critical Reviews in Toxicology
Environmental Health Perspectives
Epidemiologic Reviews
Epidemiology
Evidence Based Journal
Food and Chemical Toxicology
International Journal of Epidemiology
Journal of the American Medical Association
Journal of Clinical Epidemiology
Journal of Medical Decision-Making
Journal of the National Cancer Institute
Kennedy Institute of Ethics Journal
Nutrition and Cancer
Philosophy and Theory in Biology
Preventive Medicine
Regulatory Toxicology and Pharmacology
Social Science and Medicine
Statistics in Medicine
Theoretical Medicine and Bioethics

Faculty Appointments:

Adjunct Professor, 2014-present
Department of Family and Preventive Medicine
Division of Public Health
School of Medicine
University of Utah
Salt Lake City, UT

Adjunct Professor, 2010 - 2014
Department of Internal Medicine
Division of Epidemiology and Biostatistics
School of Medicine
University of New Mexico
Albuquerque, NM

Visiting Scholar, 2006
Federal Judicial Center
Washington, D.C.

Visiting Fellow, 2001
National Cancer Center
Tokyo, Japan

Visiting Professor (Oncology), 1999
McGill University and University of Montreal
Montreal, Quebec, Canada

Visiting Professor (Epidemiology), 1998
National School of Public Health
Madrid, Spain

Faculty Affiliate, 2001- 2010
Senior Research Fellow, 1995 – 2001
Visiting Fellow, 1994-5
Kennedy Institute of Ethics
Georgetown University, Washington, D.C.

Faculty member, 1994
Society for Epidemiologic Research
Student Workshop on Epidemiologic Methods, Miami, FL

Adjunct Associate Professor, 1994 - 2010
Department of Preventive Medicine and Biometrics
F. Edward Hebert School of Medicine
Uniformed Services University of the Health Sciences
Bethesda, MD

Associate Faculty, 1989 - 2010
Department of Epidemiology
School of Hygiene and Public Health
Johns Hopkins University, Baltimore, MD

Teaching Assistant and Lecturer (Epidemiology), 1979-80
University of North Carolina, Chapel Hill, NC

Honors and Awards:

Engineering Honor Scholar 1971-1974 (each year)
Phi Eta Sigma (freshman academic honorary) 1971
Alpha Epsilon Delta (pre-med academic honorary) 1973
Tau Beta Pi (engineering academic honorary) 1974
Phi Kappa Phi (general academic honorary) 1974
Alpha Omega Alpha (medicine academic honorary) 1977
Honors in Medicine (clinical) 1977
Honors in Obstetrics and Gynecology (clinical) 1977
On-the-Spot Cash Award (NCI): 1999, 2000
Sustained Superior Performance Cash Award (NCI): 1990-1999 (each year)
Distinguished Alumnus: Ohio State Univ. Preventive Medicine 1994
NIH Merit Award 1995
Commencement Speaker: USUHS M.P.H. Graduation 1996

Quality Step Increase (NCI) 1997, 2000
Keynote Speaker: III Congress of Chilean Society of Epidemiology 1997
Keynote Speaker: Spanish Epidemiologic Society 1998
Advances in Oncology Lecture: McGill University Cancer Center 1999
Samuel C. Harvey Lecture: American Association for Cancer Education 1999
Keynote Speaker: Korean Society for Preventive Medicine 1999
Grand Rounds: Ohio State University Cancer Center 1999
Keynote Speaker: Ethics and Research Integrity Day, University of Alberta, 2000
Keynote Speaker: EPA Conference on Environmental Statistics, 2001
J. Walter Juckett Memorial Lecture, Vermont Cancer Center, 2002
Distinguished Leadership Award, NCI Division of Cancer Prevention, 2002
NIH Merit Award, 2004
Keynote Speaker: Great Lakes Cancer Institute Symposium, 2005
Keynote Speaker: Turkish Society of Internal Medicine, 2005

Board and Committee Memberships

Member, Admissions Committee, University of Utah School of Medicine, 2014 - present

Member, Ohio State University College of Public Health Advisory Board
Columbus, Ohio, 2005 – 2013

Member, Commission on Forensic Science and Public Policy, American Judicature Society, 2005 -- 2007

Co-Chair, National Academy of Sciences Committee, 2005 - 2006
"Alternative Models to the *Daubert* Criteria"
Science, Technology, and Law Program, NAS

Chair, Prevention Working Group, 2001-2007
All-Ireland NCI Cancer Consortium
National Cancer Institute (NCI)

Chair, Scientific Education Committee, 1989- 2007
Division of Cancer Prevention, NCI

Chair, Ethics and Standards of Practice Committee, American College of Epidemiology, 1998-2001.

Member, NIH Committee on Continuing Medical Education (CME), 2000-2005

Cancer Advisory Panel, National Center for Alternative and Complementary Medicine, NIH, 1998-2002

World Health Organization Working Group on the Acceptability of Epidemiologic Evidence for Health Impact Assessment, 1999.

National Cancer Institute Cancer Training Advisory Committee, 1997-9.

Member, Advisory Committee for the National Center for Training in Cancer Prevention and Control, Centers for Disease Control and Prevention, 1995-7.

NIH Epidemiology and Clinical Trials Interest Group, 1985-2000.

NIH Committee on Generic Postdoctoral Research Training, 1994.

NCI Committee on Employee Mentoring, 1994.

Program Planning Committee, American Society of Preventive Oncology, 1991-1993.

American Cancer Society Task Force on Preventive Medicine Training, 1993.

NIH Planning Committee for the Alternative Medicine Technology Assessment Meetings, 1993.

ICCCR International Conference on Cancer Prevention. Bethesda, Maryland, February, 1991. See also: Monographs of the Journal of the National Cancer Institute. NIH Publication 91-3227, p.167, 1992.

American Society of Preventive Oncology Annual Meeting Symposium on Quality of Prevention Research. 1991.

Leader, Roundtable Discussion on Causal Inference. Society for Epidemiologic Research Annual Meeting, 1994.

Panel on Philosophy of Science in Epidemiology. Third Brazilian Congress of Epidemiology, Salvador, Bahia, Brazil, 1995.

Leader, Roundtable Discussion on Methods and Morals in Epidemiology. Society for Epidemiologic Research Annual Meeting, 1995.

NCI Roundtable Discussion on Clinical Trials Auditing, 1995.

Leader, Roundtable Discussion on Preventing Scientific Misconduct. Society for Epidemiologic Research Annual Meeting, 1996.

Education Review Committee, U.T. M.D. Anderson Cancer Center, Cancer Prevention and Education Program, 1996-1998.

Member, Ethics and Standards of Practice Committee, American College of Epidemiology, 1996-1998.

Research Interests:

Disease causation, cancer epidemiology, prevention and control, causal and preventive inference, research synthesis methods (evidentiary methods, meta-analysis, systematic reviews, inferential methods, ethical decision-making methods), philosophy of public health, ethics of biomedical research, professional ethics, medical humanities, research training, science and the law.

Recent Lectures and Invited Seminars

"Causality in Public Health and Preventive Medicine." Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, April 18, 2014.

"On the Utility of Criteria-Based Methods of Causal Inference." Society for Risk Analysis. Baltimore, MD, December 9, 2013.

"What Causes Cancer?" Huntsman Cancer Institute. Salt Lake City, UT, November 13, 2013.

"Does Red Meat Cause Colon Cancer?" Center for Advanced Study at the Norwegian Academy of Science and Letters. Oslo, Norway, November 6, 2013.

"Interpreting Scientific Evidence for Cancer Prevention." National Cancer Institute Summer Curriculum on Cancer Prevention and Control. Rockville, MD, July 11, 2013.

"Conflicts of Interest." University of California, Berkeley. Epidemiology Doctoral Seminar. Berkeley, CA, April 10, 2013.

"On the Utility of Criteria-Based Methods of Causal Inference." International Society for Environmental Epidemiology. Columbia, SC, August 30, 2012.

"How do we make causal conclusions from the 'totality of the evidence' objective and observable?" Conference on "Scientific Approaches to Strengthening Research Integrity in Nutrition and Energetics" sponsored by the University of Alabama, Birmingham. New Paltz, NY, August 2012.

"Standards of Reporting Dietary Supplements Research Studies." National Institutes of Health Office of Dietary Supplements Research Practicum. Bethesda, MD, June 2012.

"Quality of peer-reviewed published reviews: a case study of sugar-sweetened beverages and health outcomes." Institute of Medicine Food Forum. Washington, DC, September 2011.

"Registration of Epidemiological Studies" Pre-Conference Course on Epidemiological Methods, International Epidemiological Association World Congress of Epidemiology. Edinburgh, Scotland, August 2011.

"Comments on Weight of Evidence" AAAS Conference, Washington DC, February 2011.

"The Professional Responsibilities of Epidemiologists." University of California, Berkeley. March, 2010.

"Causal Inference in Cancer Epidemiology." University of California, Berkeley. March, 2010.

"Uncertainty and Weight of Evidence in Risk Assessment." ICNIRP Workshop: Evaluation and Communication of Scientific Evidence and Uncertainty - Towards a Consistent Terminology in Non-ionizing Radiation. Salzburg, Austria, November, 2009.

"Meta-analysis and causal inference: a case study of benzene and non-Hodgkin's lymphoma." Benzene09, Munich, Germany, September, 2009.

"Biological Mechanism and Causal Inference." Institute of Medicine, Washington DC, June 2009.

"A Method for Individual Causation." University of North Carolina, Chapel Hill, NC, May 2008, the American Association of Law Schools Conference on Evidence, Cleveland, Ohio, June 2008, and at Michigan State University, East Lansing, MI, October, 2009.

"Weight of Evidence and Uncertainty Assessments" DIA/FDA Workshop on Risks and Benefits, Bethesda, MD, November 2009 and ICNIRP/WHO Workshop on Risk Assessment and Terminology, Salzburg, Austria, November 2009.

"Cases and Causes" AstraZeneca Wilmington DE, November 2007, and Amgen Inc. Thousand Oaks, CA, March 2008.

"Why should epidemiology bridge the science/law "cultural chasm"? North American Epidemiology Congress plenary session, Seattle, Washington, June 2006.

"Rethinking Epidemiology" Imperial College (London), Division of Epidemiology, London, England, May 2006.

"Weight of Evidence and General Causation" Science for Judges Program, Brooklyn Law School, Brooklyn, NY, March 2006.

"Weight of Evidence: a Review of Concept and Methods." Society for Risk Analysis, Orlando, Florida, December 2005.

"The Future of Cancer Prevention" Keynote Address. Symposium, San Antonio Cancer Institute, San Antonio, Texas, November 2004; and Special Lecture at the 250th Anniversary of the Meath Hospital, Dublin, Ireland, October 2003.

"The End of Epidemiology" Columbia University, Department of Epidemiology, May 2004, University of New Mexico, May 2005 and 2010, Imperial College (London) Department of Epidemiology and Public Health, December 2005.

"Cancer Prevention in the USA" Xi'an Cancer Hospital, Xi'an, China; CICAMS Cancer Hospital, Beijing, China, October 2004.

"Biologic plausibility and other challenges to the primary prevention of cancer." American College of Preventive Medicine, Washington DC, February 2005.

"The Future of Cancer Epidemiology." Michigan State University Department of Epidemiology, East Lansing, MI, April 2005, and the University of New Mexico, Department of Family and Community Medicine, Albuquerque, NM, May 2005.

Advisory Positions

American Health Foundation, 1998-1999.
Australian Cancer Society, 1999.
Health and Environmental Sciences Institute, 2004 – 2005.
International Life Sciences Institute, 2000 – 2003.
World Health Organization, 1999, 2001.
Mead Johnson Nutrition Safety Advisory Panel, 2012 – present.
National Science Teachers Association, 2002-2014.
Brooklyn Law School, 2003, 2006.

Dissertation and Thesis Committees

Vrije University, Brussels, Belgium (Guido Goelen, M.D., Ph.D), 1999-2001

BIBLIOGRAPHY

PUBLICATIONS

Althuis MD, Weed DL, Frankenfeld CL. 2014. Evidence-based mapping of design heterogeneity prior to meta-analysis: a systematic review and evidence synthesis. Systematic Reviews (in press).

Alexander DD, Weed DL, Chang ET, et al. 2014. A systematic review of multivitamin-multimineral use and cardiovascular disease and cancer incidence and total mortality. J Amer Coll Nutr (in press).

Miller PE, Alexander DD, Weed DL. 2014. Uncertainty of results in nutritional epidemiology. Nutrition Today 49:147-52.

Althuis MD, Weed DL. 2013. Evidence mapping: Methodological foundations and application to intervention and observational research on sugar sweetened beverages and health outcomes. Am J Clin Nutr . doi: 10.3945/ajcn.113.058917.

Weed DL. 2013. The quality of nutrition and cancer reviews: a systematic assessment. Crit Rev Food Sci Nutrition 53:276-86.

Alexander DD, Weed DL, Mink PJ, et al. 2012. A weight-of-evidence review of epidemiologic studies of colorectal cancer in pesticide applicators. Int Arch Occup Environ Health 85:715-45.

Weed DL, Althuis MD, Mink PJ. 2011. Quality of reviews on sugar-sweetened beverages and health outcomes. Am J Clin Nutr 94:1340-7.

Alexander DD, Weed DL, Cushing CA, Lowe KA. 2011. Meta-analysis of prospective studies of red meat consumption and colorectal cancer. Eur J Cancer Prevention 20:293-307.

Navia JL, Byers T, Djordjevic D, Hentges E, King J, Klurfeld D, Llewellyn C, Milner J, Skrypec D, Weed DL. 2010. Integrating the totality of food and nutrition evidence for public health decision making and communication. Crit Rev Food Sci Nutrition 50:1-8.

Schreider J, Barrow C, Birchfield N, Dearfield K, Devlin D, Henry S, Kramer M, Schappelle S, Solomon K, Weed DL, Embry MR. 2010. Enhancing the credibility of decisions based on scientific conclusions: transparency is imperative. Tox Sci doi: 10.1093/toxsci/kfq102.

Weed DL. 2010. Meta-analysis and causal inference: a case study of benzene and non-Hodgkin's lymphoma. Ann Epidemiol 20:347-355.

Weed DL. 2009. Conflicts of Interest. J Epidemiol Commun Health 63:601-602.

Weed DL. 2008. Truth, Epidemiology, and General Causation. Brooklyn Law Review 73:651-665.

Griego FY, Bogen KT, Price PS, Weed DL. 2008. Exposure, epidemiology and human cancer incidence of naphthalene. Reg Tox Pharmacol 51:22-6.

Weed DL. 2007. The nature and necessity of scientific judgment. J Law Policy 15:135-164.

Collins JJ, Bukowski JA, Weed DL, Brent RL, Klein P, Boerstoel-Steefland M, Sprafka JM, Williams AL, Holsapple MP. 2007. Evaluating emerging issues in epidemiology. Regul Toxicol Pharmacol 48(3):296-307.

Dores G, Chang S, Berger VW, Perkins S, Hursting SD, and Weed DL. 2006. Evaluating research training outcomes: experience from the Cancer Prevention Fellowship Program at the National Cancer Institute. Acad Med. 81(6):535-541.

Weed DL. 2006. Commentary: Rethinking epidemiology. Int J Epidemiol. 35(3):583-586.

Parascandola M, Weed DL, and Dasgupta A. 2006. The Surgeon General's Reports on Smoking and Cancer: a historical investigation of the practice of causal inference. Emerg Themes Epidemiol. 3:1-11.

Weed DL. 2006. Evidence synthesis and general causation: key methods and an assessment of reliability. Drake Law Review 54:639-650.

Weed DL. 2006. Vision, values, and verisimilitude: a response. Risk Anal. 26:577.

Weed DL. 2005. Hail the heroes who brave front line. The Times Higher Education Supplement (London) No. 1722:14.

*Weed DL. 2005. Weight of evidence: a review of concepts and methods. Risk Anal. 25:1545-1557.

Chang, S., Hursting, S., Perkins, S., Dores, G., and Weed, D.L. 2005. Adapting postdoctoral training to interdisciplinary science in the 21st century: the Cancer Prevention Fellowship Program at the National Cancer Institute. Acad Med. 80(3):261-265.

Resnik, D.B., Kopelman, L.M., and Weed, D.L. 2004. What is the role of the precautionary principle in bioethics and the philosophy of medicine? J Med Philos. 29(3):255-258.

McKeown, R.E. and Weed, D.L. 2004. Ethical choices in survey research. Soz Praventivmed. 49:67-68.

Weed, D.L. and Dores, G. 2004. Physicians as citizens (letter). JAMA 291:2076.

Kopelman, L.M., Resnick, D., and Weed, D.L. 2004. What is the role of the precautionary principle in the philosophy of medicine and bioethics? J Med Philos. 29:255-258.

Weed, D.L. 2004. Precaution, prevention, and public health ethics. J Med Philos. 29:313-332.

Weed, D.L. and McKeown, R.E. 2003. Science and social responsibility in public health. Environ Health Perspect. 111:1804-1808.

Weed, D.L. 2003. Methodologic implications of the precautionary principle: causal criteria. Eur J Oncolo. 2:103-108.

Weed, D.L. 2003. Causation: an epidemiological perspective. J Law Policy 43:43-53.

Weed, D.L. and McKeown, R.E. 2003. Science, ethics and professional public health practice. J Epidemiol Commun. Health 57:4-5.

McKeown, R.E., Weed, D.L., Kahn, J., and Stoto, M. 2003. American College of Epidemiology Ethics Guidelines: Foundations and Dissemination. Sci Eng. Ethics 9(2):207-214.

*Weed, D.L and Mink, P. 2002. Roles and responsibilities of epidemiologists. Ann Epidemiol. 12:67-72.

Weed, D.L. 2002. Environmental epidemiology: basics and proof of cause-effect. Toxicology 181-182:399-403.

McKeown, R.E. and Weed, D.L. 2002. Glossary of ethics in epidemiology and public health: II. Applied terms. J Epidemiol Commun. Health 56:739-741.

Weed, D.L. 2002. Cancer prevention and the All-Ireland NCI Cancer Consortium. Promoting Health-The Journal of Health Promotion for Northern Ireland 18:26-27.

Weed, D.L. 2001. Methods in epidemiology and public health: does practice match theory? J Epidemiol Commun. Health 55:104-110.

Piniewski-Bond, J.F., Buck, G.M., Horowitz, R.S., Schuster, J.H.R., Weed, D.L., and Weiner, J.M. 2001. Comparison of information processing technologies. J Am Med Informatics Assoc. 8:174-184.

Weed, D.L. 2001. A radical future for public health. Int J Epidemiol. 30:440-441.

Merrill, R.M. and Weed, D.L. 2001. Measuring public health burden of cancer through lifetime and age-conditional risk estimates. Ann Epidemiol. 11:547-553.

Burke, W., Coughlin, S.S., Lee, N.C., Weed, D.L., and Khoury, M. 2001. Application of population screening principles to genetic screening for adult-onset conditions. Genet Test. 5:201-211.

Parascandola, M. and Weed, D.L. 2001. Causation in epidemiology. J Epidemiol Commun. Health 55:905-912.

Weed, D.L. and McKeown, R.E. 2001. Glossary of ethics in epidemiology and public health: I. Technical terms. J Epidemiol Commun. Health 55:855-857.

Weed, D.L. 2001. Theory and practice in epidemiology. Ann NY Acad Sci. 954:52-62.

Stoto, M.A., Hermalin, A.I., Li, R., Martin, L., Wallace, R.B., and Weed, D.L. 2001. Advocacy in epidemiology and demography. Ann NY Acad Sci. 954:76-87.

Weed, D.L. 2000. History of Cancer Prevention: Pioneers of progress: Major Greenwood, Austin Bradford Hill, and the development of the randomized clinical trial (1900-1950). PreventionPost 2:2-3.

Weed, D.L. 2000. The rise and fall of the clinical trial paradigm. PreventionPost 2:1:16.

Weed, D.L. 2000. Interpreting epidemiologic evidence: how meta-analysis and causal inference methods are related. Int J Epidemiol. 29:387-390.

Connor, R.J., Boer, R., Prorok, P.C., and Weed, D.L. 2000. An investigation of design and bias issues in case-control studies of cancer screening using microsimulation. Am J Epidemiol. 151:991-998.

Weed, D.L. 2000. Epidemiologic evidence and causal inference. Hematology/Oncology Clin N America 14:797-807.

Weed, D.L. 2000. History of Cancer Prevention: Joseph Cullen: Champion of Cancer Prevention and Control. PreventionPost 2:2:10.

Weed, D.L. 2000. Heroes and champions. PreventionPost 2:2:12.

Weed, D.L. 1999. Towards a philosophy of public health. J Epidemiol Commun. Health 53:99-104.

Potischman, N. and Weed, D.L. 1999. Causal criteria in nutritional epidemiology. Am J Clin. Nutrition 69(Suppl):1309S-1314S.

Weed, D.L. and Coughlin, S.S. 1999. New ethics guidelines for epidemiology: background and rationale. Ann Epidemiol. 9:277-280.

Weed, D.L. 1999. Book review of: *Philosophy in Epidemiology and Public Health*. Epidemiol. Monitor.

Ratnasinghe, D.D., Weed, D.L., and Shankar, S. 1999. Cancer knowledge and misconceptions among Hispanic El Salvadorian men in the Washington DC area. J Immigrant Health 1:207-213.

Weed, D.L. and Hursting, S.D. 1999. The authors reply (letter). Am J Epidemiol. 150:218-219.

Weed, D.L. 1999. History of Cancer Prevention: Cancer prevention in the "Roaring Twenties." PreventionPost 1:6.

Weed, D.L. 1999. The DCP Newsletter team (editorial). PreventionPost 1:12.

Weed, D.L. 1999. Higher standards for epidemiologic studies-replication prior to publication? (letter). JAMA 282:937.

Weed, D.L. 1998. Preventing scientific misconduct. Am J Public Health 88:125-129.

Weed, D.L. 1998. Beyond black box epidemiology. Am J Public Health 88:12-14.

Breslow, R.A. and Weed, D.L. 1998. Review of epidemiologic studies of alcohol and prostate cancer: 1971-1996. Nutrition and Cancer 30:1-13.

Breslow, R.A. and Ross, S.A., and Weed, D.L. 1998. Quality of reviews in epidemiology. Am J Public Health 88:475-477.

Weed, D.L. and Hursting, S.D. 1998. Biologic plausibility in causal inference: current method and practice. Am J Epidemiol 147:415-425.

Cronin, K.A., Weed, D.L., Prorok, P.C., and Connor, R.J. 1998. Case-control studies of screening: theory and practice. J National Cancer Inst. 90:498-504.

Weed, D.L. and McKeown, R.E. 1998. Epidemiology and virtue ethics. Int J Epidemiol. 27:343-348.

McKeown, R.E. and Weed, D.L. 1998. Authors' response to comment on "Epidemiology and virtue ethics." Int J Epidemiol. 27:348-349.

Huerta, E.E. and Weed, D.L. 1998. "Cuidando su Salud" (Spanish language radio in preventive medicine and public health). Cancer (Suppl) 83:1805-1808.

Weed, D.L. 1997. Methodologic guidelines for review papers. J Nat Cancer Inst. 89:6-7.

Weed, D.L. and Kramer, B.S. 1997. Response to Brind et al. (letter). J Nat Cancer Inst. 89:588.

Bulterys, M., Morgenstern, H., and Weed. D.L. 1997. Quantifying the expected versus potential impact of a risk-factor intervention program. Am J Public Health 87:867-868.

Weed, D.L. 1997. Underdetermination and incommensurability in contemporary epidemiology. Kennedy Institute of Ethics J. 7:107-127.

Weed, D.L. 1997. Meta-analysis under the microscope. J Nat Cancer Inst. 89:904-905.

Weed, D.L. 1997. The behavior-biology interface in cancer prevention and control. Prev Med. 26:S37-S41.

Merrill, R.M., Weed, D.L., and Feuer, E.J. 1997. The lifetime risk of developing prostate cancer in white and black men. Cancer Epidemiol Biom Prev, 6:763-768.

Weed, D.L. 1997. On the use of causal criteria. Int J Epidemiol. 26:1137-1141.

Gerlach, K.K., Marino, C., Weed, D.L., and Hoffman-Goetz, L. 1997. Lack of colon cancer coverage in seven women's magazines. Women & Health 26:57-68.

Weed, D.L. 1996. The sea of person time. Int J Epidemiol 25:1-4.

Weed, D.L. 1996. Book Review of: *The Fight for Public Health: Principles and Practice of Media Advocacy*. Prev Med, 25:86.

Weed, D.L. and Gorelic, L.S. 1996. The practice of causal inference in cancer epidemiology. Cancer Epidemiol Biomark Prev. 5:303-311.

Weed, D.L. 1996. Weed Responds to: The future of epidemiology: a humanist response. Am J Pub Health 86:1029-1030.

Weed, D.L. 1996. Book review of: Changing the Odds: Cancer Prevention through Personal Choice and Public Policy. Oncology 10:1432.

Weed, D.L. and Kramer, B.S. 1996. Induced abortion, bias and breast cancer: why epidemiology hasn't reached its limit. J Nat Cancer Inst. 88:1698-1700.

Weed, D.L. 1995. Epidemiology, the humanities, and public health. Am J Pub Health 85:914-918.

Houn, F., Bober, M.A., Huerta, E.A., Hursting, S., Lemon, S., and Weed, D.L. 1995. The association between alcohol and breast cancer: popular press coverage of research. Am J Pub Health 85:1082-1086.

Weed, D.L. 1994. Science, ethics guidelines, and advocacy in epidemiology. Ann Epidemiol. 4:166-171.

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Weed, D.L. 1994. Book Review of: Apricots and Oncogenes: On Vegetables and Cancer Prevention. Am J Epidemiol. 139:743-744.

Weed, D.L. 1994. Between science and technology: the case of antihistamines and cancer. J Nat Cancer Inst. 86: 740-741.

Coughlin, S.S., Benichou, J. and Weed, D.L. 1994. Attributable risk estimation in case control studies. Epidemiol Rev. 16:51-64.

Weed, D.L. 1994. Alcohol, breast cancer, and causal inference: where ethics meets epidemiology. Contemporary Drug Problems 21:185-204.

Greenwald, P.G., Kramer, B.K., and Weed, D.L. 1993. Expanding horizons in breast and prostate cancer prevention and early detection. J Cancer Education 8:91-107.

Husten, C., Weed, D.L, and Kaluzny, A.R. 1993. Training researchers in cancer prevention and control: a description and evaluation of NCI's Cancer Prevention Fellowship Program. J Cancer Education 8:281-290.

Pommerenke, F. and Weed, D.L. 1991. Physician compliance: Improving skills in preventive medicine practices. Am Fam Physician 43:560-568.

Weed, D.L. 1991. The merger of bioethics and epidemiology. J Clin Epidemiol. 44:15S-22S.

Cairoli, V.J. and Weed, D.L. 1991. NCI Report on the Cancer Education Program. J Cancer Education 6:65-66.

Connor, R.J., Prorok, P.C., and Weed, D.L. 1991. The case-control design and the assessment of the efficacy of cancer screening. J Clin Epidemiol. 44:1215-1221.

Clark, L.C., Patterson, B.H., Weed, D.L., and Turnbull, B.W. 1991. Design issues in cancer chemoprevention trials using micronutrients: application to skin cancer. Cancer Bulletin 43:519-524.

Koopman, J.S. and Weed, D.L. 1990. Epigenesis theory: A mathematical model relating causal concepts of pathogenesis in individuals to disease patterns in populations. Am J Epidemiol. 132:366-390.

Greenwald, P., Cullen, J.W., and Weed, D.L. 1990. Introduction: cancer prevention and control. Semin Oncol. 17:383-390.

Weed, D.L., Greenwald, P., and Cullen, J.W. 1990. The future of cancer prevention and control. Semin Oncol. 17:504-509.

Weed, D.L., Selmon, M., and Sinks, T. 1988. Links between categories of interaction. Am J Epidemiol. 127:17-27.

Weed, D.L. and Trock, B. 1988. Interactions and public health decisions. J Clin Epidemiol. 41:207-209.

Weed, D.L. 1987. The author replies. (Re: "On the logic of causal inference"). Am J Epidemiol. 126:157-158.

Weed, D.L. 1987. Epidemiology's triple crown. J Chronic Dis. 40:905-906.

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ABSTRACTS

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PRESENTATIONS:

A Mortality Study in Communications Workers. Society for Epidemiologic Research Student Workshop on Methods, Minneapolis, Minnesota, June, 1980.

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Preventive Interactions. 18th Annual Meeting of the Society for Epidemiologic Research, Chapel Hill, North Carolina, June, 1985.

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Uniformed Services University of the Health Sciences, Bethesda, Maryland, May, 1991, May, 1992, April 1993, April 1994.

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Ethics and Cancer Prevention. National Cancer Institute, Bethesda, Maryland, December, 1989.

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Centers for Disease Control, National Institute of Occupational Safety and Health, Robert A. Taft Laboratories, Cincinnati, Ohio, February, 1990.

Yale University School of Medicine, Department of Epidemiology and Public Health, New Haven, Connecticut, April, 1990.

University of Virginia, College of Medicine, Division of Epidemiology and Virology, Charlottesville, Virginia, October, 1990.

University of North Carolina, School of Public Health, Department of Epidemiology, Chapel Hill, North Carolina, November, 1991.

Harvard University, School of Public Health, Department of Epidemiology, Boston, Massachusetts, December, 1991.

Case Studies in Epidemiological Ethics. Yale University School of Medicine, Department of Epidemiology and Public Health, New Haven, Connecticut, April, 1990.

Inferential Issues in the Study of Alcohol and Breast Cancer. AMC Cancer Research Center, Denver, Colorado, December, 1990.

Epidemiology and the Humanities. Society for Health and Human Values, St. Louis, Missouri, October, 1991.

Bringing Ethics into Causal Inference in Epidemiology. University of Virginia, College of Medicine, Division of Epidemiology and Virology, Charlottesville, Virginia, April, 1992.

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Cancer Prevention Training in the Preventive Oncology Branch. American Cancer Society Board of Directors Meeting, Atlanta, Georgia, November 1992.

Ethical Issues in Prophylactic Mastectomy. American Society of Preventive Oncology, Tucson, Arizona, March 1993.

Ethical Considerations in Moderate Alcohol Drinking. Addiction Research Foundation International Symposium, Toronto, Ontario, May 1993.

Ethics in Epidemiology. PHS Epidemiology Training Program Seminar, Bethesda, Maryland, August 1993, and Uniformed Services University of the Health Sciences, Basic Epidemiology I, Bethesda, Maryland, November 1993, November 1994, November 1995.

Alcohol and Breast Cancer. University of Hawaii Cancer Center, Honolulu, Hawaii, September 1993.

Public Health Posters from the National Library of Medicine. Society for Health and Human Values, Rosslyn, Virginia, November 1993.

Untangling Decisions in Health Matters: The Case of Cancer Prevention. Baltimore Ethical Society, Baltimore, Maryland, April 1994.

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Preventive Medicine and the Press: A Case Study. Ohio State University Preventive Medicine Alumni Conference, Columbus, Ohio, September 1994.

Causal Inference in Cancer Epidemiology: A Methodologic Review. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, September 1994.

Division of Cancer Prevention and Control, NCI, Bethesda, Maryland, September 1994.

Department of Epidemiology, University of Washington School of Public Health and Community Medicine, Seattle, Washington, September 1995.

Epidemiology, Humanities, and Public Health. Department of Epidemiology and Preventive Medicine, University of Maryland, Baltimore, Maryland, September 1994.

Should Epidemiologists be Advocates? Centers for Disease Control and Prevention Course on Government Employees and Public Policy, Atlanta, Georgia, January 1995.

A New Ethic for Epidemiology? Third Brazilian Congress of Epidemiology, Salvador, Bahia, Brazil, April 1995.

Causality, Data and Inference. George Washington University School of Medicine, Washington D.C., May 1995.

The Future of Epidemiology. Uniformed Services University of the Health Sciences, Bethesda, MD, August 1995, August 1996, August 1997.

Beyond Black Box Epidemiology: Behavior and Biology. American College of Epidemiology Annual Meeting, St. Louis, MO, September 1995.

Causal Conclusions, Public Health Recommendations and Methods of Ethical Reasoning: A Practical Approach. American Public Health Association Annual Meeting, San Diego, CA, October 1995.

Biologic Evidence and Human Cancer Causation. Department of Epidemiology, MD Anderson Cancer Center, Houston, TX, March 1996.

Epidemiology Branch, National Institute for Environmental Health Sciences, Research Triangle Park, NC, July 1996.

American Health Foundation, Valhalla, NY, January 1998. Department of Oncology, McGill University, Montreal, QC, Canada, February 1999.

Preventing Scientific Misconduct. Department of Epidemiology and Biostatistics, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, March 1996.

Preventive Medicine Residency Program, Centers for Disease Control and Prevention, Atlanta, GA, March 1996.

Department of Chemistry, University of Maryland, College Park, MD, April 1996.

University of Hawai'i at Manoa, Honolulu, HI, August 1996.

Department of Biometrics and Preventive Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, November 1996 and November 1997.

MD Anderson Cancer Center, Houston, TX, July 1998.

Department of Oncology, Royal Victoria Hospital, McGill University, Montreal, QC, Canada, February 1999.

Office of Research Integrity, U.S. Public Health Service, Rockville, Maryland, September 2000.

Epidemiology and Virtue Ethics. XIVth Congress of the International Epidemiological Association, Nagoya, Japan, August 1996.

Association or Causation: Myths and Legends. NIH Research Festival Workshop, Bethesda, MD, September 1996.

On the Need for Ethics in the Community of University Scholars. University of South Carolina, Columbia, SC, March 1997.

Communicating Cancer Information: an American Perspective. German Cancer Research Center, Heidelberg, Germany, April 1997.

Annual Meeting of the European Association for Cancer Education, Brussels, Belgium, April 1997.

Women's Health and the Media: The Role of the Medical Journal. Healthy Women 2000 Conference, Washington DC, June 1997.

Principles and Practice of Cancer Prevention and Control. NCI Medical Oncology Lecture Series, Bethesda, MD, August 1997.

Ethics and Cancer Screening. Cancer Conference: Integrating Public Health Programs for Cancer Control, Atlanta, GA, September 1997.

NIH Research Festival. Bethesda, MD, October 1997.

University of Puerto Rico, San Juan, Puerto Rico, February 1998.

Pavilion du Chum, University of Montreal, Montreal, QC, Canada, February 1999.

Publishing and Authorship. Cancer Prevention Fellows Data Club Meeting, Bethesda, MD, September 1997.

Towards a Philosophy of Epidemiology. Department of Social and Preventive Medicine, SUNY-Buffalo, Buffalo, NY, September 1997.

Causal Criteria in Nutritional Epidemiology. ILSI Conference on the Role of Epidemiology in making Nutritional Recommendations. Washington, D.C., October 1997.

Philosophical Foundations for the Practice of Epidemiology. III Congress of the Chilean Society of Epidemiology. Vina del Mar, Chile, October 1997.

16th Meeting of the Spanish Society of Epidemiology. Sevilla, Spain, October 1998.

Determining Causality from Epidemiological Studies.

III Congress of the Chilean Society of Epidemiology. Vina del Mar, Chile, October 1997.

Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, MA, December 1997.

University of Puerto Rico, San Juan, Puerto Rico February 1998.

Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada, February 1999.

End of the Era of Weak Associations? An Historical Study of Epidemiologic Discovery. NIH Historical Office Symposium on Evidence and Action: How epidemiologists make decisions about science and the public's health. NIH Clinical Center, Bethesda, MD, March 1998.

Department of Epidemiology. School of Public Health. University of North Carolina, Chapel Hill, NC, April 1998.

Center for Clinical Epidemiology and Biostatistics. University of Pennsylvania Medical Center, Philadelphia, PA, May 1998.

MD Anderson Cancer Center. Houston, TX, July 1998.

Department of Epidemiology and Biostatistics, Yale University, New Haven, CT, November 1998.

Department of Epidemiology, University of California, Berkeley, Berkeley, CA, March 1999.

Channing Lab, Harvard University, May 1999.
Department of Health Evaluation Sciences, University of Virginia, Charlottesville, VA, January 2000.

Department of Epidemiology, Michigan State University, East Lansing, MI, February 2000.

Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, April 2000.

Epidemiology at a Crossroads. Seminar for the Cosmetics, Fragrance, and Toiletries Association. Morristown, NJ, April 1998.

Epidemiologists and Risk: Theory, Method, and Practice. Workshop on Epidemiology and Toxicology. Washington, DC, May 1998.

The Interpretation of Meta-Analyses with reference to Causal Inference and Public Health Decisionmaking. Society for Epidemiologic Research Symposium on the Methods and Applications of Meta-Analysis. Chicago, IL, June 1998.

Roles and Responsibilities of Epidemiologists. Department of Epidemiology, University of North Carolina, Chapel Hill, NC, March 1999.

Causation and Biology. Society for Epidemiologic Research Symposium on the Future of Causes in Epidemiology. Baltimore, MD, June 1999.

Epidemiologic Evidence and the Precautionary Principle. International Society for Environmental Epidemiology. Athens, Greece, September 1999.

Improving Cancer Screening: An American Perspective. Symposium on Cancer Screening. Catholic University of Korea Cancer Center. Seoul, Korea, October 1999.

Causality and Inference in Cancer Epidemiology: We've Got Some Problems.

Ohio State University James Cancer Hospital. Columbus, OH, October 1999.

Department of Food Science and Human Nutrition. Michigan State University, East Lansing, MI, February 2000.

Department of Epidemiology. Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, April 2000.

Our future is not epidemiology.calm. American Public Health Association Special 70th Anniversary for the Epidemiology Section. Chicago, IL, November 1999.

American College of Epidemiology Ethics Guidelines: Foundations and Dissemination. AAAS Conference on Research Integrity, Washington, DC, April 2000.

Teaching Ethics and Public Health: Curriculum Content. ASPH/HRSA Workshop on Ethics and Public Health, Washington, DC, May 2000.

Science, Ethics and the Future of Preventive Oncology. Seminars in Clinical and Molecular Oncology, National Cancer Institute, Bethesda, MD, July 2000.

Precautionary Principle and the Philosophy of Public Health. WHO Workshop on the Precautionary Principle, Rome, Italy, May 2001.

Science, Ethics and the Future of Epidemiology.

International Epidemiological Association Regional Asia Meeting, Kitakyushu, Japan, September 2001.

Kyoto University School of Public Health, Kyoto, Japan, September 2001.

National Cancer Center, Tokyo, Japan, September 2001.

Cancer Prevention in the 21st Century Istituto Superiore di Sanita, Rome, Italy, May 2002.

Roles and Responsibilities of Epidemiologists Istituto Superiore di Sanita, Rome, Italy, May 2002.

Promoting Research Integrity Cleveland Clinic Foundation, Cleveland, Ohio, May 2002.

Scope and Importance of Public Health World Bank/WHO Conference on Public Health Challenges in the Middle East and North Africa, Beirut, Lebanon, June 2002.

The Precautionary Principle and the Philosophy of Public Health International Society of Environmental Epidemiology, Vancouver, BC, August 2002.

CURRICULUM VITAE

PERSONAL INFORMATION:

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Marital Status: Married; two children; three grandchildren

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EDUCATION:

Yale University, New Haven, Conn., Ph.D. (Physiology), 1968
(Thesis: "Evidence for acute ACTH release by extrahypothalamic mechanisms")
Yale University, New Haven, Conn., M.S. (Physiology), 1965
New York University, New York, N.Y., A.B. (Biology), 1963

POSTDOCTORAL TRAINING:

Postdoctoral Fellow in Physiology, 1968 - 1970
University of Virginia
Charlottesville, Virginia

ACADEMIC APPOINTMENTS:

Professor Emeritus of Physiology and Biophysics, 2010-present
School of Medicine
Medical College of Virginia
Virginia Commonwealth University
Richmond Virginia

Professor of Physiology and Biophysics, 1988-2009

School of Medicine
Medical College of Virginia (MCV)
Virginia Commonwealth University (VCU)
Richmond, Virginia

Affiliate Professor of Dentistry (MCV\VCU), 1988-2009
Associate Professor of Physiology (MCV\VCU), 1979 - 1988
Assistant Professor of Physiology (MCV\VCU), 1970 - 1979

MEMBERSHIP - SCIENTIFIC, HONORARY AND PROFESSIONAL SOCIETIES:

Society of Toxicology
The Endocrine Society (Emeritus)
American Physiological Society (Emeritus)
Society for Experimental Biology and Medicine (Emeritus)
International Society for Regulatory Toxicology and Pharmacology (ISRTP)
Virginia Academy of Science
American Association for the Advancement of Science (inactive)
American Society of Andrology (inactive)
Histochemical Society (inactive)
Society of the Sigma Xi (inactive)

SPECIAL AWARDS, FELLOWSHIPS, AND OTHER HONORS:

Awards

Horace V. Stunkard Prize in Biology, New York University, 1963.
Beta Lambda Sigma, Biological Honor Society, New York University, 1963.
Delta Phi Alpha, National Honor Society for German Scholarship, 1963.
Zeta Beta Tau Fraternity, Gamma Chapter Award for Academic Achievement, New York University, 1963.
Society of the Sigma Xi, University of Virginia, 1969.
NIH Postdoctoral Fellowship, 1969-1970.
Award for Excellence in Teaching by First Year Medical Class, MCV, 1971.
Award for Excellence in Teaching by Deans of Professional Schools, MCV, 1973.
Honorable Mention: Dr. Heinz Karger Prize Competition for an original research paper in the area of "Cytological and histochemical approaches to the diagnosis of tumours," 1978.
Award for "Outstanding Contributions to Medical Education", First Year Medical Class, MCV, 1979.
Award for Teaching in Endocrine Course, First Year Medical Class, MCV, 1984.
Award for Best Professor of Reproduction, First Year Medical Class, MCV, 1985.
Award for Best Syllabus of the Year, First Year Medical Class, MCV, 1985.
Award for Best Professor of Endocrinology/Reproduction, First Year Medical Class, MCV, 1986.
Certificate of Appreciation in Recognition of Outstanding Service Given to the 1988 Metro Richmond State Employees Combined Charitable Campaign, 1988.
Acknowledgment from Endocrine Society for extra assistance with presentation of the 1989

Program and Meeting of the Society.

Faculty Member of the Year, Recognition Day Award, Physiology Graduate Student Association, 1992-1993.

Outstanding Teacher Award for High Evaluation in M-1 Physiology Course (2001-2002), School of Medicine, Medical College of Virginia of Virginia Commonwealth University.

Third Annual Stephen and Mary Krop Lectureship in Pharmacology, Georgetown University Medical Center, Washington, D.C., 2002.

Outstanding Teacher Award in the Department of Physiology (2003), School of Medicine, Medical College of Virginia of Virginia Commonwealth University.

Outstanding Teacher Award for High Evaluation in M-1 Physiology Course (2004-2005), School of Medicine, Medical College of Virginia of Virginia Commonwealth University.

Outstanding Teacher Award for High Evaluation in M-1 Physiology Course (2006-2007), School of Medicine, Medical College of Virginia of Virginia Commonwealth University.

Outstanding Teacher Award for High Evaluation in M-1 Physiology Course (2007-2008), School of Medicine, Medical College of Virginia of Virginia Commonwealth University.

Outstanding Teacher Award for High Evaluation in M-1 Physiology Course (2008-2009), School of Medicine, Medical College of Virginia of Virginia Commonwealth University.

Faculty Teaching Excellence Award, Virginia Commonwealth University School of Medicine, 2009. (School of Medicine's highest recognition for teaching).

Recognized for teaching accomplishments by the American Physiological Society as noted in the following article: Tipton, CM: A section devoted to profiles of renown teachers and to the recognition and accomplishments of physiology teachers within the society, Adv Physiol Educ 34: 163-166, 2010.

Grants

Co-Investigator, "Biochemical Correlates with Human Breast Cancer"; NIH Grant CA-17116, May, 1975 to April 30, 1978, $145,377.

Travel Grant from Endocrine Society to attend 58th Annual Meeting of Society in San Francisco, June, 1976.

Travel Grant from Endocrine Society to attend VI International Congress of Endocrinology, Melbourne, Australia, February 1980.

Principal Investigator, "Prolactin Binding in Human Breast and Prostate Cancers", Developmental Grant from NIH to MCV Cancer Center, March 1, 1979 to March 30, 1980, $3,000.

Principal Investigator, "Prolactin Binding in Normal and Neoplastic Prostate", NIH Grant CA-23653, August 1, 1978 to July 3l, 1981, $73,245 (Direct Costs).

Principal Investigator, "Prolactin Binding in Normal and Neoplastic Prostate", NIH Grant CA-23653, August 1, 1981 to Dec. 30, 1985, $167,732 (Direct Costs).

Principal Investigator, "Effects of oral erythrosine (FDC Red Dye No. 3) on thyroid function in man and rats." Contract sponsored by Tri-Valley Growers of California. September 1, 1984 to December 1, 1987, $44,714.

Principal Investigator, "The role of placental lactogen in alcohol-induced intrauterine growth retardation." Grant from the Butler Fund of the Medical College of Virginia Foundation, January 1, 1989 to December 31, 1989, $4,053.

Principal Investigator, "The role of placental lactogen in alcohol-induced intrauterine growth retardation," Jeffress Research Grant, Thomas F. Jeffress and Kate Miller Jeffress

Memorial Trust, Sovran Bank, N.A., January 1, 1989 to December 31, 1990, $52,750.

Principal Investigator, "Elucidation of the antilympholytic effect of prolactin," Gustavus and Louise Pfeiffer Research Foundation, April 1, 1991 to March 31,1992, $33,186.

Principal Investigator, "Structure-function studies of prolactin proliferative and anticytolytic actions," Virginia Commonwealth University Grants-in-Aid, July 1, 1992 to June 30, 1993, $7,000.

Principal Investigator, "The role of p53, bcl-2, and bax in the control of apoptosis of Nb2 lymphoma cells," Grant from the A.D. Williams Fund of the Medical College of Virginia, April 1, 1996 to December 31, 1997, $10,000.

Principal Investigator, "Mechanisms of apoptosis and anti-apoptosis," Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University School of Hygiene and Public Health, February 1, 1998 to January 30, 1999, $5,000.

Principal Investigator, "Hormonal modulation of p53, bcl-2, and bax and apoptosis control in Nb2 lymphoma cells," Grant from Thomas F. Jeffress and Kate Miller Jeffress Memorial Trust, NationsBank, N.A., July 1, 1996 to June 30, 2002, $30,000.

Principal Investigator, "G-screen microassay for the identification of xenoglucocorticoids, Grant from the Thomas F. Jeffress and Kate Miller Jeffress Memorial Trust, Bank of America, July 1, 2003 to June 30, 2012, $45,000.

Recipient, grant associated with 2009 Faculty Teaching Excellence Award for scholarship and education development, $3,000.

Invited Seminars and Papers, Session Chairs

Invited speaker: Symposium on Hormone Receptor Immunocytochemistry, Twenty-ninth annual meeting of the Histochemical Society, Vancouver, B.C., April, 1978.

Invited author: September, 1979 symposium issue on genitourinary disease in the journal, "Human Pathology".

Invited speaker: Columbia University Reproductive Endocrinology Lecture Series, June, 1980.

Invited speaker: National Prostatic Cancer Project Workshop on the Prostatic Cell. Roswell Park Memorial Institute, Buffalo, New York, March, 1981.

Invited speaker: National Prostatic Cancer Project Conference on Prostate Cancer. A Decade of Progress and New Horizons. Bethesda, Maryland, January, 1984.

Invited speaker: Department of Anatomy, University of Minnesota, Minneapolis, Minnesota, February 1984.

Invited speaker: Symposium on Male Reproductive Toxicology, "Use of gonadotropic hormones and sex steroids in assessing male reproduction". Annual Meeting of the American College of Toxicology, Fairfax, Virginia, November, 1985.

Invited speaker: "The use of gonadotropic hormone and gonadal steroids in the assessment of male reproduction." Biology Department, James Madison University, Harrisonburg, Virginia, January, 1986.

Invited author: "Prolactin Receptors". In Peptide Receptors, M. Kalimi and J. Hubbard, editors, Walter de Gruyter & Co., 1987.

Invited speaker: "Environmental tobacco smoke and pulmonary function in children", Indoor Air Pollution Advisory Group, Center for Environmental Health and Human Toxicology, Washington, D.C., January 14, 1988.

Invited author: "Immunohistochemical and biochemical studies of the prolactin-prostate interrelationship." In: Prolactin and Lesions in the Breast, Prostate and Uterus, H.

Nagasawa, editor, CRC Press, 1989.

Invited author: Review article entitled, "A critical analysis of the relationship between parental smoking and pulmonary performance in children." Zeitschrift fur Das Offentliche Gesundheitswesen, 1989.

Invited speaker: "Effects of environmental tobacco smoke on respiratory and cardiovascular systems," Association for Research on Indoor Air, September 2, 1989, Hong Kong.

Invited speaker: "Parental smoking and respiratory health and pulmonary function in children: A review of the literature and suggestions for future research," International Symposium on Environmental Tobacco Smoke, McGill University, Montreal, Canada, November 4, 1989.

Invited author: "Receptors, receptor regulation, membrane fluidity, and prolactin processing." The Prostate as an Endocrine Gland. W.E. Farnsworth and R. Ablin, editors, CRC Press, Inc. 1989.

Invited speaker: "Prolactin studies in prostate, mammary gland, and Nb2 lymphoma cells," Prolactin Gordon Conference, Oxnard, California, February 1, 1990.

Invited speaker: "Prolactin-glucocorticoid interactions on Nb2 lymphoma cells," R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, November 30, 1990.

Invited speaker: "Prolactin-glucocorticoid interactions on Nb2 lymphoma cells, "Neuropharmacology Branch, Department of Medical Neurosciences, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C., March 15, 1991.

Invited speaker: "Apoptosis: Hormonal control and role in chemotherapeutic agent mediated cytotoxicity," Population Council, Rockefeller University, New York, New York, February 3, 1994.

Invited speaker: "Mechanisms of apoptosis and anti-apoptosis", Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, February 25, 1998.

Session Chair, Apoptosis II, 37th Annual Meeting of the Society of Toxicology, Seattle, Washington, March 3, 1998.

Invited speaker: "Endocrine disruption - history, fact and fantasy of gender bending chemicals." Third Annual Stephen and Mary Krop Lectureship in Pharmacology, Georgetown University Medical Center, Washington, D.C., November 22, 2002.

Invited speaker: "Physiological role and toxicological effects of glucocorticoids on reproduction." Continuing Education Course "The effects of non-reproductive hormones on the reproductive system, and the implications for toxicology." Society of Toxicology Annual Meeting, Salt Lake City, Utah, March 9, 2003.

Session Chair, Endocrine Disruptors, 45th Annual Meeting of the Society of Toxicology, San Diego, California, March 8, 2006.

Invited speaker: "Is There a Place for a Physiologist in Toxicology." Student Day Symposium: "Life After Graduation: Stretching Your Degree to the Max." National Capital Area Chapter, Society of Toxicology, Virginia Bio-Technology Research Park, Virginia Commonwealth University, January 23, 2008.

Invited speaker: Keynote Presentation - "The Endocrine System: Overview and Some Issues to Consider in Endocrine Disruption." Workshop: "Conducting and Assessing the Results of Endocrine Screening." International Society of Regulatory Toxicology and Pharmacology (ISRTP), National Institutes of Health, Bethesda, Maryland, February 20, 2008.

Visiting Professor of Physiology (13 lectures on endocrine/reproduction to first year medical students), American University of the Caribbean (AUC), Cupecoy, St. Maarten, Netherland Antilles, August 28 to September 19, 2009.

Invited speaker: Keynote Presentation - "The Endocrine System: Overview and Its Relevance to EDSP Screening." (video presentation). Workshop: "The Endocrine Disruptor Screening Program: What Can Screening Results Tell Us About Potential Adverse Endocrine Effects?" International Society of Regulatory Toxicology and Pharmacology (ISRTP), National Institutes of Health, Bethesda, Maryland, September 9, 2009.

Invited speaker: "Endocrine Disruption and Personal Care Products", Environmental Workshop, 2009 Sciences Symposium. "Environmental Assessment for Personal Care Products", Personal Care Products Council, Airport Marriott Hotel, Newark, New Jersey, October 29, 2009

Invited speaker: "Endocrine Disruption and Personal Care Products", Workshop: Current Issues in Safety Assessment, 2009 Sciences Symposium. "Environmental Assessment for Personal Care Products", Personal Care Products Council, Airport Marriott Hotel, Newark, New Jersey, October 29, 2009.

Invited speaker: "Can Tier 1 Test Data Inform Priority Setting for Human Health Risk Assessment", Workshop on Scientific Methods for Evaluating EDSP Screening Data & Estimating Dose-Response for Endocrine Disruption, Annual Meeting of the Society for Risk Assessment, Renaissance Baltimore Harborplace Hotel, Baltimore, Maryland, December 6, 2009.

Visiting Professor of Physiology (10 lectures on endocrine/reproduction to first year medical students), Trinity University School of Medicine, St. Vincent, British West Indies, January 25 to February 5, 2010.

Invited speaker: "Endocrine Disruption and Personal Care Products", Webinar: "Endocrine Disruption and Personal Care Products-Science and Regulatory Developments," Personal Care Products Council, July 21, 2010.

Invited speaker: "Endocrine Disruption and Personal Care Products", Meeting of the International Cooperation on Consensus Regulation (ICCR) for ICCR Regulators, Invited Regulators, and Industry, Hilton Washington, DC/Rockville Hotel and Executive Center, Rockville, Maryland, July 11, 2012.

Invited speaker: "Basic Concepts of Endocrinology: Issues Relevant to Endocrine Disruptor Screening," Technical session entitled "Endocrine Disruption: Its Potential Impact on Green Chemistry: A Facilitated Dialog Between NGOS, Academics, Industry and Government," 17th Annual Green Chemistry & Engineering Conference, ACS Green Chemistry Institute, Bethesda North Marriott Hotel & Conference Center, North Bethesda, Maryland, June 18, 2013.

MAJOR COMMITTEES:

University

M-I Endocrine Curriculum, 1970-1972, 1984-1987.
M-II Endocrine Curriculum, 1970-1971.
M-II Reproduction Curriculum, 1971-1972.
Biological Seminar, Physiology Department Representative, 1971-1972.
Faculty Senate Student Affairs Committee, 1971-1972.

Physiology Department Animal Care, 1971-1972.
Dental Physiology Course, Chairman, 1972-1974, 1980.
Adrenal Section, M-I Endocrine Curriculum, Chairman, 1972-1973.
Adrenal Section, Endocrine-Reproduction Curriculum, Chairman, 1973-1974.
Graduate Committees for several Ph.D. and M.S. candidates in Physiology, Pharmacology, Biochemistry, Anatomy, Microbiology, 1970-present.
Physiology Department Promotions and Tenure Committee, 1975-1976.
Coordinator Medical School Orientation Program for Virginia State College premedical students, 1975-1976.
Steering Committee, School of Medicine Self-Study, MCV, 1976.
Physiology Department Professional Education Committee, 1975-1977.
Medical School Promotions Committee (non-voting member), 1974-1977.
M-I Reproduction Curriculum, 1977-1987.
School of Basic Sciences Committee on Committees, 1979-1982.
School of Dentistry Admissions Committee, 1979-1982.
School of Dentistry Class Committee, 1979-1980.
Tenure and/or Promotions Committees for several faculty members, 1978-present.
School of Basic Sciences Faculty Committee For Self Study, 1982-1983.
Graduate Course in Endocrine Physiology, Director, 1982, 1987, 1992.
Faculty Senate, 1983-1986.
Faculty Senate Committee on Academic Programs and Research, Chairman, 1983-1985.
University Radiation Safety Committee, Subcommittee on Research Use of Radioisotopes, 1983-1984.
Search Committee for Chairman, Department of Physiology & Biophysics, MCV, 1985.
Judging Committee, 13th Annual John C. Forbes Graduate Students Honors Day, 1985.
University Grievance and Appeals Panel, 1985-1988.
Department of Physiology Committee on Core Curriculum, 1986-1989.
Department of Physiology Committee on Affiliate Appointments, 1986-1989.
American Cancer Society Institutional Grant Review Committee, 1986-1990.
Reproduction Subject Matter Committee, MI to MIV, 1987.
School of Basic Health Sciences Committee on Dental Curriculum, 1987-1995.
School of Basic Health Sciences, School Grievance and Appeals Board, 1989-1992 (acting chair, 1990).
Judging Committee, Kinloch Nelson Honors Day, School of Medicine, 1989.
School of Medicine Student Research Committee, Medical Class of 1993, 1989-1993.
School of Medicine Appeals Committee for Students, 1990-1993, Acting Chairman, 1991-1992.
Physiology Department Graduate Student Steering Committee, 1992-1994.
Physiology Department, Faculty Liaison with Chair, 1994-1996.
Physiology Department, Graduate Admissions Committee, 1974-1986, 1994-2008.
Physiology Department Seminar Series, Chairman, 1979; 1983-1984, 1991-1992, 1994-1995.
School of Medicine, Committee on Curriculum Renewal, Subcommittee on Women's Health, 1997.
School of Dentistry, Implementation Committee for Basic Science Curriculum for Dental Residents, 1999-2009.
School of Medicine, Internal Review Committee, Department of Otolaryngology Residents Programs, 2002.
School of Dentistry, D1 Class Committee, 2002-2009.

School of Dentistry, Academic Performance Committee, 2004-2009.
Department of Physiology and Biophysics, Executive Education Committee, 2008-2009.
Department of Physiology and Biophysics, Teaching Leadership Committee, 2008-2009.
School of Medicine Teaching Excellence Awards Selection Committee, 2010-2012.

Professional

Ad Hoc Consultant, National Heart and Lung Institute Institutional Research Fellowship Grant Application Review Committee, 1976.

Ad Hoc manuscript reviewer for Endocrinology, Endocrine Journal, Journal of the National Cancer Institute, The Prostate, Journal of Histochemistry and Cytochemistry, Cancer Research, Proceedings of the Society for Experimental Biology and Medicine, Science, Journal of Andrology, Neuroendocrinology, Life Sciences, Food and Chemical Toxicology., Experimental Cell Research, Hormone and Metabolic Research, Archives of Biochemistry and Biophysics, Cellular and Molecular Biological Research, American Journal of Respiratory Cell and Molecular Biology, Immunotoxicology, Agency for Toxic Substances and Disease Registry (ATSDR). Molecular Carcinogenesis, Journal of Toxicology and Environmental Health, Science World.

Ad Hoc book proposal reviewer for CRC Press, Wiley.

Ad Hoc Grant reviewer for National Science Foundation, National Prostatic Cancer Project, National Institutes of Health, American Osteopathic Association, North Dakota Experimental Program to Stimulate Competitive Research (EPSCoR), NationsBank (Jeffress Memorial Trust), Department of Veterans Affairs, Agency for Toxic Substances and Disease Registry (ATSDR) for Association of Minority Health Professions Schools, Ohio Cancer Research Associates.

Special Study Section, National Institutes of Health, March 29, 1982.

Member, Indoor Air Pollution Advisory Group, Center for Environmental Health and Human Toxicology, Washington, D.C., 1985-1988.

External Reviewer of Peer Review Panel Report entitled, "An Inquiry Into the Mechanism of Action of FD&C Red No.3", submitted to the Commissioner of Food and Drug, December, 1986.

Public Relations Committee, American Society of Andrology, 1985-1988.

Liason Committee, American Society of Andrology, 1987-1988.

Development Committee, Endocrine Society, 1987-1992.

Panel Member (Grant reviewer), Special Emphasis Panel (SEP), Role of Hormones and Growth Factors in Prostate Cancer, RFA: DK-01-008, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, August 23, 2001.

Editorial Board, PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, 1990-1996.

Editorial Board, THE PROSTATE, 1986-2000.

Editorial Board, TOXIC SUBSTANCE MECHANISMS, 1996-2002.

Editorial Board, TOXIC MECHANISMS AND METHODS, 2002-present.

Allocations Committee, Jeffress and Gwathmey Memorial Trusts, Virginia Academy of Science Representative, 2008-2011, Chair (2009).

Principal Editor, The Science World (TSW), Terrestrial Environmental Toxicology and TSW Toxicology Cluster, 2009-present.

OTHER SIGNIFICANT SCHOLARLY RESEARCH OR ADMINISTRATIVE EXPERIENCE:

Graduate Students Trained

J. Travers Edwards, Jr., M.S., 1972
(Thesis: "The effects of prolactin and growth hormone on adrenal 5α-reductase in the rat.").

Jeanne P. Smith, M.S., 1977
(Thesis: "An immunohistochemical localization of prolactin binding sites in rat ventral prostate epithelia.").

Robert S. Vick, Ph.D., 1986
(Thesis: "Isolation and characterization of cleaved prolactin generated by target tissue.").

Vicky Lien Ying Wong, Ph.D., 1986
(Thesis: "Proteolytic cleavage of prolactin by target tissues with special emphasis on rat mammary gland.").

Susan E. Fletcher, Ph.D., 1991
(Thesis: "Prolactin-glucocorticoid interactions in Nb2 lymphoma cells.").

Neda Hashemi, M.S., 1993
(Thesis: "The role of apoptosis in mediation of antineoplastic agent-induced cytotoxicity.").

Holly Lavoie, Ph.D., 1994
(Thesis: "Investigation of intracellular signals mediating the anti-apoptotic action of prolactin in Nb2 lymphoma cells.").

Angelo Guanzon, M.S., 1998
(Thesis: "Immunocytochemical study of apoptosis signaling in Nb2 lymphoma cells.").

Suhas Badarinath, M.S., 1999
(Thesis: "Examination of signals involved in dexamethasone induced apoptosis in Nb2 lymphoma cells.").

Devang Patel, M.S., 1999
(Thesis: "Correlation of visualized glucocorticoid receptor and apoptosis in individual clones of Nb2 cells.").

Rhodaline Rebano, M.S., 2000
(Thesis: "Hormonal control of apoptosis and signal expression in sublines of Nb2 lymphoma cells.").

Charlotte Cockrell, M.S., 2000
(Thesis: "Functional characterization of mitogen-dependent and self perpetuating Nb2 lymphoma cell lines.").

Elizabeth Gannon, M.S., 2001
(Thesis: "Modification and analysis of prolactin dependent and glucocorticoid sensitive Nb2 lymphoma cells.").

Gennifer Wiltshire, M.S. 2001
(Thesis: "A comparative study of signal expression in Nb2 lymphoma sublines using immunocytochemistry.").

John Shurm, Jr. Ph.D. 2002
(Thesis: "Identification of glucocorticoid receptor mediated interactions with non-steroidal environmental chemicals").

Christopher Jones, M.S., 2004
(Thesis: "A microassay for the detection of glucocorticoid receptor activity in non-steroidal chemicals").

Postdoctoral Trainees

Mark M. Compton, Ph.D., December, 1979 to August, 1983
Jitendra R. Dave, Ph.D., December, 1981 to October, 1983

Major Teaching Assignments

MI Endocrine-Reproduction, 1970-2011.
Physiology 502, Dental Physiology, 1970-2001 (Course Director 1972-1974, 1980).
Physiology 607 (617), Graduate Endocrine Physiology/Cell Signaling, 1982 - present (taught Fall semester of alternate years), Course Director 1984, 1988, 1992, 1996, 2000.
Physiology 361, Nursing Pathophysiology, 1985-1990 (Director, 1987).
Physiology 461, Physiology for Physical Therapists, 1989-1993..
Physiology 505, Physiology for Industrial Hygienists 1988-1993.
Associate Coordinator, First Year Medical Curriculum, MCV, 1 974-1975.
Coordinator, First Year Medical Curriculum, MCV, 1975-1977.
Member of Ad Hoc Medical Curriculum Steering Committee acting in lieu of Dean of Curriculum, MCV, 1975-1976.
Seminar in Physiology (Director, 1979, 1983-84, 1991-92, 1994).
Review for Medical Board Examinations, National Medical School Review, University of South Florida, Tampa, Florida, May, 1994.
Physiology 502/506, Dental and Pharmacy Physiology, Course Director, 2002-2008.
Physiology 502, Dental Physiology, Course Director, 2009.

BIBLIOGRAPHY:

Papers published (in peer reviewed journals)

Witorsch, R.J. and A. Brodish: Conditions for the reliable use of lesioned rats for the assay of CRF in tissue extracts. Endocrinology 90:552-557, 1972.
Witorsch, R.J. and A. Brodish: Evidence for acute ACTH release by extra-hypothalamic mechanisms. Endocrinology 90:1160-1167, 1972.
Witorsch, R.J. and J.I. Kitay: Influence of the ovary, pituitary and age on adrenal 5 alpha-reductase activity in the rat. Endocrinology 90:1374-1379, 1972.
Witorsch, R.J. and J.I. Kitay: Pituitary hormones affecting adrenal 5 alpha-reductase activity: ACTH, prolactin and growth hormone. Endocrinology 91:764-769, 1972.
Leftwich, E.I., R.J. Witorsch and P. Witorsch: A critical evaluation of positive end-expiratory pressure in refractory hypoxemia. Annals of Internal Medicine 79:187-193, 1973.
Colby, H.D., R.J. Witorsch, J.L. Caffrey and J.I. Kitay: Effects of steroid suppression and gonadectomy on adrenal 5 alpha-reductase activity and corticosterone production in rats. Acta Endocrinologica 74:568-575, 1973.
Poland, J.L., T.D. Myers, R.J. Witorsch and R.B. Brandt: Steroid influence on cardiac glycogen. Proc Soc Exp Biol Med 150:148-150, 1975.

Witorsch, R.J. and J.T. Edwards: Comparison of effects of prolactin and growth hormone on adrenal 5 alpha-reductase in hypophysectomized rats. Proc Soc Exp Biol Med 151:689-693, 1976.
Nolin, J.M. and R.J. Witorsch: Detection of endogenous immunoreactive prolactin and rat mammary epithelial cells during lactation. Endocrinology 99:949-958, 1976.
Brown, P.W., R.J. Witorsch, W.L. Banks, Jr., and W. Lawrence: A convenient method for freezing and storage of breast cancer tissue for estrogen receptor protein assay. Arch Surg 112:183-185, 1977.
Witorsch, R.J. and J.P. Smith: Evidence for androgen-dependent intracellular binding of prolactin in rat ventral prostate gland. Endocrinology 101:929-928, 1977.
Witorsch, R.J.: Immunohistochemical studies of prolactin binding in sex accessory organs of the male rat. J Histochem Cytochem 26:565-580, 1978.
Witorsch, R.J.: Immunohistochemical demonstration of intracellular prolactin binding sites (IPBS) in R3327 rat prostatic carcinomas. Hormone Res 10:268-281, 1979.
Witorsch, R.J.: The application of immunoperoxidase methodology for the visualization of prolactin binding sites in human prostate tissue. Human Pathology 10:521-532, 1979.
Cohen, I.K., C.W. Moncure, R.J. Witorsch and R.F. Diegelmann: Collagen synthesis in capsules surrounding dimethylbezanthracene-induced rat breast tumors and the effect of pretreatment with beta-aminoproponitrile. Cancer Research 39:2923-2927, 1979.
Witorsch, R.J.: Evidence for human placental lactogen immunoreactivity in rat pars distalis. J Histochem Cytochem 28:1-9, 1980.
Witorsch, R.J: Evaluation of immunoperoxidase stained tissue sections with an electrophoresis densitometer. J. Histochem Cytochem 30:179-182, 1982.
Witorsch, R.J.: Regional variations in the testicular dependence of prolactin binding and its possible relationship to castration-induced involution in rat prostate gland. The Prostate 3:459-473, 1982.
Dave, J.R. and R.J. Witorsch: Increased detection of prolactin binding of rat ventral prostate after treatment with dextran-coated charcoal: Evidence for a direct dihydrotestosterone-prolactin interaction. Endocrinology. 111:2144-2146, 1982.
Dave, J.R. and R.J. Witorsch: Indomethacin decreases both prolactin binding and membrane fluidity of ventral and dorso-lateral lobes of rat prostate gland. The Prostate, 4:119-128, 1983.
Compton, M.M. and R.J. Witorsch: Proteolytic fragmentation of rat prolactin by the ventral prostate gland. The Prostate 4: 231-246, 1983.
Dave J.R. and R.J. Witorsch: Modulation of prolactin binding sites in vitro membrane fluidizers. I. Effects on adult rat ventral prostatic membranes. Biochem Biophys Res Communications 113:220-228, 1983.
Dave J.R. and R.J. Witorsch: Indomethacin decreases both luteinizing hormone binding and fluidity of testicular microsomal membranes in rat. Prostaglandins, Leukotrienes and Medicine 12:371-380, 1983.
Dave, J.R. and R.J. Witorsch: Modulation of prolactin binding sites in vitro by membrane fluidizers. II. Age-dependent effects in rat ventral prostatic membranes. Biochim. Biophys. Acta, 772:321-327, 1984.
Abbey, L.M. and R.J. Witorsch: Prolactin binding in normal minor salivary gland tissue. An immunohistochemical study. Oral Surgery, Oral Medicine, and Oral Pathology. 58:682-687, 1984.
Compton, M.M. and R.J. Witorsch: Proteolytic degradation and modification of rat prolactin by

subcellular fractions of the rat ventral prostate gland. Endocrinology, 115:476-484, 1984.
Dave, J.R. and R.J. Witorsch: Prolactin increases serum lipid fluidity and prolactin binding and lipid fluidity of rat prostatic membranes. American J Physiol 248 (Endocrinol. Metab. 11): E687-E693, 1985.
Abbey, L.M. and R.J. Witorsch, Prolactin binding in minor salivary gland tumors. Oral Surgery, Oral Medicine, and Oral Pathology 60:44-49, 1985.
Dave, J.R., R.J. Witorsch and M.Y. Kalimi: Endocrine mediated parallel changes in hepatic glucocorticoid and prolactin receptors. Biochim Biophys Acta 845:276-282, 1985.
Dave, J.R., R.J. Krieg, Jr., and R.J. Witorsch: Modulation of prolactin binding sites in vitro by membrane fluidizers. III. Effects on male prostatic and female hepatic membrane in alcohol-fed rats. Biochim Biophys Acta 816: 313-320, 1985.
Witorsch, R.J., R.S. Vick, L.M. Abbey and M.J. Wilson: A systematic study of age-dependent changes in prostatic morphology and prolactin binding of ACI rats. The Prostate 7:327-344, 1985.
Dave, J.R. and R.J. Witorsch: Modulation of prolactin binding sites in vitro by membrane fluidizers. IV. Differential effects on plasma membrane and Golgi fractions of male prostate and female liver in the rat. Biochem Biophys Res Commun134: 1122-1128, 1986.
Wong, V.L.Y., M.M. Compton, and R.J. Witorsch: Proteolytic modification of rat prolactin by subcellular fractions of the lactating rat mammary gland. Biochim Biophys Acta 81: 167-174, 1986.
Vick, R.S., V. Wong, and R.J. Witorsch: Biological, immunological, and biochemical characterization of cleaved prolactin generated by lactating mammary gland. Biochim. Biophys. Acta. 931: 196-204, 1987.
Gardner, D.F., R.D. Utiger, S.L. Schwartz, P. Witorsch, Meyers, B., L.E. Braverman, and R.J. Witorsch: Effects of Oral Erythrosine (2',4',5',7'-Tetraiodofluorescein) on thyroid function in normal men. Toxicology and Applied Pharmacology 91: 299-304, 1987.
Witorsch, R.J.: Moderate alcohol consumption and increased incidence of breast cancer in women. New England J. Med. 317: 1288, 1987 (letter to the editor).
Paul, T., B. Meyers, R.J. Witorsch, S. Pino, S. Chipkin, S.H. Ingbar, and L.E. Braverman: The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism 37: 121-124, 1988.
Witorsch, R.J., and P. Witorsch: A critical analysis of the relationship between parental smoking and pulmonary performance in children. Zeitschrift fur Das Offentliche Gesundheitswesen. 51: 78-83, 1989.
Jennings, A.S., S.L. Schwartz, P. Witorsch, , D.F. Gardner, and R.J. Witorsch: Effects of oral erythrosine (2',4',5',7'-tetraiodofluorescein) on the pituitary-thyroid axis in rats. Toxicology and Applied Pharmacology. 103: 549-556, 1990.
Hood, R.D., J.M. Wu, R.J. Witorsch, and P. Witorsch: Environmental tobacco smoke exposure and respiratory health in children: An updated critical review and analysis of the epidemiological literature. Indoor Environment 1: 9-35, 1992.
Witorsch, P., and R.J. Witorsch, Analysis of potential confounding variables in epidemiologic studies of parental/household smoking and respiratory health in pre-school children. Indoor Environment 2: 71-91, 1993.
Fletcher-Chiappini, S.E., M.M. Compton, H.A. LaVoie, E.B. Day, and R.J. Witorsch: Glucocorticoid-prolactin interactions in Nb2 lymphoma cells: Antiproliferative versus anticytolytic effects. Proc. Soc. Exptl. Biol. Med. 202: 345-352, 1993.

Witorsch, R.J.. E.B. Day, H.A. LaVoie, N. Hashemi, and J.K. Taylor: Comparison of glucocorticoid - induced effects in prolactin dependent and autonomous rat Nb2 lymphoma cells. Proc. Soc. Exptl. Biol. Med. 203: 454-460, 1993.

LaVoie, H.A. and R.J. Witorsch: Investigation of intracellular signals mediating the anti-apoptotic action of prolactin in Nb2 lymphoma cells. Proc. Soc. Exptl. Biol. 209: 257-269, 1995.

Witorsch, R..J.: Toxic effects on the seminiferous epithelium and Sertoli cell. Toxic Substance Mechanisms 15: 195-218, 1996 (review).

Witorsch R..J. and P. Witorsch: Environmental tobacco smoke and birthweight of offspring: A critical review and analysis of the epidemiological literature. Indoor + Built Environment 5:219-231, 1996.

Witorsch R..J.: Letter to the Editor (Prolactin, anti-angiogenesis, and the prostate) The Prostate 34: 302, 1998.

Witorsch R..J. and P. Witorsch: Environmental tobacco smoke and respiratory health in children: A critical review and analysis of the literature from 1969 to 1998. Indoor + Built Environment 9: 246-264, 2000.

Witorsch R..J.: Endocrine disruption: a critical review of environmental estrogens from a mechanistic perspective. Toxic Substance Mechanisms 19: 53-78, 2000.

Witorsch R..J..: Low dose in utero effects of xenoestrogens in mice and their relevance to humans: an analytical review of the literature. Food and Chemical Toxicology 40: 905-912, 2002.

Witorsch R.J.: Endocrine disruptors: Can biological effects and environmental risks be predicted? Regulatory Toxicology and Pharmacology 36: 118-130, 2002.

Borgert, C.J., J.S. Lakind, and R.J. Witorsch.: A critical review of methods for comparing estrogenic activity of endogenous and exogenous chemicals in human milk and infant formula. Environmental Health Perspectives 111: 1020-1036 2003.

Cooke, P.S., D.R. Holsberger, R.J. Witorsch , P.W. Sylvester, J.M. Meredith, K.A. Treinen, and R.E. Chapin, Thyroid hormone, glucocorticoids, and prolactin at the nexus of physiology, reproduction, and toxicology. Toxicology and Applied Pharmacology.194: 309-335, 2004.

Goodman, J.E., E.E. McConnell, I.G. Sipes, R.J. Witorsch, T.M. Slayton, C.J. Yu, A.S. Lewis, L.R. Rhomberg: An updated weight of the evidence evaluation of reproductive and developmental effects of low doses of bisphenol A. Critical Reviews in Toxicology 36: 387-457, 2006.

Goodman,, J.E., R.J. Witorsch, E.E. McConnell, I.G. Sipes, T.M. Slayton, C.J. Yu A.M. Franz, L.R. Rhomberg. Weight-of-evidence evaluation of reproductive and developmental effects of low doses of bisphenol A: 2008 update. Critical Reviews in Toxicology 39: 1-75, 2009.

Witorsch, R.J. and J.A. Thomas. Personal care products and endocrine disruption: A critical review of the literature. Critical Reviews in Toxicology 40(S3): 1-30, 2010 (doi:10.3109/10408444.2010.515563). Listed among 2010's most viewed toxicology articles at informhealthcare.com.

Witorsch, R.J. Critical analysis of endocrine disruptive activity of triclosan and its relevance to human exposure through the use of personal care products. Critical Reviews in Toxicology 44 (6): 535-555, 2014 (doi: 10.3109/10408444.2014.910754).

Abstracts

Witorsch, R.J., A. Brodish: Hypothalamic CRF assayed in rats with hypothalamic lesions. Fed. Proc. 27:217, 1968.

Witorsch, R.J.: Evidence for acute ACTH release by extrahypothalamic mechanisms. Ph.D. Thesis, Yale University, 1968. Diss. Abst. (b) 30(2):826, 1969.

Witorsch, R.J. J.I. Kitay: Influence of the ovary, ACTH, and age on adrenal 5 alpha-reductase in the rat. Fed. Proc. 29:707, 1970.

Witorsch, R.J. and J.I. Kitay: Inhibitory effect of prolactin on adrenal 5 alpha-reductase in the rat. Excerpta Med. Internat. Cong. Series 210:170, 1970.

Myers, T.D., J.L. Poland, R.J. Witorsch, R.B. Brandt: Steroid influence on cardiac glycogen. Virginia J. Science, Vol. 2, 1974.

Nolin, J.M., R.J. Witorsch: Endogenous prolactin (PRL) enters mammary alveolar cells. Fed. Proc. 35:219, 1976.

Witorsch, R.J., J.P. Smith, J.M. Nolin: Evidence for androgen-dependent intracellular binding of prolactin in rat ventral prostate gland. Proc. 58th Ann. Mtg., Endo. Soc.:66, 1976.

Witorsch, R.J.: Immunohistochemical demonstration of prolactin binding sites in some sex accessory organs of the male rat. Proc. 59th Ann. Mtg. Endo. Soc.:281, 1977.

Maher, R.W., R.J. Witorsch: Evidence for prolactin binding in epithelial cells of rat epididymis and vas deferens. Fed. Proc. 37:381, 1978.

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Other

My immunohistochemical approach to the study of hormone receptors was discussed (including photomicrographs) in the second and third editions of "Immunocytochemistry" by L.A. Sternberger, John Wiley and Sons, New York, 1979, 1986.

Participant: Training Workshop on Hybridomas and Monoclonal Antibodies, Medical College of Virginia, April 6-7, 1984.

Panelist: Panel discussion by outstanding lecturers on "The Faculty as Teachers"; Orientation for New Faculty, MCV/VCU School of Medicine, September 18, 1984.

Member: MCV Cancer Center, 1986-1990.

Organizing committee: Prolactin and Immune Function Working Group, February, 1990.

Consultant/expert witness on general and endocrine physiologic and reproductive abnormalities that may result from potential environment health hazards. Consultation has been given with regard to the following issues: effects of agent orange, trichloroethylene, polychlorobiphenyls (PCBs) and related compounds, perflourocarbons (PFCs), ethylene oxide, formaldehyde, environmental tobacco smoke, alcohol; Red Dye No. 3 and thyroid function; polydimethylsiloxanes (silicones) and breast cancer; oral contraceptives and cerebrovascular effects; estrogens, alcohol, and breast cancer; bisphenol A and endocrine disruption; arsenic toxicity, statins, anabolic steroids.

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