

# History of the Endocrine Disruptor Field: On the Back of Giants!

A personal perspective 2016

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# People...

It's all about the vision, dedication, and commitment of people.\*

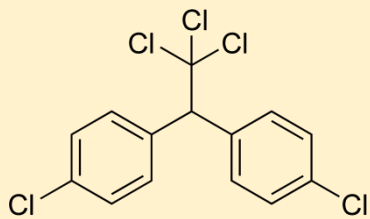
- Sir Charles Dodd (BPA)
- Leon Golberg (DES)
- Roy Hertz
- Rachel Carson
- Howard Bern
- Theo Colborn
- Pete Myers
- John McLachlan
- Taisen Iguchi

- Lou Guillette
- Ana Soto & Carlos Sonnenschein
- Niels Skakkebaek
- John Sumpter
- Bruce Blumberg
- Andreas Kortenkamp
- Åke Bergman
- Andrea Gore
- Fred vom Saal

\*Select list, many more scientists could/should be included.

# Rachel Carson: Patron of the Modern Environmental Movement

The unintended impacts of DDT on vertebrates nearly led to the extinction of the brown pelican and the bald eagle.



1947

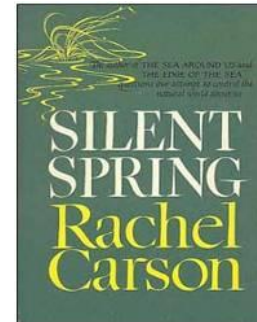
DDT causes eggshell thinning in bald eagles

1953

DDT found to be estrogenic

1972

EPA bans DDT



1962: Silent Spring



Rachel Carson

# Founding Father of Comparative Endocrinology: Howard Bern (1920-2012 )

Professor of Zoology, UC Berkeley  
1948-2012

Mentor to: Taisen Iguchi  
Lou Guillette, Tyrone Hayes

Leader in understanding DES effects  
on development

1992: “Extrapolating from what is known about the developmental effects of other weak estrogens, there should be concern about DES-like role these environmental estrogens could play if ingested (or inhaled) extensively by mothers during a critical period of development of their offspring in utero.”



Courtesy of Retha Newbold

# Early origins of EDC: Roy Hertz

“I think that we are now actually setting up a **steroid cycle** in our environment, and we have to give very serious consideration to its implications for our subsequent development and growth and possibly reproductive functions“

(Hertz, 1958 *Recent Prog Horm Res*)

# Theo Colborn: Pioneer on EDCs (1927-2014)

## Responsible for countless contributions related to EDCs, including the following:

- Broad **conceptualization** and early **dissemination** of the idea of endocrine-disruptors in the environment
- Advancement of the outline on a **new theory** of environmental disease that encompassed the work of many other disciplines (Wingspread, 1991)
- **Organizer** of Erice, Sicily EDC Conference (1995) and EDSTAC, EPA (1996)
- At age 76, **founded The Endocrine Disruption Exchange (TEDX)**, a research organization devoted to understanding how environmental exposures to EDCs interfere with development and health

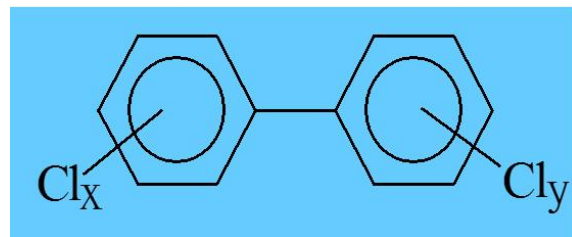
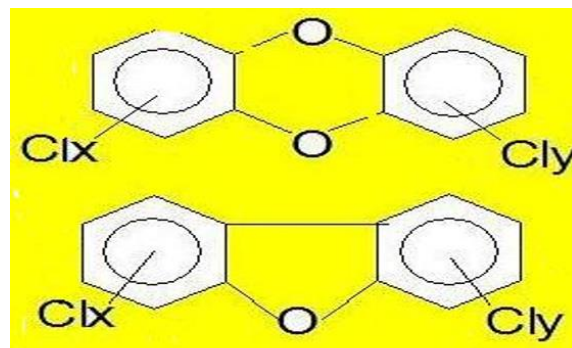
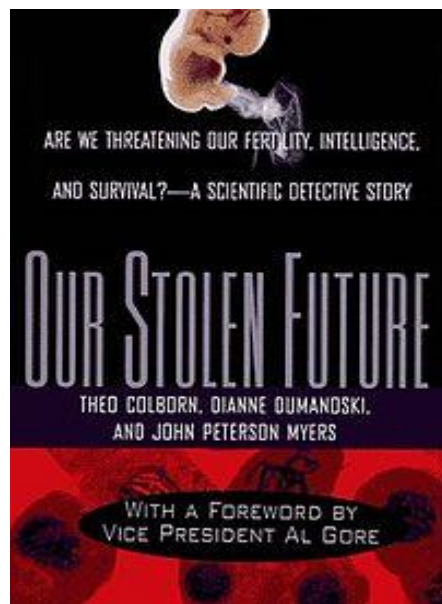


# Our Stolen Future

1996



Colborn, Dumanoski, Peterson

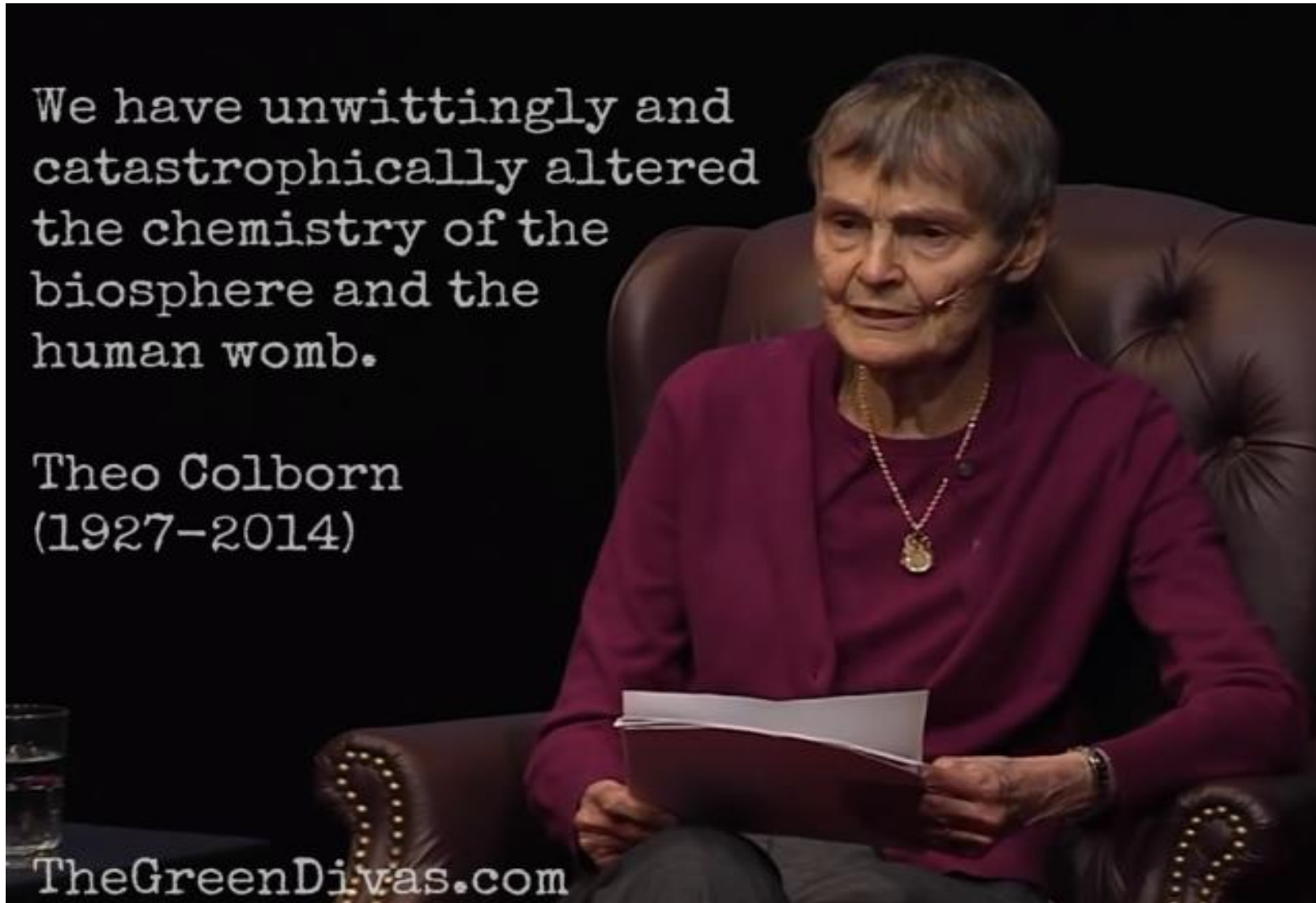


Chemicals that, at certain doses, can interfere with the endocrine (or hormone) system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife.

We have unwittingly and  
catastrophically altered  
the chemistry of the  
biosphere and the  
human womb.

Theo Colborn  
(1927-2014)

TheGreenDivas.com





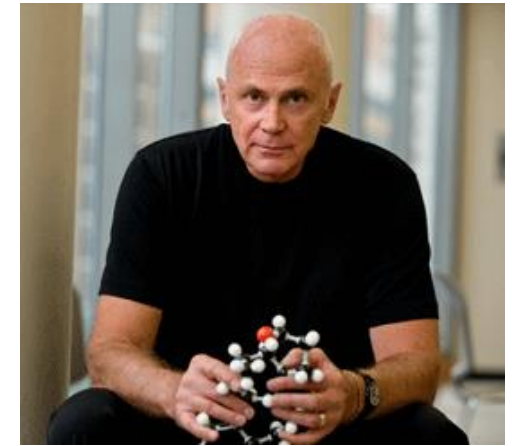
# “Pete” Myers: The Force Behind the Scenes

- VP of research at National Audubon Society mid 1980's
- Director of W. Alton Jones Foundation (hired Theo Colborn)
- Organizer and contributor of Wingspread Conference (1991)
- Co-author of Our Stolen Future (1996)
- Environmental Health Sciences
  - Science Communication Network
  - Advancing Green Chemistry
  - Environmental Health News
  - Daily Climate
- Everywhere...moving the field



# John McLachlan: Environmental Estrogens

- Former Scientific Director NIEHS
- McLachlan & Newbold found that
  - Exposure to exogenous estrogens during fetal development will profoundly alter sexual differentiation (1975 and onward)
  - DES is a transplacental carcinogen
  - DES epigenetically imprints genes during genital tract development
  - Estrogenic signaling mechanisms of different chemicals
  - Developmental exposure to DES can cause obesity in offspring



John McLachlan



Retha Newbold



# Lou Guillette: An EDC Superhero (1956-2016)

- Noticed that alligators in Lake Apopka had fewer eggs and the newborn alligators had birth defects
- Discovered that developmental exposure to environmental contaminants were responsible for the reproductive defects
- Became a leader in field of EDCs and was a great **scientist, educator, mentor, communicator and translator of work in wildlife to animals and humans**



“People don’t appreciate how much wildlife and the things living around us can tell us about the health of the environment, and actually tell us something about our own health. If the environment isn’t healthy for a baby alligator or baby dolphin, it probably isn’t healthy for us as well.”

- Lou Guillette

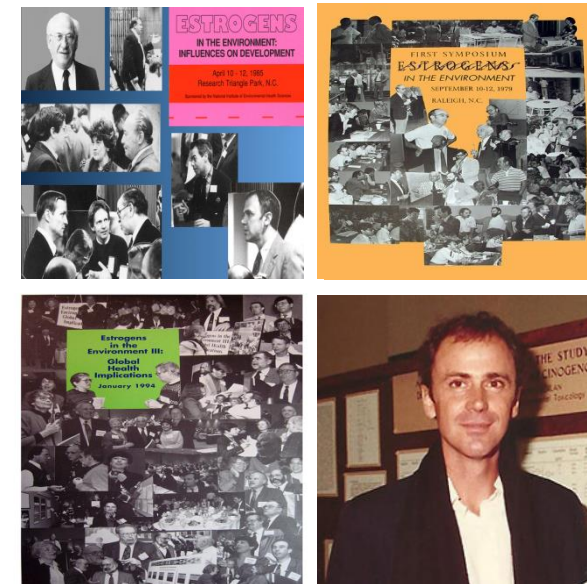
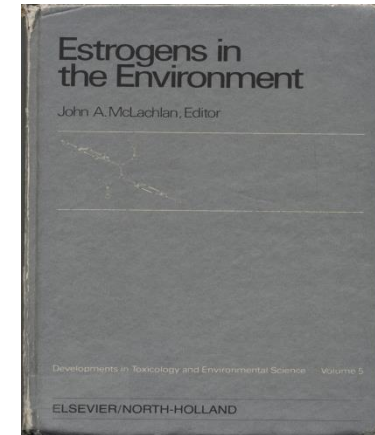
# Lou Guillette...

Gynecology at MUSC was a good fit. Roger Newman, MD, the Maas Chair for Reproductive Sciences in MUSC's Department of Obstetrics and Gynecology who was instrumental in recruiting Lou into his department noted, "One legacy Guillette leaves is that he sparked interest among animal-based researchers who took note of his interdisciplinary collaborations with clinical researchers and physicians." Newman said he blazed a trail in crossing traditional boundaries of how science can be performed. After all, Newman said, "there aren't many researchers as comfortable talking with physicians and basic scientists as they are 'wrangling alligators' in the field. Though Guillette's loss is a setback, his legacy will continue not only in the students he influenced, but also in how he worked at the frontiers of multiple scientific disciplines building bridges across those gaps."

# Key Conferences & Workshops

# Estrogens in the Environment: 1979, 1985, 1994, and 1997

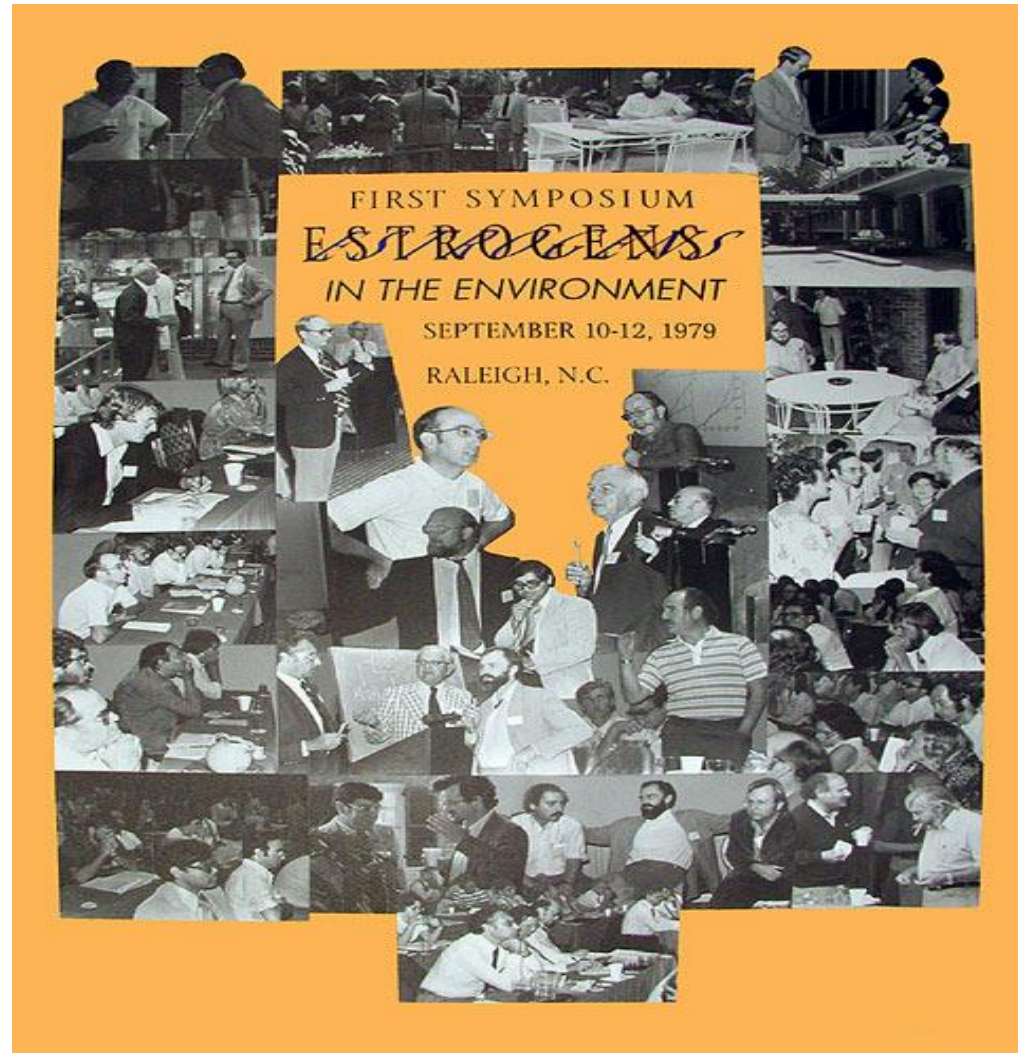
- Interest in environmental estrogens stemmed from John McLachlan's (NIEHS) research on DES toxicity
- The conference focused on a variety of topics related to EDCs, including:
  - Impact of hormonally active environmental agents in a global ecosystem
  - Patterns of distribution of chemicals in the environment
  - Comparison of health effects in humans and wildlife



# Estrogens in the Environment: 1979

**NIEHS: John McLachlan**

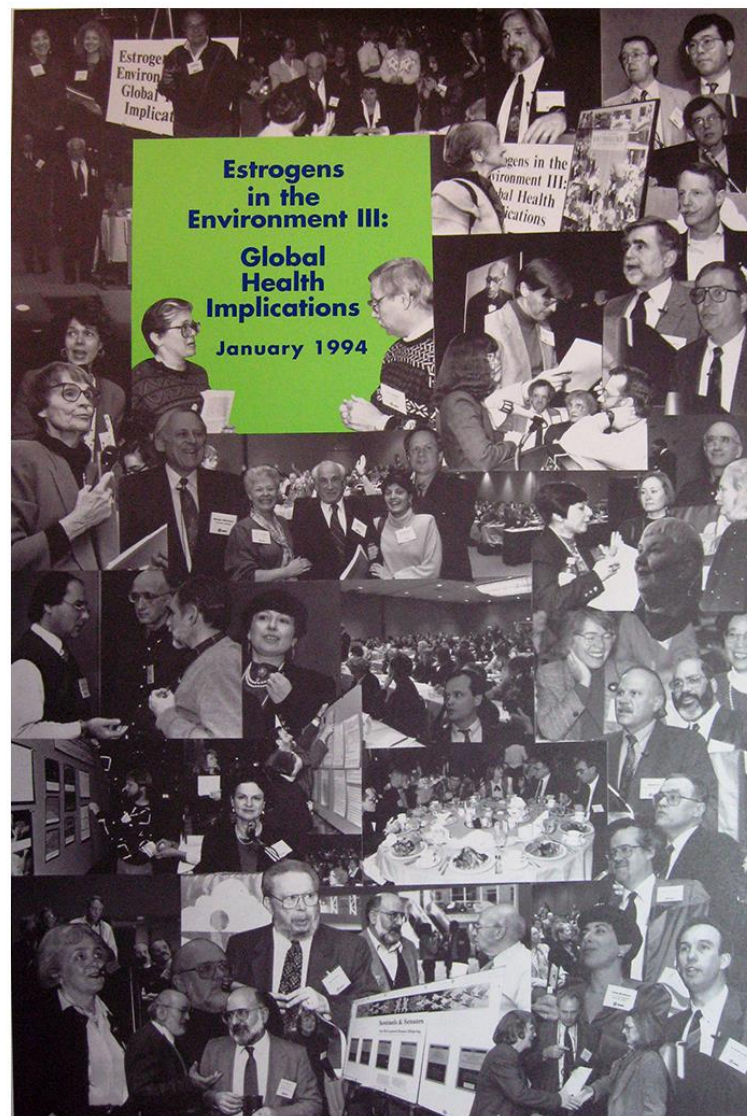
Interest in environmental estrogens stemmed from research on DES toxicity.



# Estrogens in the Environment III

Held in Washington, DC in 1994 and published in EHP (McLachlan and Korach, 1995)

Focused on, impact of hormonally active environmental agents in a global ecosystem; patterns of distribution of chemicals in the environment; comparison of health effects in humans and wildlife; impact of hormonally active environmental agents in a global ecosystem





# Wingspread Conference 1991: Birth of the Fields of EDCs and Developmental Origins of Disease

- Diverse group of scientific fields together for first time with an opportunity to learn from each others work.
- Consensus statement formulated the **endocrine disruptor hypothesis** and offered a unifying thematic focus for diverse research activities (causality statements were key).
- “We are certain of the following: A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the **potential to disrupt the endocrine system of animals, including humans.**”
- **Any perturbation of a developing organism’s endocrine system may alter its development, and typically these effects are irreversible.**

# Wingspread Conference 1991: Participants

- **Dr. Howard A. Bern**, Endocrinologist, Cancer Research Lab, U. of California, Berkeley, CA
- Dr. Phyllis Blair, Prof. of Immunology, U. of California, Berkeley, CA
- Sophie Brasseur, Marine Biologist, Research Institute for Nature Management, Texel, The Netherlands.
- **Dr. Theo Colborn**, Senior Fellow, World Wildlife Fund, Inc., W. Alton Jones Foundation, Inc., Washington, DC
- **Dr. Gerald R. Cunha**, Developmental Biologist, Dept. of Anatomy, U. of California, San Francisco, CA
- Dr. William Davis, Research Ecologist, U.S. EPA, Environmental Research Lab, Sabine Island, FL
- Dr. Klaus D. Dohler, Director Research, Pharma Bissendorf Peptide GmbH, Hannover, Germany
- Mr. Glen Fox, Contaminants Evaluator, National Wildlife Research Center, Environment Canada, Quebec, Canada.
- Dr. Michael Fry, Research Faculty, Dept. of Avian Science, U. of California, Davis, CA.
- **Dr. Earl Gray**, Section Chief, Dev. & Reproductive Toxicology Section, U.S. EPA, Research Triangle Park, N.C.

# Wingspread Conference 1991: Participants II

- Dr. Richard Green, Prof. of Psychiatry in Residence, School of Medicine, U. of California, Los Angeles, Ca.
- Dr. Melissa Hines, Asst. Prof. in Residence, Dept. of Psychiatry, School of Medicine, U. of California, Los Angeles, CA.
- Mr. Timothy Kubiak, Environmental Contaminants Specialist, Dept. of Interior, U.S. Fish & Wildlife Service, E. Lansing, MI
- Dr. John McLachlan, Director, Div. of Intramural Research, Chief, Laboratory of Reproductive & Developmental Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, N.C.
- Dr. J.P. Myers, Director, W. Alton Jones Foundation, Inc., Charlottesville, VA.
- Dr. Richard Peterson, Prof. of Toxicology & Pharmacology, School of Pharmacy, Univ. of Wisconsin, Madison, WI.
- Dr. P.J.H. Reijnders, Head, Section of Marine Mammalogy, Research Institute for Nature Management, Texel, Netherlands.
- Dr. Ana Soto, Associate Prof., Dept of Anatomy & Cellular Biology, Tufts Univ. School of Medicine, Boston, MA.
- Dr. Glen Van Der Kraak, Asst. Prof., College of Biological Sciences, Dept. of Zoology, Univ. of Guelph, Ontario, Canada.
- Dr. Frederick vom Saal, Prof., College of Arts & Sciences, Div. of Biological Sciences, Univ. of Missouri, Columbia, MO.
- Dr. Pat Whitten, Asst. Prof., Dept. of Anthropology, Emory University, Atlanta, GA

# First Actual Endocrine Disruptor Conference

## **Environmental Endocrine-Disrupting Chemicals: Neural, Endocrine, Behavioral Effects**

- Held in Erice, Sicily (1995)
- Organized by **Theo Colborn**
- Outputs included:
  - Erice consensus statement
  - Discussions about neural, behavioral, and endocrine effects

# First Gordon Conference on Environmental Endocrine Disruptors

## Environmental Endocrine Disruptors

- Held in Plymouth, New Hampshire (1998)
- Funded by American Chemical Society
- Organized by **Harriette L. Phelps**, an aquatic toxicologist who studied TBT, and **Brent Palmer**, a comparative reproductive biologist specializing in lower vertebrates



Harriette L. Phelps



Brent Palmer

# First EDC Gordon Conference: Program

**John C. Wingfield** - University of Washington

*"Field Endocrinology: A Different Perspective from the Laboratory"*

**Rosalind M. Rolland** - Tufts University

*"Endocrine Disruption in Teleosts: Field and Laboratory Evidence"*

**Keith A. Grasman** - Wright State University

*"Immunotoxicology Studies in Wildlife: Investigative Approaches, Endocrine-Immune Interactions, and Ecological Implications"*

**John Leatherland** - Guelph University, Canada

*"Consumption of "environmentally contaminated" fish and thyroid function in wildlife"*

**Eduardo Gaitan** - VA Medical Center, Jackson, MS

*"Environmental Goitrogenesis"*

**Tyrone Hayes** - University of California, Berkeley

*"Endocrine Disruption in Amphibians: The search for an appropriate Hypothesis"*

**Brent Palmer & Kyle Selcer** - University of Kentucky & Duquesne University

*"Vitellogenin as a biomarker for environmental endocrine disruptors"*

Red indicates still active in EDC field.

# First EDC Gordon Conference: Program

(continued)

**Taisen Iguchi** - Yokohama City University, Japan

*“Developmental effect of estrogens on the fish (Fundulus), Frog (Xenopus) and Mou”*

**Stanley Dodson** - University of Wisconsin, Madison

*“Low dose effects of Atrazine on sex determination in Daphnia”*

**Peter Mattheissen** - CEFAS, England

*“Oestrogenic effects in the marine environment”*

**Gerald A. LeBlanc** - North Carolina State University

*“Metabolic androgenization and developmental toxicity in invertebrates”*

**Frederick vom Saal** - University of Missouri

*“The Effects of Estrogenic Chemicals on Development of the Reproductive System in Males”*

**Wade Welshons** - University of Missouri

*“Natural and xenoestrogen action - how the fetus is reached”*

**Daniel M. Sheehan** - National Center for Toxicological Research

*“Effects of Estrogenic Chemicals on Development of the Reproductive System in Females”*

**Nicolas Olea** - University of Granada, Spain

*“Xenoestrogens, cryptorchidism and cancer”*

Red indicates still active in EDC field.

# First EDC Gordon Conference: Program (continued)

**Shanna H. Swan** - California Department of Health Services

*"Human Trends in Reproductive and Neurobehavioral Abnormalities: Relationship of Developmental Exposure to Endocrine Disruptors"*

**Margaret McCarthy** - University of Maryland at Baltimore

*"Developmental Effects of Endocrine Disruptors on Neuroendocrine Function"*

**Francoise Brucker-Davis** - World Wildlife Fund

*"Mechanisms of Thyroid Disruption"*

**Gail Prins** - University of Illinois

*"Cell-Cell Mediated Signals Associated with Estrogen-Induced Developmental Defects in the prostate gland"*

**Alice Hontela** - Université du Québec à Montréal

*"Adrenal Responses to Environmental Pollutants in Fish and Wildlife"*

**Dennis B. Lubahn** - University of Missouri-Columbia

*"Is There Really an ER Gamma?"*

**John McLachlan** - Center for Bioenvironmental Research

*"Environmental Endocrine Signals: Lessons from Embryos and Evolution"*

Red indicates still active in EDC field.



# Historically Important Accidents (chemicals with endocrine activity)

- **Seveso, Italy:** A 1976 chemical factory explosion near Seveso, Italy exposed residents to high levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin). <https://pubmed.ncbi.nlm.nih.gov/30179766/>
- **Yusho, Japan:** The Yusho incident is an unprecedented mass food poisoning that occurred in Japan in 1968. It was caused by the ingestion of rice bran oil contaminated with polychlorinated biphenyls (PCBs) and various dioxins and dioxin-like compounds, such as polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). <https://pubmed.ncbi.nlm.nih.gov/26010306/>
- **Yucheng, Japan:** Yucheng ("oil-disease") victims were Taiwanese people exposed to polychlorinated biphenyls (PCBs) and their heat-degradation products, mainly polychlorinated dibenzofurans (PCDFs), from the ingestion of contaminated rice oil in 1978-1979 <https://pubmed.ncbi.nlm.nih.gov/14963712/>.
- **PBB, Michigan:** Cattle on about 25 Michigan farms were exposed to as much as 250 g per head of PBB when it was accidentally mixed in cattle feed in 1973 to 1974. Approximately 85% of the Michigan population received some exposure to PBB because dairy product marketing involves mixing milk from many farms. A few cases of high human exposure, which may have been as great as 10 g, occurred when residents of the more highly exposed farms consumed their own products. <https://pubmed.ncbi.nlm.nih.gov/3002722/>

# Conferences...Recurring

- **Dioxin Conferences:** Every year since 1983, the analytical testing community involved in dioxins and POPs analysis and research have been meeting at the International Symposium on Halogenated Persistent Organic Pollutants, commonly known as Dioxin Conference.
- **Brominated Flame Retardant Conferences:** 2021 marks the 20th anniversary of the BFR Symposia. In 2001, Professor Ake Bergman organized the first symposium in Stockholm, Sweden. Over the past 20 years, there have been major advances in the analysis, fate and toxicity of these compounds.
- **Prenatal Programming and Toxicity (PPTox):** There have been six PPTOX conferences since 2007 with a general focus on the role of environmental exposures and nutrients during development on subsequent diseases/dysfunctions later in life. The meetings have examined the animal and human data supporting this hypothesis (developmental basis of disease) by disease, organ system, and mechanism in order to review the current state of the literature and to identify mechanisms for the effects as well as to identify research gaps and challenges and to integrate the basic and applied science. PPTox conferences are organized by Philippe Grandjean.
- **Copenhagen Workshops (COW) on Endocrine disruptors:** Since 2000, the Department of Growth and Reproduction in Copenhagen Denmark regularly hosts international scientific workshops on endocrine disrupters, known as the COW workshops.
- **US Dohad Society:** The United States Developmental Origins of Health and Disease Society was founded in 2016 and is an affiliate of the International DOHaD Society. Our organization is focused on all facets of the study of the fetal origins and early life programming of health and disease.
- **Gordon Conference on Environmental Endocrine Disruptors:** Every two years since 1998 the Gordon Conferences has sponsored a conference on environmental endocrine disruptors.

# Conferences...

- European Workshop on the impact of endocrine disruptors on human health and wildlife, Weybridge UK, December 2-4, 1996
- International Symposium on EDCs in Japan (1988-2007)
- e.Hormone, Tulane University (1999-2010)
- Weybridge+ 15 November 10, 2006, Helsinki, Finland
- Low Dose Effects and Non-monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice Berlin, September 11-13 2012 NIEHS/Joint Research Centre of European Union
- 25 years of Endocrine Disruption Research: Past Lessons and Future Directions (NIEHS), September 18-20, 2016 NIH

# Key Publications

# Support for the Importance of EDCs in Human Health

- WHO/UNEP Reports 2002, 2012
- Endocrine Society Statements on EDCs 2009, 2012, 2015
- SIACM Nairobi, 2012, Mexico City, 2013, Geneva, 2015
- Royal College of Obstetricians and Gynecologists, 2013
- American Society for Reproductive Medicine/American Congress of Obstetricians and Gynecologists, 2013
- FIGO Opinion: Reproductive Health Impacts of Exposure to Toxic Environmental Chemicals, 2015
  - Royal College of Obstetricians and Gynecologists
  - Endocrine Society
  - American Society of Reproductive Medicine
  - European Society of Human Reproduction and Embryology
  - Society of Obstetricians and Gynecologists of Canada

# A Paper that Changed the Way We Think: DES and Vaginal Cancer in Offspring (1971)



The NEW ENGLAND  
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ORIGINAL ARTICLE [ARCHIVE](#)

## Adenocarcinoma of the Vagina — Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women

Arthur L. Herbst, M.D., Howard Ulfelder, M.D., and David C. Poskanzer, M.D.  
N Engl J Med 1971; 284:878-881 | [April 22, 1971](#) | DOI: 10.1056/NEJM197104222841604

# The Founding Paper (1993)

## **Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans**

***Theo Colborn,<sup>1</sup> Frederick S. vom Saal,<sup>2</sup> and Ana M. Soto<sup>3</sup>***

<sup>1</sup>W. Alton Jones Foundation and World Wildlife Fund, Washington, DC, 20037 USA;

<sup>2</sup>Division of Biological Sciences and John M. Dalton Research Center, University of Missouri, Columbia, MO 65211 USA; <sup>3</sup>Department of Anatomy and Cellular Biology, Tufts University, Boston, MA 02111 USA

*Environ Health Perspect*, 101: 378-384

# Decline in Sperm Quality (1992): Niels Skakkebaek

BMJ. 1992 Sep 12; 305(6854): 609–613.

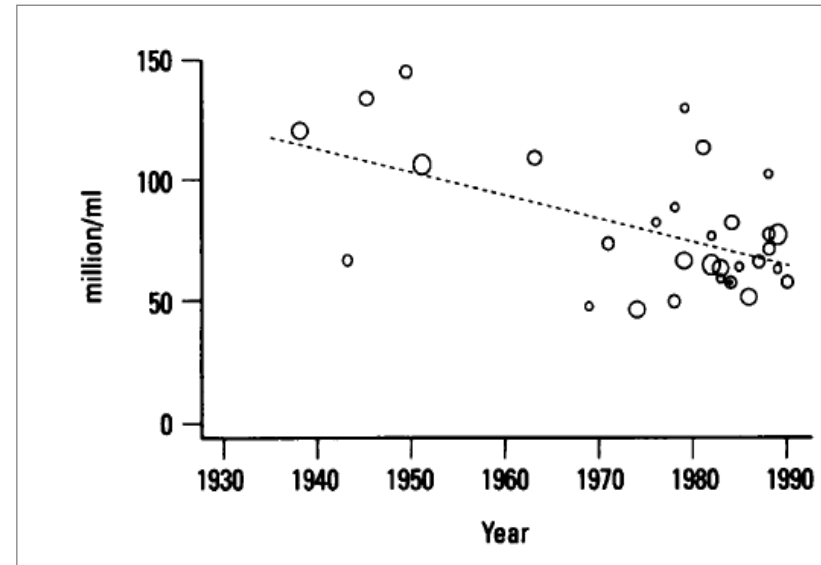
## **Evidence for decreasing quality of semen during past 50 years.**

[E. Carlsen](#), [A. Giwercman](#), [N. Keiding](#), and [N. E. Skakkebaek](#)



Niels Skakkebaek

*Conclusions* – “There has been a genuine decline in sperm quality over the past 50 years. As male fertility is to some extent correlated with sperm count the results may reflect an overall reduction in male fertility. The biological significance of these changes is emphasized by a concomitant increase in the incidence of genitourinary abnormalities such as testicular cancer and possibly also cryptorchidism and hypospadias, suggesting a growing impact of factors with serious effects on male gonadal function.”



Linear regression of mean sperm density reported in 61 publications



# Estrogenicity of Sewage Entering British Rivers: John Sumpter

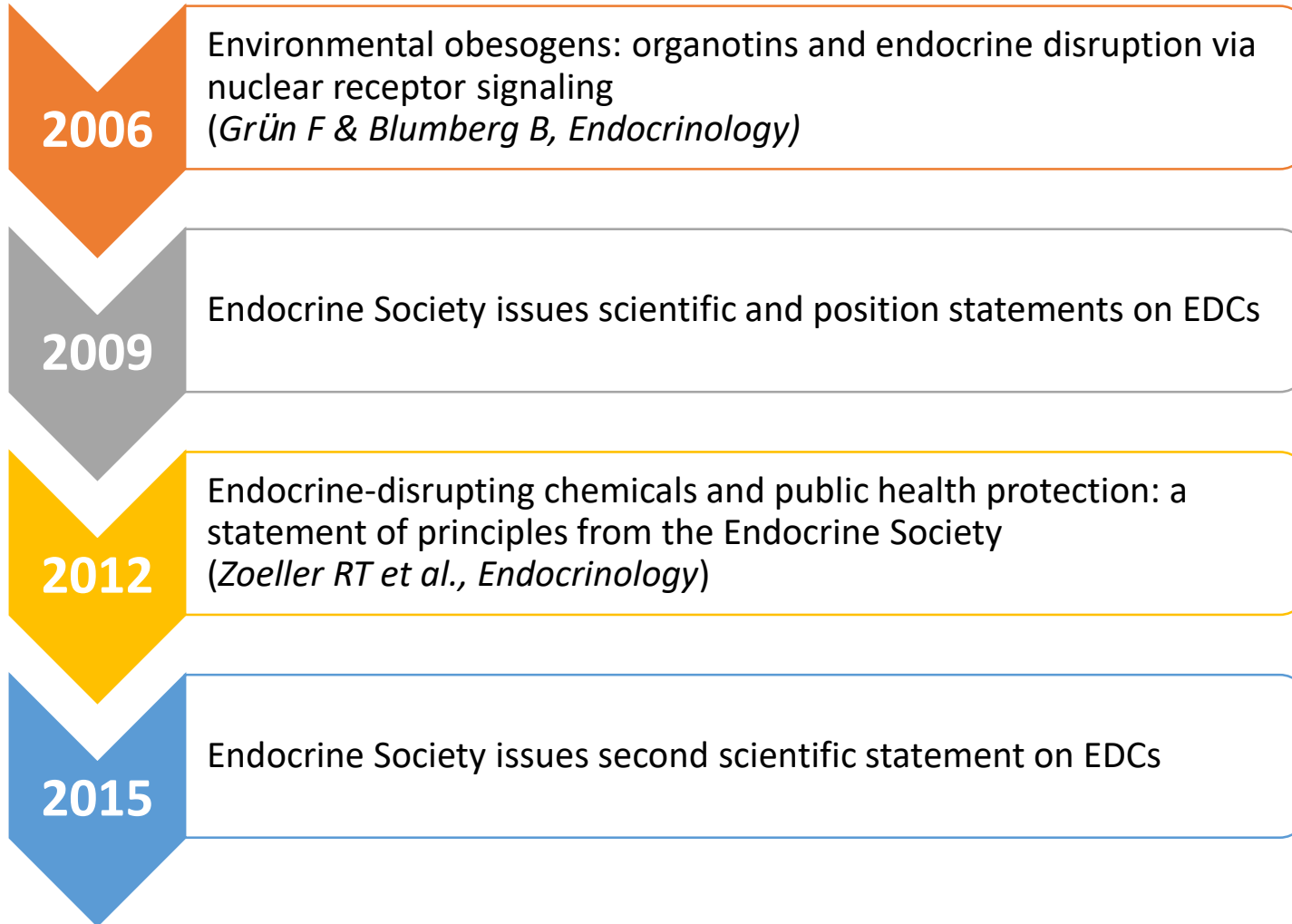
- Feminized responses in fish to environmental estrogens  
*Tox Lett, 82-83, 1995*
- Xenoendocrine disruptors- environmental impacts  
*Tox Lett 337-342, 1998*

In the case of fish exposed to STW effluent, the effects observed (vitellogenin synthesis and 'feminization' of males) are considered indicative of exposure to 'oestrogens,' and hence the search has been for 'real' oestrogens and/or chemicals that mimic oestrogens (so-called xenoestrogens). Representatives of both groups of chemicals are certainly present in effluents.



John Sumpter

# More Publications



Bruce  
Blumberg



R.Thomas  
Zoeller



Andrea  
Gore

# EDCs: Impacts on Science & Research

# Perspective: Reproductive Endocrinology and Human Health in the 20th Century -- A Personal Retrospective

*Neena B. Schwartz*  
*Department of Neurobiology and Physiology*  
*Northwestern University*

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The five contributions to reproductive endocrinology with the most impact on human health over the past 100 years:

- First in order of importance has to be the pill.
- The next most important application of basic endocrine biology is the technique of RIA.
- The third selection is the concept of regulation of the secretions of the anterior pituitary by neurohormones.
- Fourth would be the identification of hormone receptors, particularly steroid receptors.
- **A fifth application of basic endocrinology to human reproductive health is the discovery of contaminating "endocrine disruptors" in the environment, which are detrimental to animal reproductive health and most likely to human health as well.**

# Discoveries that Changed Careers & the EDC Field



**Bruce Blumberg**

- Found that TBT bound to PPAR/RXR, induced fat cell differentiation , led to obesity, in vivo and effects of exposure were transmitted to unexposed generations.



**Tyrone Haynes**

- Found that atrazine demasculinized frogs



**Pat Hunt**

- Discovered that BPA was leaching from animal cages and causing meiotic changes, including aneuploidy in oocytes from control mice



**Fred vom Saal**

- Noted the BPA altered prostate development

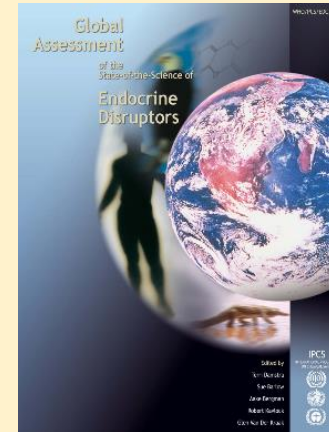


**Ana Soto & Carlos Sonnenschein**

- Discovered the first estrogen in plastics (nonylphenol)
- Developed the E-SCREEN assay, with which they identified many other environmental estrogens

# Global Support for EDCs in Human Health

- **2002: Global assessment of Endocrine Disruptors report (IPCS)**
- **2011: State of the Art Assessment of Endocrine Disruptors, European Union (A. Kortenkamp)**
- **2013: Global assessment of the State of the science of endocrine disruptors (UNEP/WHO)(Åke Bergman)**



# Research Initiatives: United States

## W. Alton Jones

- **1993:** Endocrine Disruptors and pesticides

## NIEHS

- **1995:** Endocrine Disrupting Chemicals and Women's Health Outcomes (NIEHS/Office on Women's Health)
- **2000:** Endocrine Disruptors: Epidemiological Approaches (NIEHS, CDC, EPA, NCI)
- **2003-2019:** Centers for Children's Environmental Health and Disease Prevention Research (NIEHS/EPA)
- **2003-2005:** Fetal Basis of Disease
- **2012** : Transgenerational inheritance in mammals after environmental exposures (TIME)
- **2014** : Environmental chemicals in the development of obesity, type 2 diabetes, and metabolic syndrome
- **2015-** : Children's Exposure Analysis Resource (CHEAR)
- **2016-** : Environmental influences on child health outcomes (ECHO)
- **2017** : Environmental influences on placental origins of development (sPOD)
- **2020** : Pregnancy as a vulnerable time period for women's health

# Research Initiatives: United States

## EPA

- **1996-2016:** STAR (Science to Achieve Results) Program
  - 1996: STAR Endocrine Disruptor Screening Program was developed



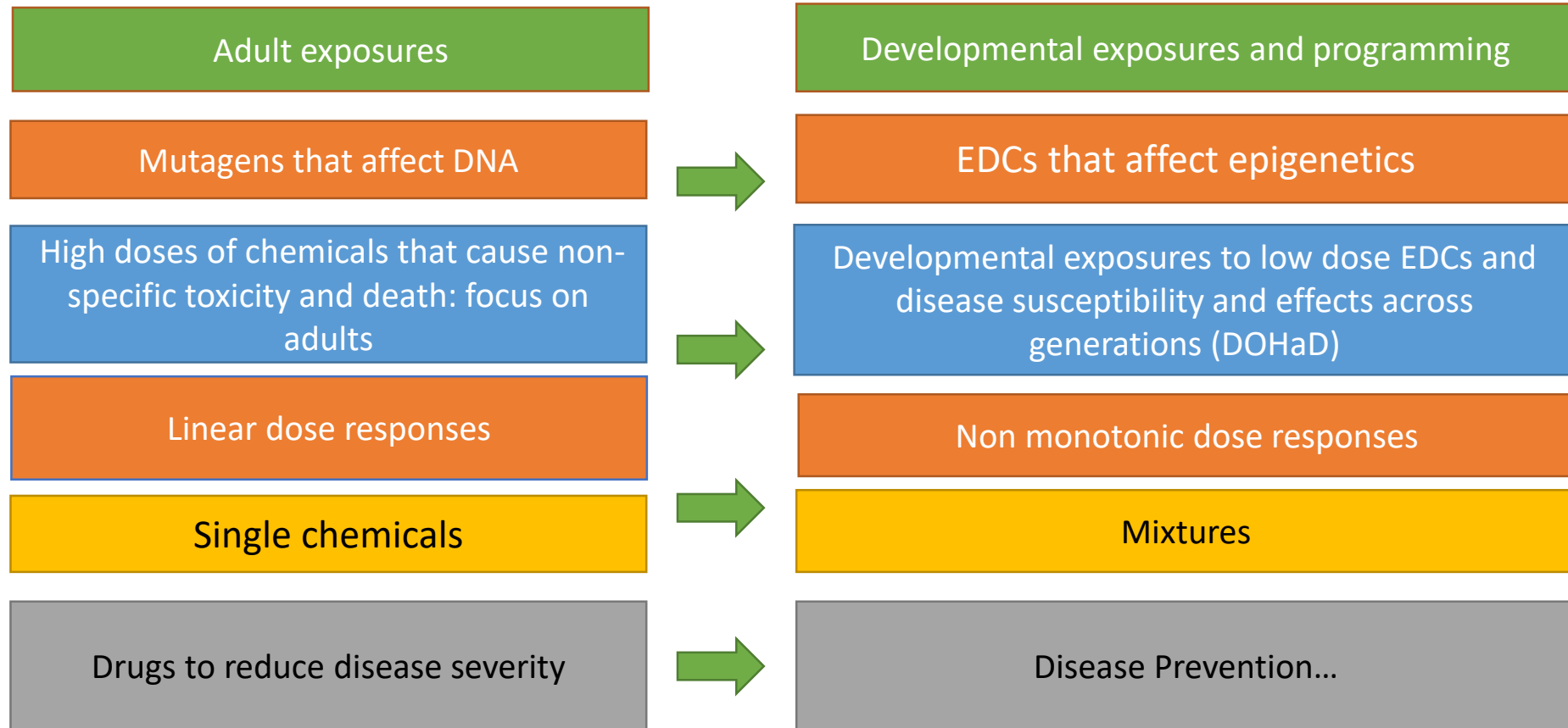
# Scientific Areas Profoundly Impacted by EDC Field\*

- Steroid receptors
- Comparative endocrinology
- Developmental origins of disease
- Transgenerational effects
- Epigenetics
- Mixtures
- Wildlife biology
- Epidemiology
- Green chemistry
- Climate change
- Toxicity testing
- Toxicology
- \* more...



# EDCs Have Changed Scientific Thinking...

EDCs have caused us to think about things differently, and our focus has been shifted from:



Everyone has a body burden, which causes increased disease susceptibility and also effects from ancestral exposures, causing 'evolutionary changes' in humans over generations.  
Artificial selection vs natural selection (*D. Crews*)

# The Future (Our Goal)

- Look up “ Endocrine Disruptor” on globnet

## **Endocrine Disruptor**

An archaic term no longer in use. Has not been used since 2030 when there were no longer any chemicals in use that could be considered an endocrine disruptor.

We can all be proud of the  
accomplishments we have made in the last  
25 yrs...

This is not the end but just the end of the beginning...

the future is in your hands!