25 anos dos Desreguladores Endocrinos: O que sabemos sobre eles?

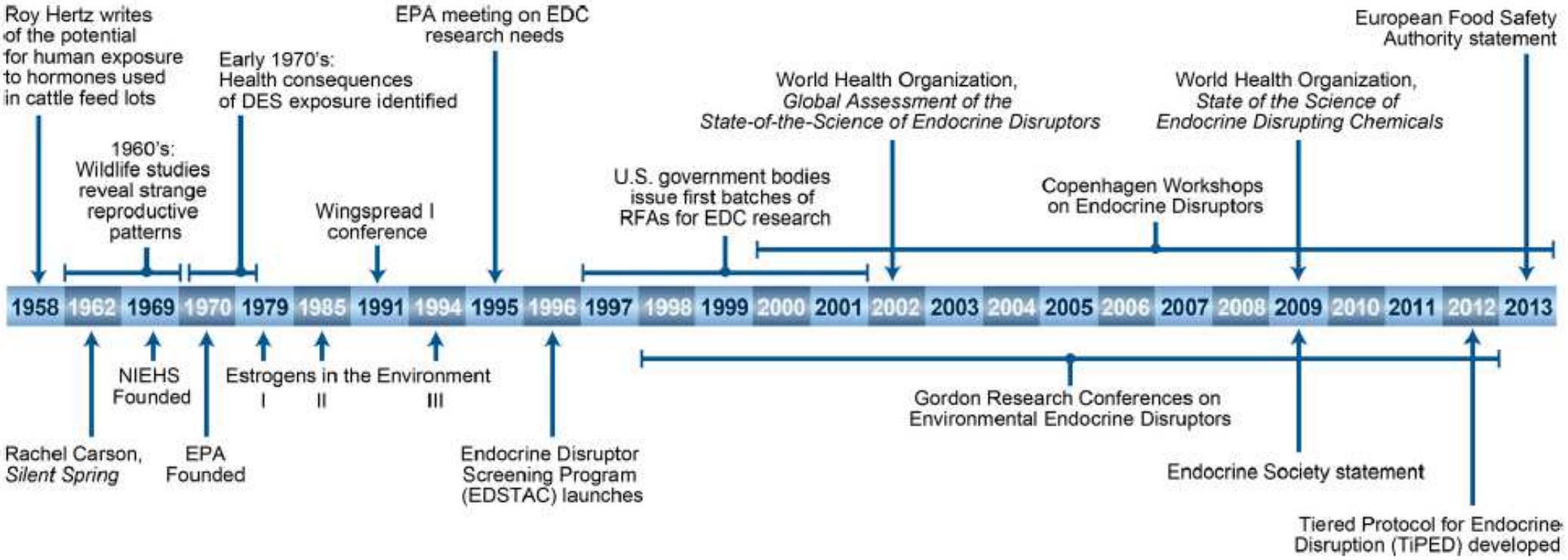
MARIA IZABEL CHIAMOLERA, MD, PHD

PRESIDENTE DO DEPARTAMENTO DE ENDOCRINOLOGIA BÁSICA - SBEM

MEMBRO DA COMISSÃO DE DESREGULADORES ENDOCRINOS - SBEM

LABORATÓRIO DE ENDOCRINOLOGIA MOLECULAR E TRANSLACIONAL - UNIFESP

Desde 1991…



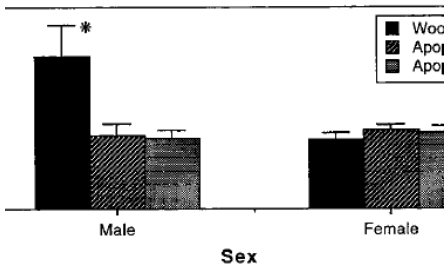
Schug, TT et al. Molecular Endocrinology 30: 833, 2016.

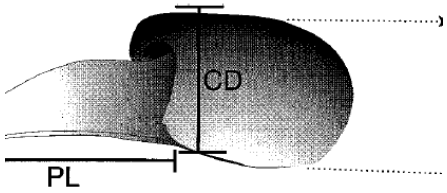
Dietilestilbestrol (DES)

- Primeiro estrogênio sintético – 1938
- DES – tratamento para previnir abortamento em milhões de gestantes entre 1938 – 1971
- Efeito transgeracional com envolvimento do receptor estrogênico
- Associação entre o uso de DES durante a gestação das mães e adenocarcinoma de células claras de vagina em jovens mulheres e meninas (Herbst et al, NEJM, 1971) – ação do FDA
- FDA suspende liberação do DES – 2000

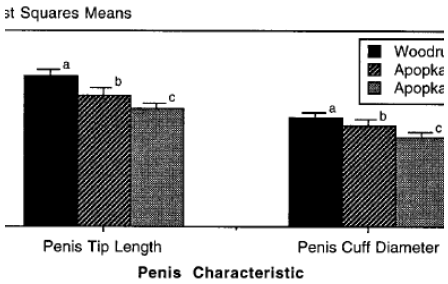
- Silent Spring - escrito por Rachel Carson em 1962
- Série de artigos publicada pela revista New Yorker
- Lista de best-sellers do New York Times
- Inspirado na preocupação crescente do público com a poluição e os pesticidas
- Influenciou o banimento do DDT em 1972 nos EUA

Evidências em Animais



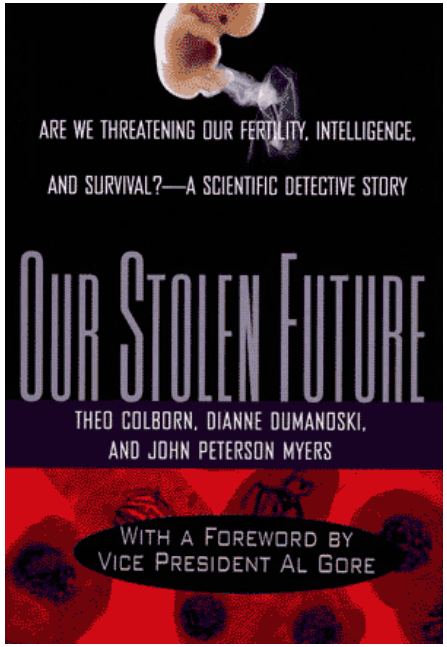


ıgram of the alligator penis showing the morphom
l in this study. PL, length of the penis tip; CD, dian
cuff.



1996, Guillette LJ, et al. "Reduction in Penis Size and Plasma Testosterone Concentrations in Juvenile Alligators Living in a Contaminated Environment". General and Comparative Endocrinology.

Wingspread Conference - 1991



- Julho de 1991 - Wingspread Conference - World Wild Life
- 21 cientistas de diversos países, 15 disciplinas pesquisas relevantes sobre alterações transgeracionais de saude
- ‘‘Chemically Induced Alterations in Sexual Development: The Wildlife /Human Connection’’ (Colborn and Clement, 1992)
- O futuro roubado - 1996

Desreguladores Endócrinos – Definição

Desregulador endócrino **(DE)**: Substância ou uma mistura de substâncias exógenas que alteram uma ou várias funções do sistema endócrino e tem, consequentemente, efeitos adversos sobre a saúde num organismo intacto, sua descendência ou (sub)populações.

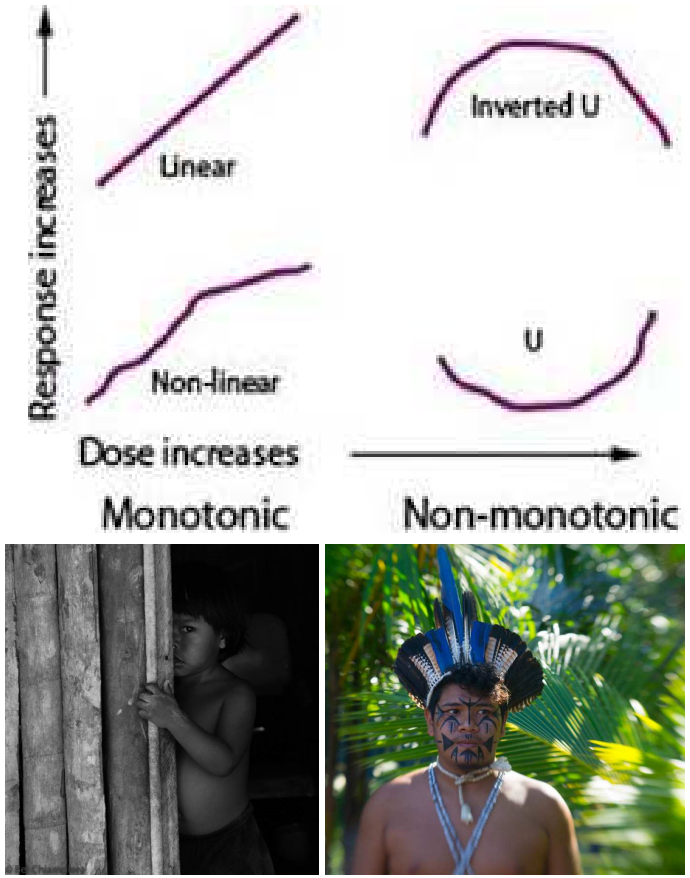
FONTE: COMISSÃO DAS COMUNIDADES EUROPÉIAS
Bruxelas, 17.12.1999
Programa Internacional de Segurança Química (IPCS)
Comitê Científico da Toxicidade Ecotoxidade e Ambiente (CCTEA)

Desreguladores Endócrinos - Definição

- Compostos Exógenos – potencial de alterar regulação hormonal e do sistema endócrino normal

- Interferência:
  - Produção
  - Liberação
  - Metabolismo
  - Eliminação
  - Mimetizar efeitos naturais dos hormônios
  - Mecanismos Epigenéticos

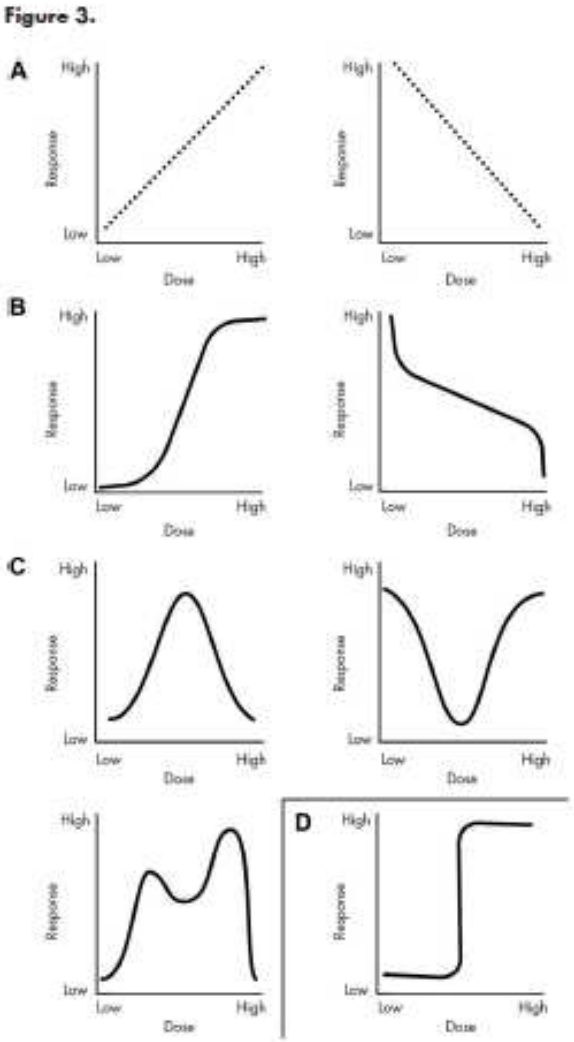
(Casals-Casas, C; Desvergne, B; 2011)
(Stein, RA; 2011)

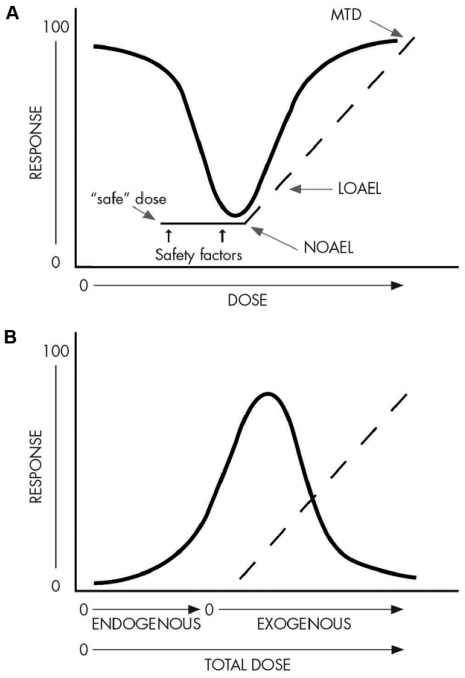


Conceitos Básicos

- Paradigma de Dose-Resposta da Toxicologia – Curvas dose-resposta não-monotonicas

- Janela de Exposição





Vandenberg et al. 2012

Conceitos Básicos

- Paradigma de Dose-Resposta da Toxicologia – Curvas dose-resposta não-monotonicas
- Mecanismos: citotoxicidade, especificidade tecidual e celular de receptores e cofatores, seletividade de receptores, desensibilização e down-regulation de receptores, competição de receptores e alças de feedback negativos endocrinos.

Reprod Toxicol. 2013 July ; 38: 1–15. doi:10.1016/j.reprotox.2013.02.002.

Regulatory Decisions on Endocrine Disrupting Chemicals Should be Based on the Principles of Endocrinology

Laura N. Vandenberg[1], Theo Colborn[2], Tyrone B. Hayes[3], Jerrold J. Heindel[4], David R. Jacobs Jr[5], Duk-Hee Lee[6], John Peterson Myers[7], Toshi Shioda[8], Ana M. Soto[9], Frederick S. vom Saal[10], Wade V. Welshons[11], and R. Thomas Zoeller[12]

2.1 Issue #1: Why should the study of EDCs rely on endocrine principles?

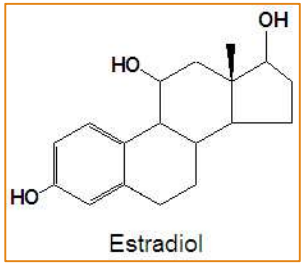
Principle 1: Hormones are responsible for the health and well-being of animals (including humans) from the time of conception until death and control and integrate the systems of the body

Principle 2: The effects of hormones are mediated by highly specific interactions with receptors and the response is context dependent

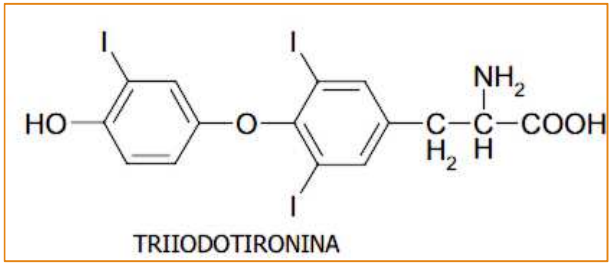
Principle 3: Hormones act at low doses

Principle 4: Hormones can exhibit non-linear, and often non-monotonic, dose response curves

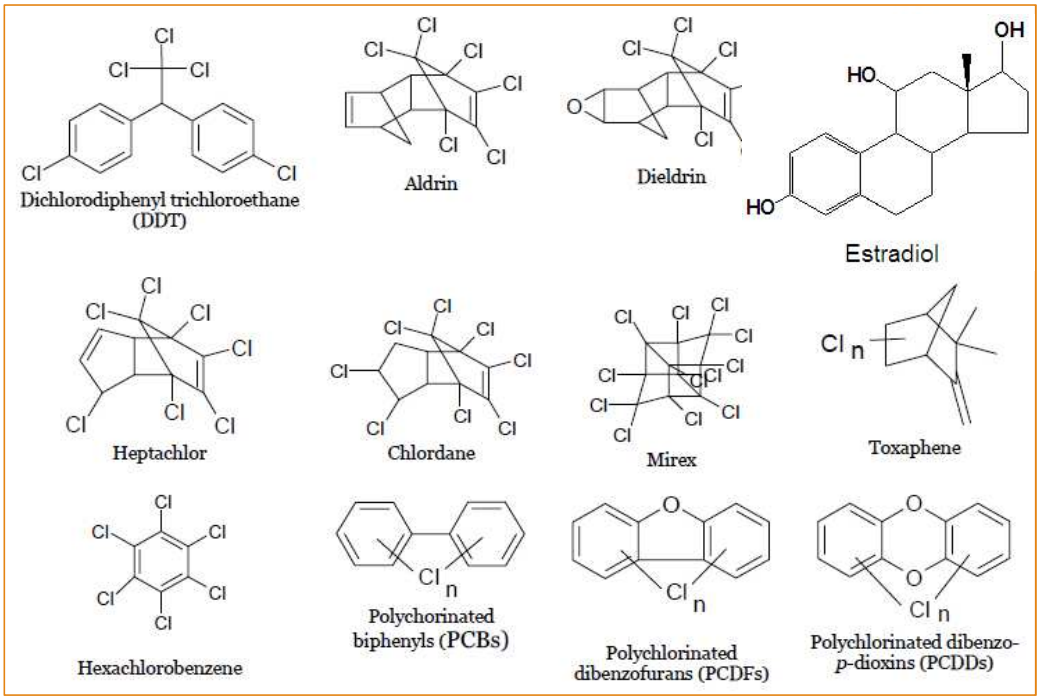
Principle 5: The effects of hormones are life-stage dependent



Estradiol



TRIIODOTIRONINA



POPs "Persistent Organic Pollutants" Mais Comuns!

Quais Evidências Existem??

Evidencias dos Desreguladores Endocrinos

Table 1. Legacy Endocrine Dispurting Chemicals

Compound	Use/Source	Disease Links	References
BPA	Plastics, thermal receipts	Breast and other cancers, metabolism, puberty, neurobehavioral	83–86
Phthalates	Plastics, fragrances	Low sperm count, metabolism, birth defects, asthma, neurobehavioral	87, 88
PCBs	Electrical coolant and other uses	Cancer, developmental issues	89
PBDEs	Flame retardants	Thyroid disruption, neurological issues	90, 91
Lead	Drinking water, paint, gasoline	Neurological issues, premature birth, kidney disorders	92, 93
Mercury	Burning coal, seafood	Neurological issues, diabetes	94
Dioxin	Formed in industrial processing	Cancers, sperm quality, fertility, neurobehavioral	95, 96
DDT/DDE/DDD	Pesticides	Cancers, developmental toxicity	96
Arsenic	Drinking water, animal feed, herbicides, fertilizers	Cancers, diabetes, immune suppression, neurodevelopment, cardiovascular disease	97, 98
Cadmium	Tobacco smoke, fertilizers	Cancers, reproductive issues	99
Atrazine	Herbicide	Alterations in pubertal development	100
Alkylphenols and p-Nonyl-phenol	Detergents, additives	Breast cancer	101, 102

Schug, TT et al. Molecular Endocrinology 30: 833, 2016.

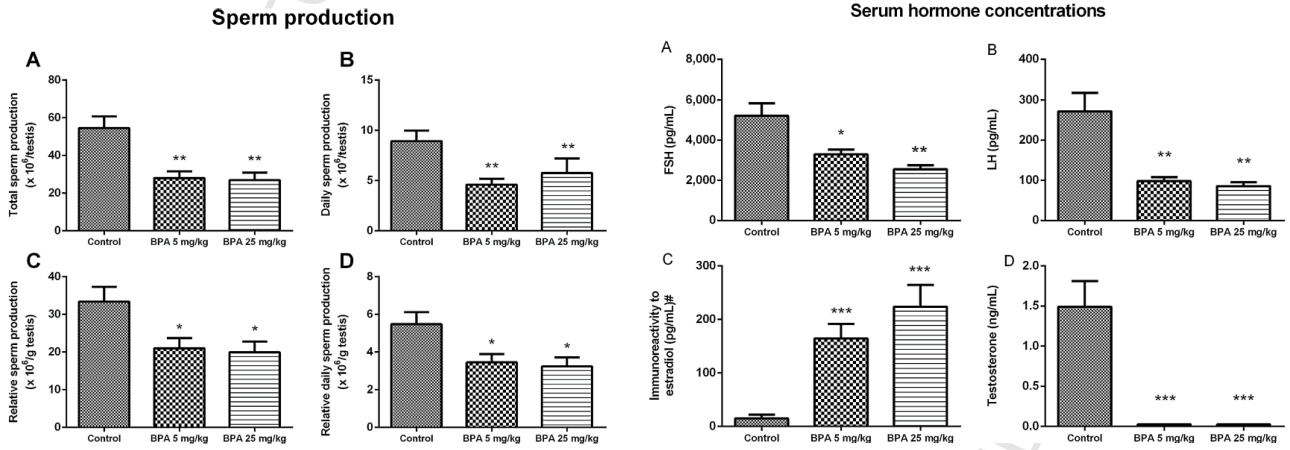
Contents lists available at ScienceDirect

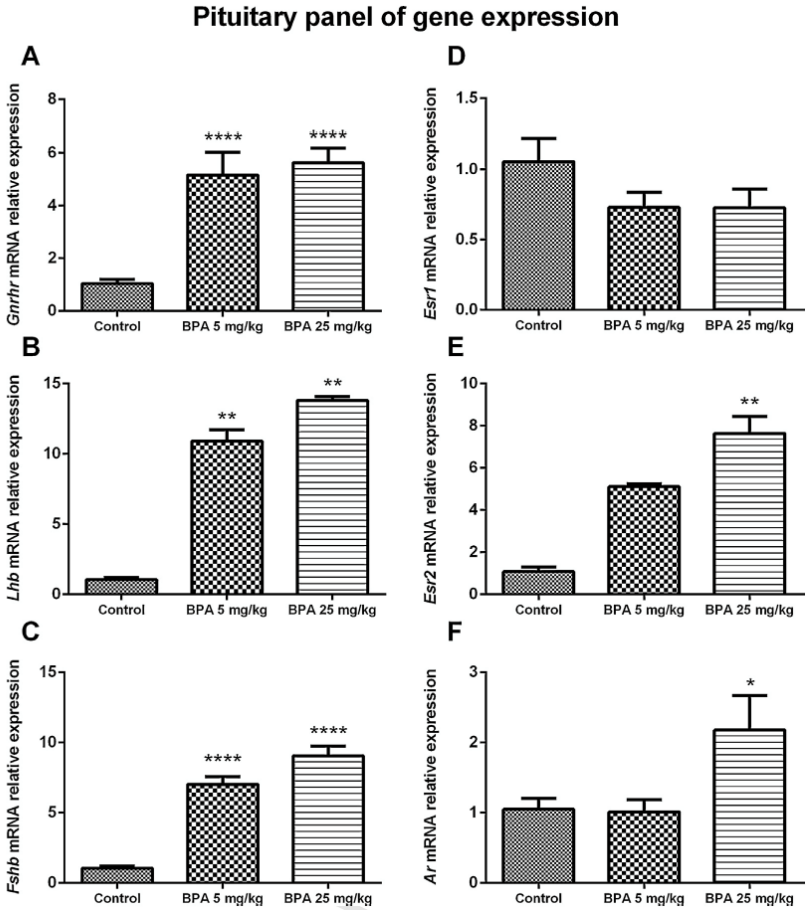
Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Adult exposure to bisphenol A (BPA) in Wistar rats reduces sperm quality with disruption of the hypothalamic–pituitary–testicular axis

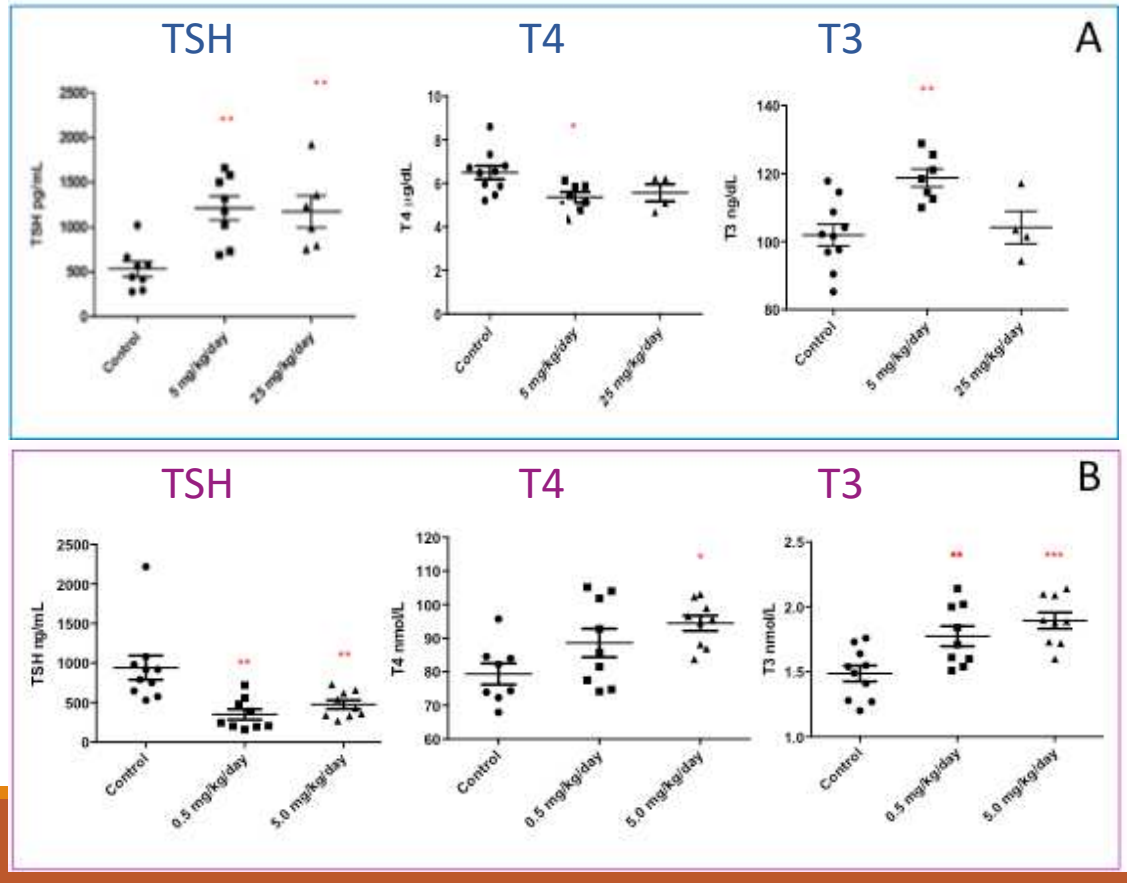
Patricia Wisniewski [a], Renata M. Romano [a], Marina M.L. Kizys [b], Kelen C. Oliveira [b], Teresa Kasamatsu [b], Gisele Giannocco [b], Maria I. Chiamolera [b], Magnus R. Dias-da-Silva [b], Marco A. Romano [a,*]





Padrão Hormonal Oposto Dependendo da Janela de Exposição

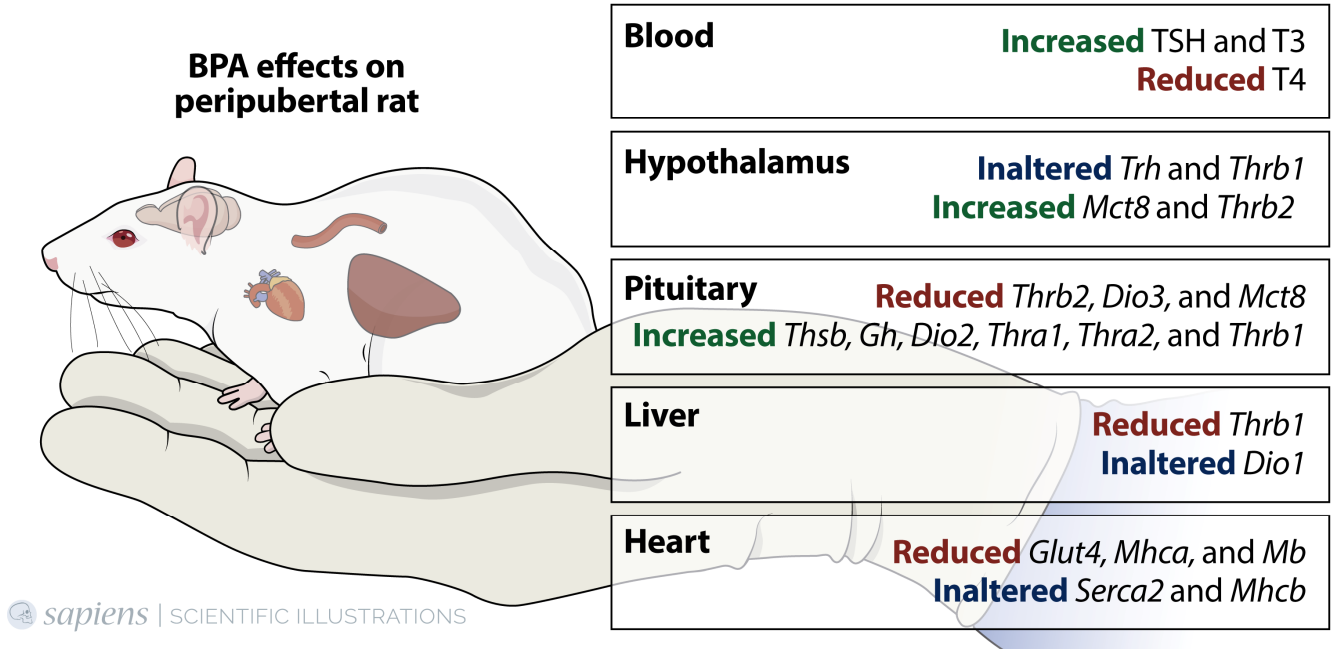
Níveis Séricos



Exposição Peripuberal

Exposição Perinatal

* p < 0,05 ** p < 0,01 *** p < 0,001 **** p < 0,0001



Desregulação do Eixo Tirodiano – BPA-PP

Estudo HOME

- Estudo HOME – Health Outcomes and Measures of the Environment
  - Grávidas 16 semanas – 1263 mulheres elegíveis – 468 recrutadas e 389 foram seguidas
  - Medida de BPA na urina – 16 e 26 semanas
  - Medida de TSH, T3 e T4 – soro da mãe com 16 sem e no cordão umbilical

- Correlação negativa da medida de BPA na urina às 26 semanas com TSH em neonatos do sexo feminino.

Romano, ME. Environmental Research, 2015

Maternal Urinary Bisphenol A during Pregnancy and Maternal and Neonatal Thyroid Function in the CHAMACOS Study

Jonathan Chevrier,[1] Robert B. Gunier,[1] Asa Bradman,[1] Nina T. Holland,[1] Antonia M. Calafat,[2] Brenda Eskenazi,[1] and Kim G. Harley[1]

[1]Center for Children's Environmental Health Research, School of Public Health, University of California, Berkeley, Berkeley, California, USA; [2]Division for Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

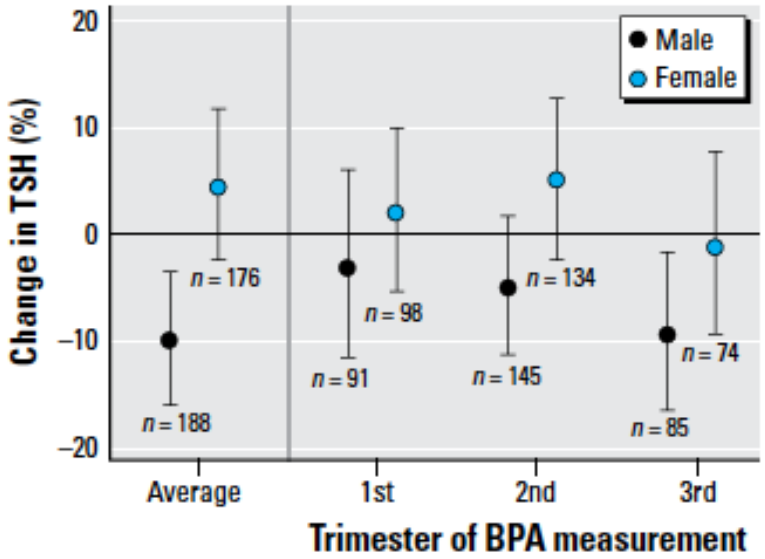


Figure 1. Change in neonatal TSH for each doubling in maternal urinary BPA concentration (µg/g creatinine) by infant sex and trimester of BPA measurement.

476 gestantes

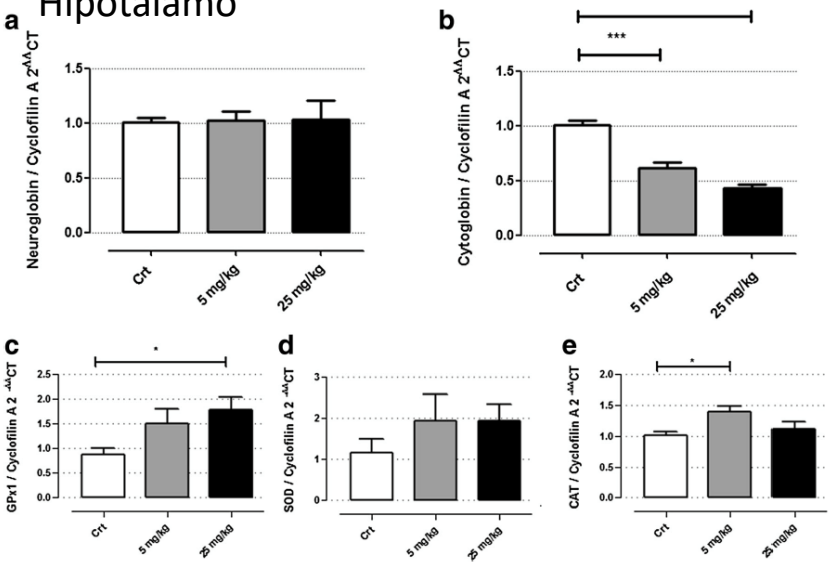
Metab Brain Dis
DOI 10.1007/s11011-017-0066-5

ORIGINAL ARTICLE

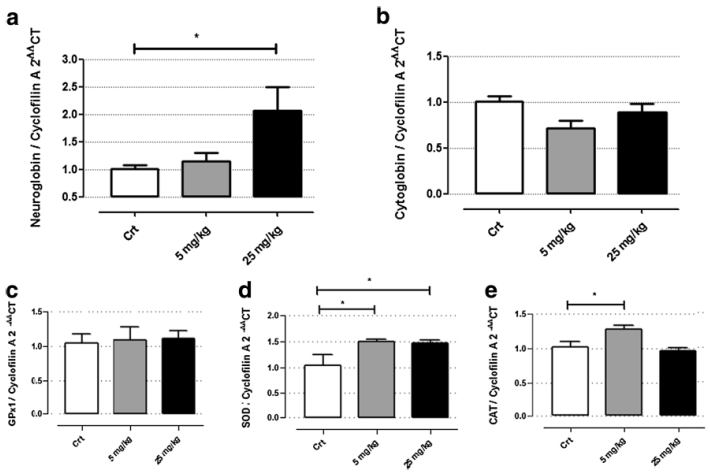
Anatomical specificity of the brain in the modulation of Neuroglobin and Cytoglobin genes after chronic bisphenol a exposure

Rodrigo Rodrigues da Conceição [1] · Janaina Sena de Souza [1] · Kelen Carneiro de Oliveira [1] · Rui Monteiro de Barros Maciel [1] · Marco Aurélio Romano [2] · Renata Marino Romano [2] · Magnus Régios Dias da Silva [1] · Maria Izabel Chiamorela [1] · Gisele Giannocco [1,3,4]

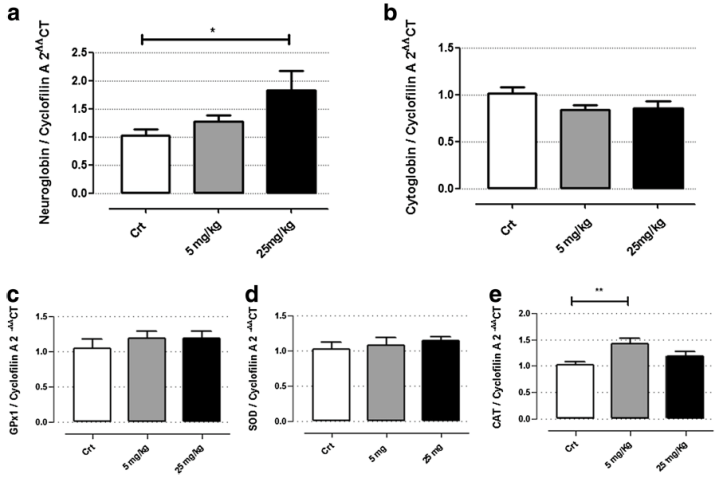
Hipotálamo



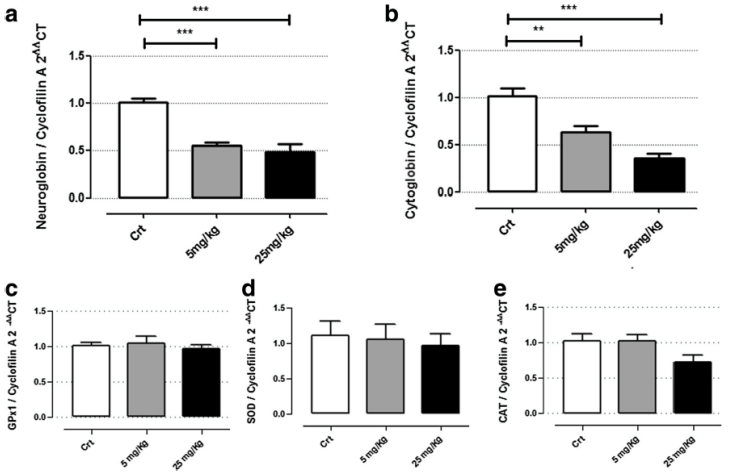
Córtex



Cerebelo



Hipocampo

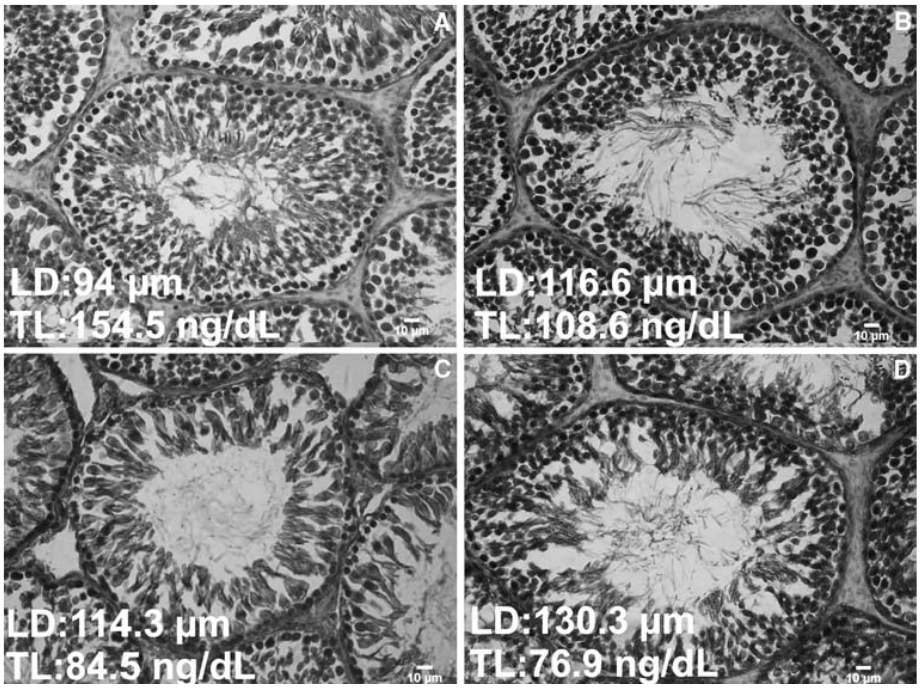


Arch Toxicol (2010) 84:309–317
DOI 10.1007/s00204-009-0494-z

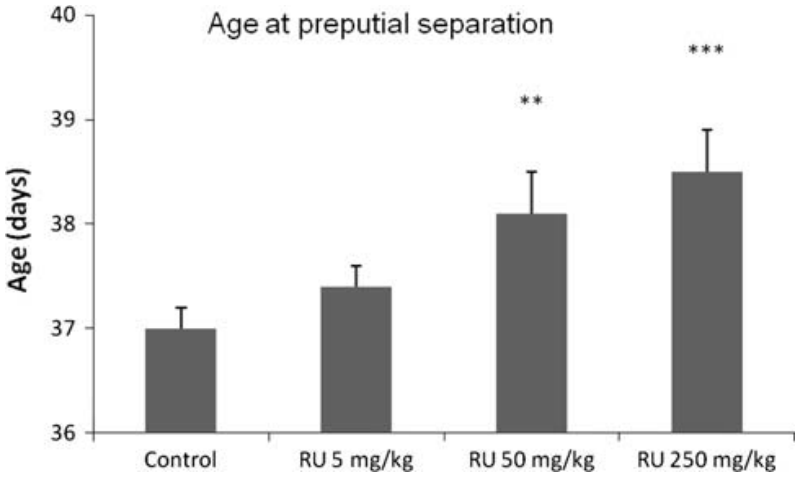
REPRODUCTIVE TOXICOLOGY

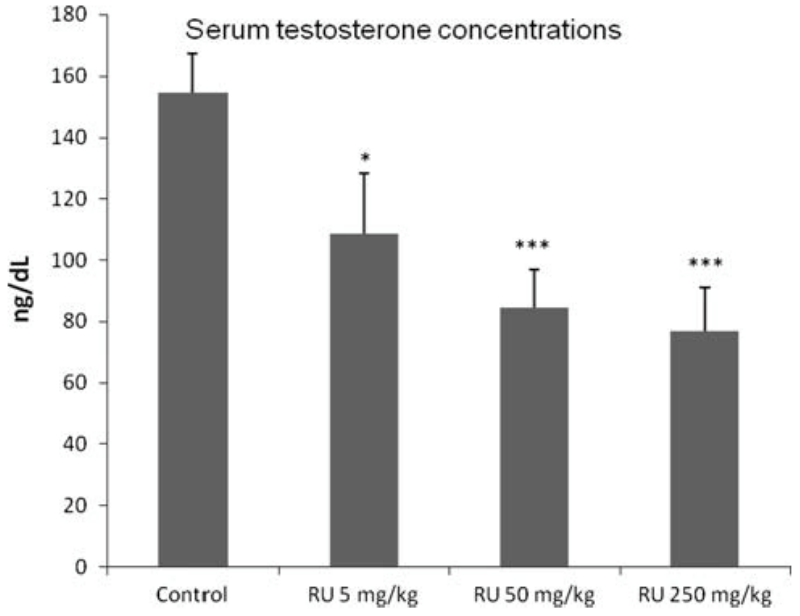
Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology

R. M. Romano · M. A. Romano · M. M. Bernardi · P. V. Furtado · C. A. Oliveira



Tubulos Semínifero



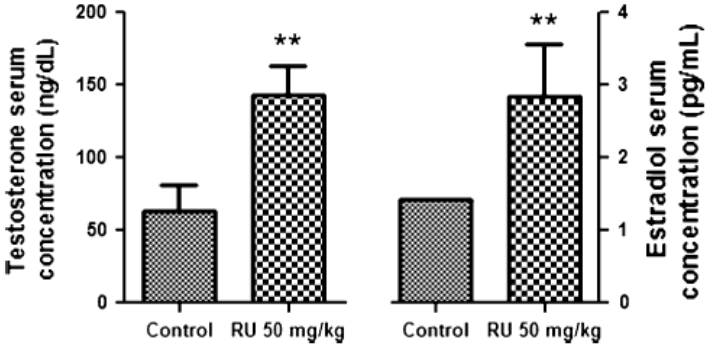


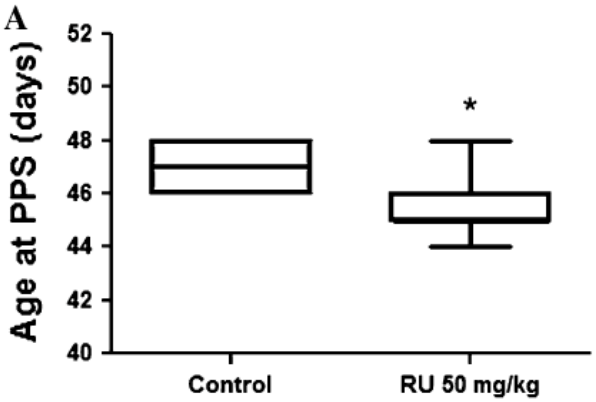
Arch Toxicol (2012) 86:663–673
DOI 10.1007/s00204-011-0788-9

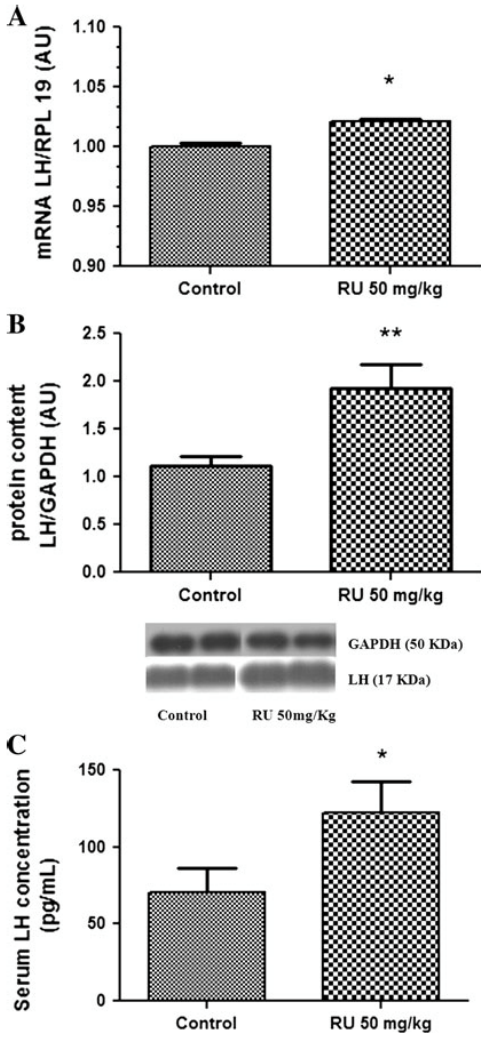
REPRODUCTIVE TOXICOLOGY

Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression

Marco Aurelio Romano · Renata Marino Romano · Luciana Dalazen Santos · Patricia Wisniewski · Daniele Antonelo Campos · Paula Bargi de Souza · Priscila Viau · Maria Martha Bernardi · Maria Tereza Nunes · Claudio Alvarenga de Oliveira







Toxicology 377 (2017) 25–37

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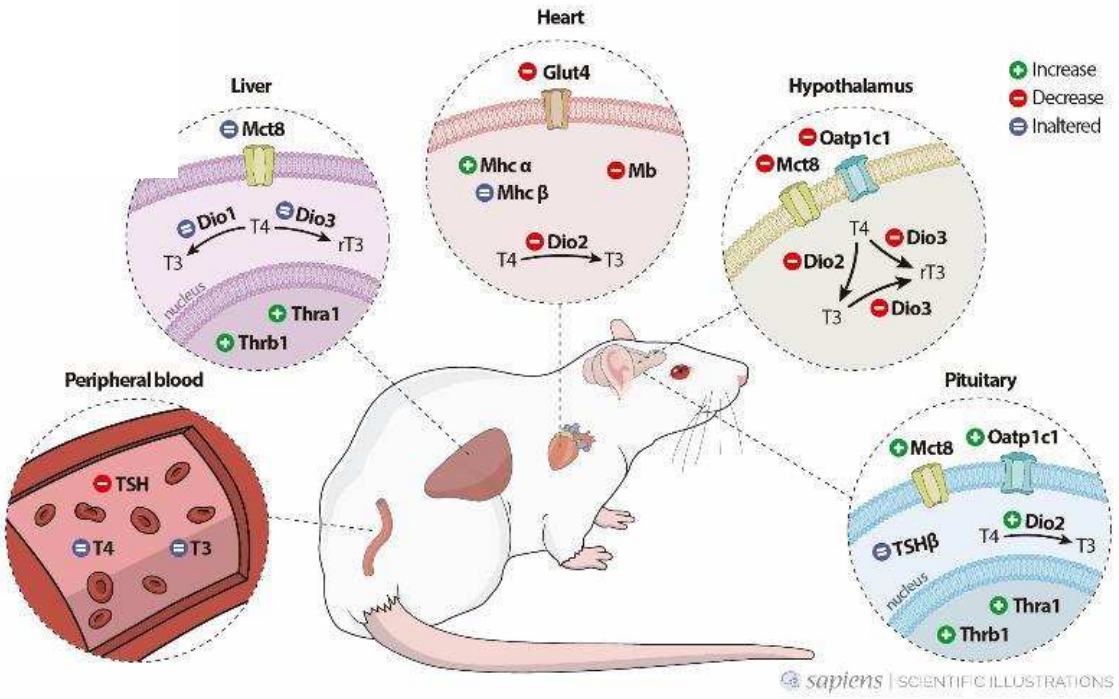
journal homepage: www.elsevier.com/locate/toxicol

Perinatal exposure to glyphosate-based herbicide alters the thyrotrophic axis and causes thyroid hormone homeostasis imbalance in male rats

Janaina Sena de Souza[a, 1], Marina Malta Letro Kizys[a, 1], Rodrigo Rodrigues da Conceição[a], Gabriel Glebocki[a], Renata Marino Romano[b], Tania Maria Ortiga-Carvalho[c], Gisele Giannocco[a], Ismael Dale Cotrim Guerreiro da Silva[d], Magnus Regios Dias da Silva[a], Marco Aurélio Romano[b], Maria Izabel Chiamolera[a,*]

[a] Universidade Federal de São Paulo, Unifesp/EPM, Departamento de Medicina, Disciplina de Endocrinologia Clínica, Laboratório de Endocrinologia Molecular e Translacional (LEMT), São Paulo, Brazil
[b] Universidade Estadual do Centro-Oeste, Departamento de Farmácia, Guarapuava, Brazil
[c] Universidade Federal do Rio de Janeiro, UFRJ, Instituto de Biofísica Carlos Chagas Filho, Laboratório de Endocrinologia Translacional, Rio de Janeiro, Brazil
[d] Universidade Federal de Sao Paulo, Unifesp/EPM, Departamento de Ginecologia, São Paulo, Brazil



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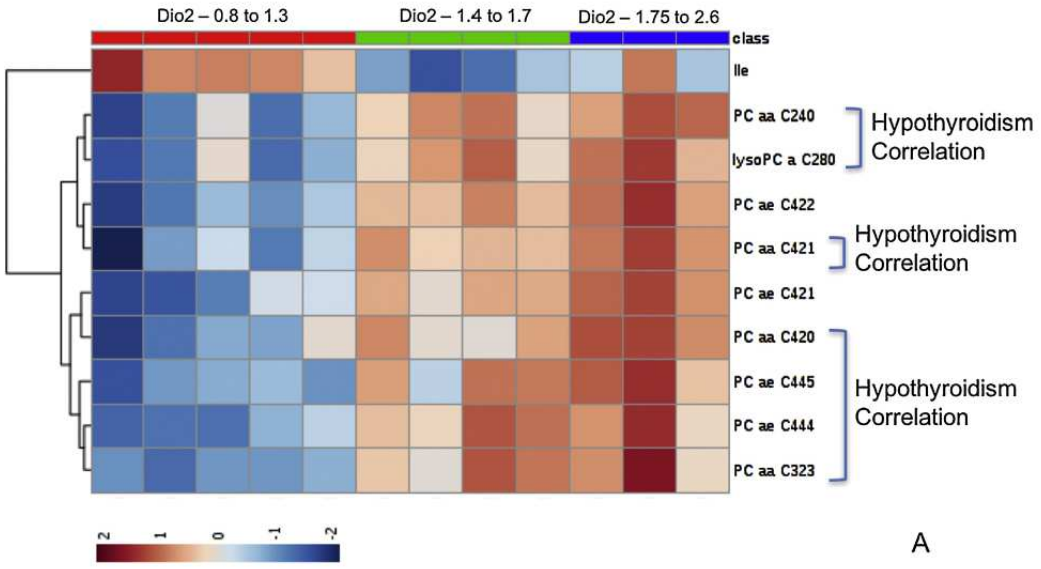
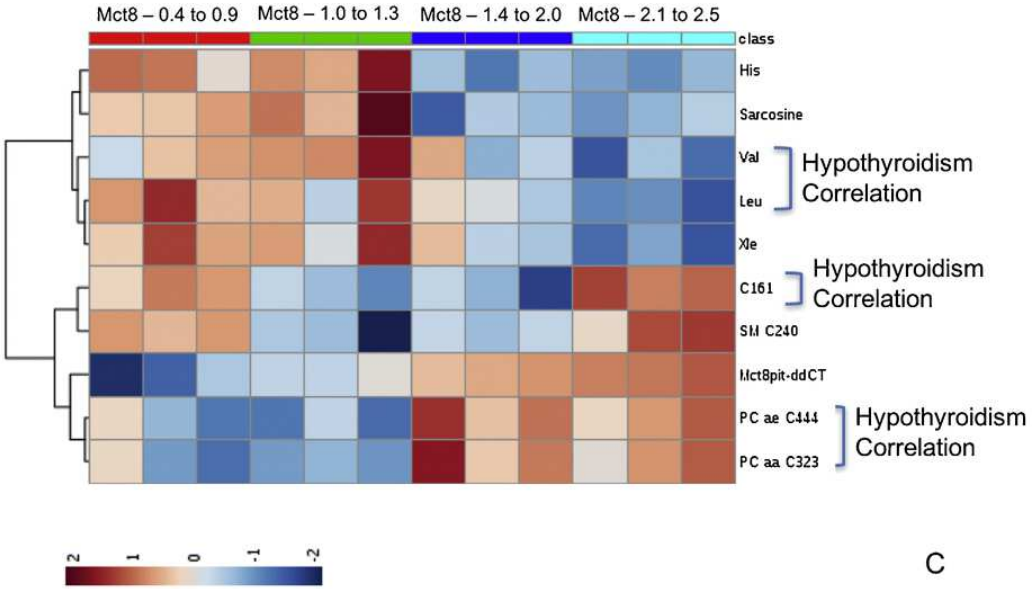
Metabolomic Correlation with Pituitary *Dio2* Expression



A

Metabolomic Correlation with Pituitary *Mct8* Expression



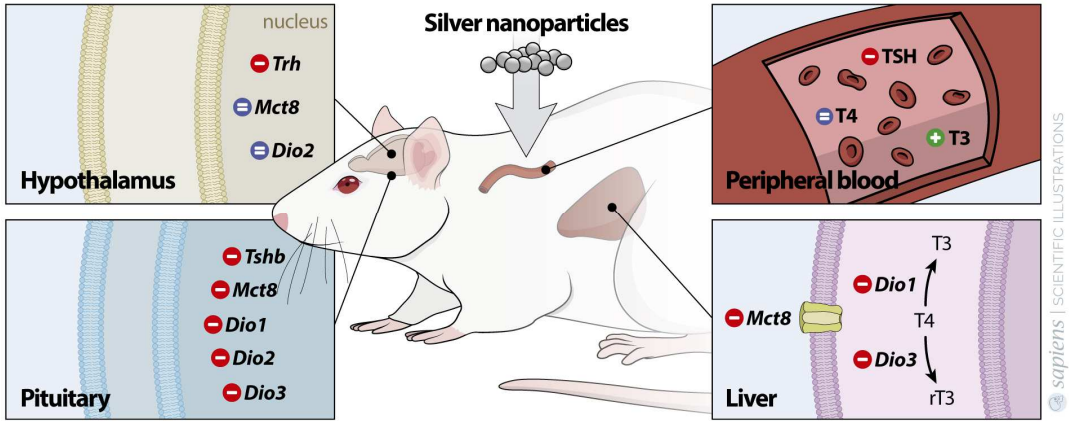
C

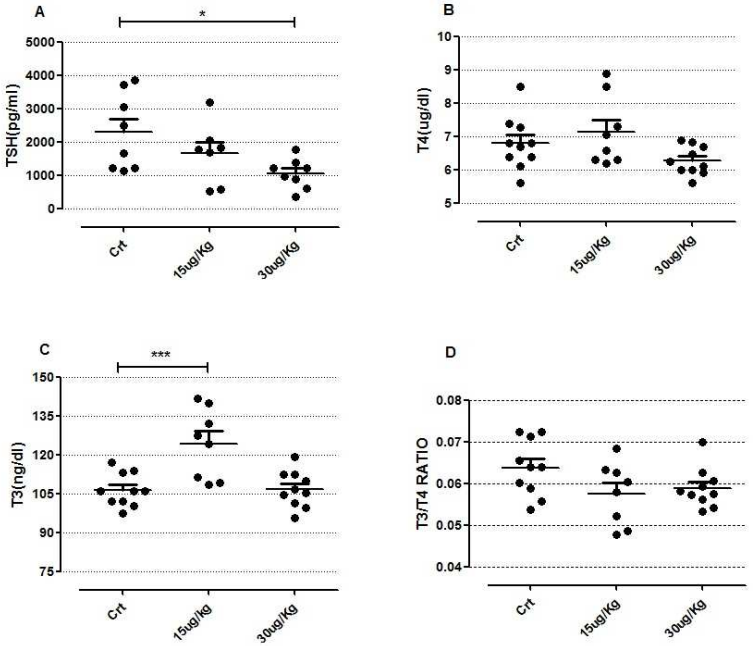
Nanopartícula de Prata

- Nanopartículas de prata (AgNPs) - aglomerados de átomos de prata com diâmetros, variam de 1 a 100 nm;

- Aplicações crescentes em campo médico, indústria alimentar e setor têxtil devido ao seu excelente potencial antibacteriano.

Alteração no Metabolismo do Hormônio Tiroidiano com AgNP





O que podemos fazer?

Recomendações para a população da U.S. Environmental Protection Agency – EPA:

- Educação sobre os Desreguladores Endócrinos,
- Uso de alimentação “orgânica” sempre que possível,
- Evitar uso doméstico de pesticidas,
- Informar-se e fazer campanha contra o uso uso de pesticidas em escolas e creches,
- Informar-se sobre a origem de peixes, rios e lagos contaminados,
- Evitar aquecer alimentos em recipientes plásticos, ou armazenar alimentos gordurosos em recipientes, sacos ou filmes plásticos,
- Não dar para crianças pequenas mordedores ou pequenos brinquedos plásticos,
- Apoio a leis mais rígidas e pesquisas sobre desreguladores,
- Lavar bem e descascar frutas e vegetais,
- Seguir todas as precauções para o uso de pesticidas,
- Armazenar pesticidas e outros químicos domésticos fora do alcance das crianças.

Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

Recommendations beyond research for the next 5 years include:

- Educate the public, the media, politicians, and governmental agencies on ways to keep EDCs out of food, water, and air and to protect developing children in particular.
- Develop industrial partners such as "green chemists" and others who can create products that test and eliminate potential EDCs.
- Recognize that EDCs are an international problem and develop international collaborations.
- Cultivate the next generation of EDC researchers, green chemists, physicians, and public health experts with expertise in endocrine systems.
- Funding agencies need to go beyond the "one scientist, one project" and "one clinician, one patient" perspective to fund team science and healthcare.
- Funding agencies need to prioritize EDC research in the basic, clinical, and epidemiological realms, especially considering that the cost of research and prevention will result in substantial cost savings in treatment and mitigation.
- Emphasize the need for precaution and prevention.
- Determine how much evidence is enough based on rigorous, peer-reviewed science—keeping in mind that absolute proof of harm or proof of safety is not possible.

Endocrine Reviews, December 2015, 36(6):593–602