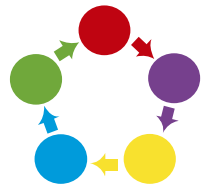
ENDOCRINE DISRUPTORS AND DETOXIFICATION STRATEGIES

Filomena Trindade, MD, MPH, AAARM, ABFM, ABOIM, IFMCP

Email: info@drtrindade.com

www.drtrindade.com

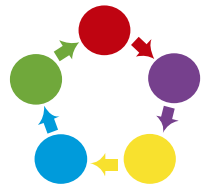


DISCLOSURES

- Disclosure of Financial Relationships:
  - None
- Off-Label Usage
  - None

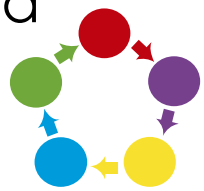
OBJECTIVES

- DEFINE ENDOCRINE DISRUPTION
- DISCUSS 4 MAIN AREAS
  - ENDOCRINE DISRUPTORS AND FERTILITY
  - INSULIN RESISTANCE AND ENDOCRINE DISRUPTION
  - THYROID DISORDERS AND ENDOCORINE DISRUPTORS
  - CANCER/ESTROGEN METABOLISM AND ENDOCRINE DISRUPTION
- REVIEW MY TREATMENT PROTOCOL FOR ENDORCRINE DISRUPTION



WHAT ARE ENDOCRINE DISRUPTORS?

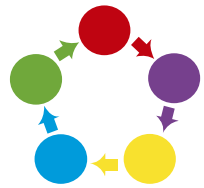
- Endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.
- A **potential endocrine disruptor** is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations.
- In February 2013, UNEP and WHO released the report State of the Science of Endocrine Disrupting Chemicals - 2012 which identifies concerns, including evidence in humans, laboratory animals, and wildlife that exposure to endocrine-disrupting chemicals can result in adverse effects and highlighted that an important focus should be on reducing exposure.



https://www.unenvironment.org/pt-br/node/1190

WHAT ARE ENDOCRINE DISRUPTORS (EDCS)?

- **U.S. Environmental Protection Agency (EPA) defines EDCs as:**
  - "An exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes".

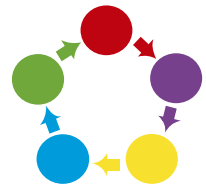


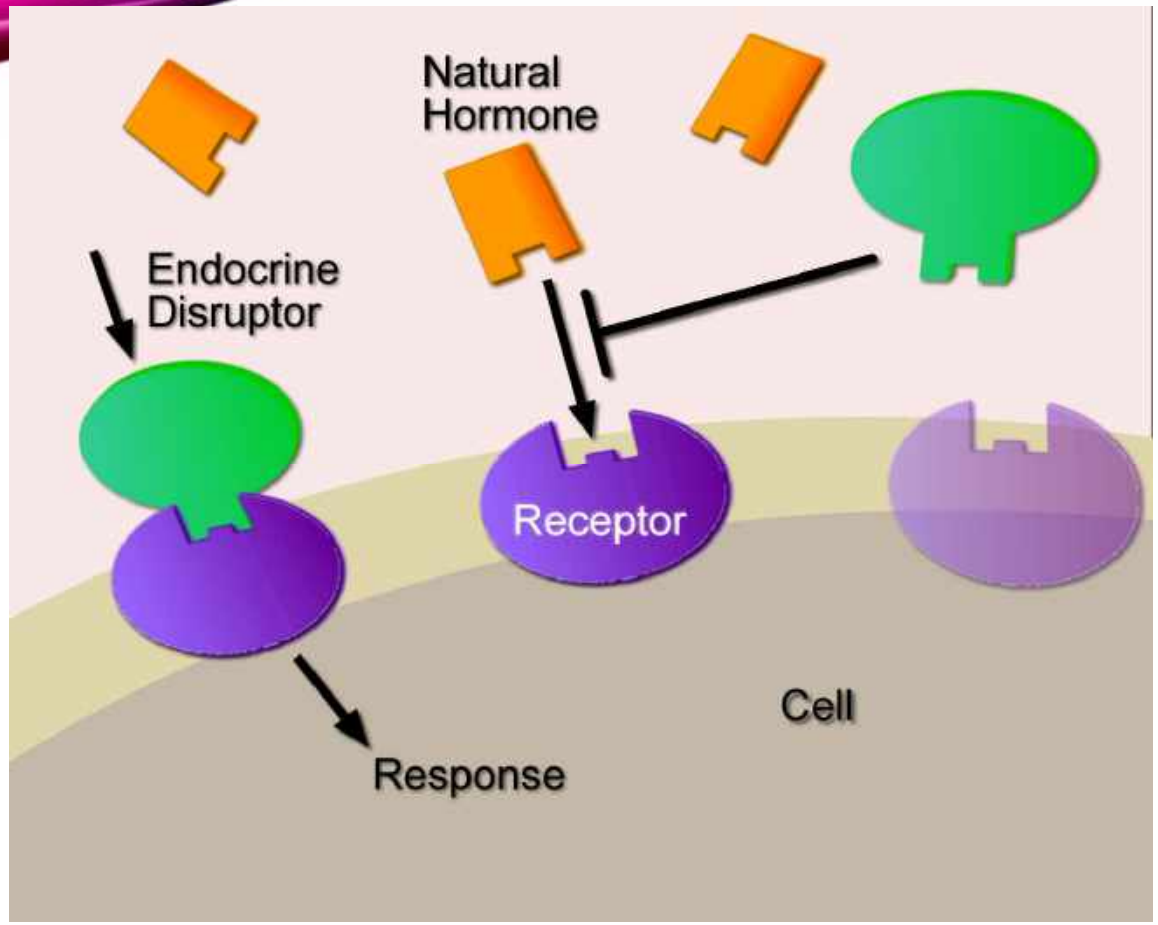
HOW DO EDCS CAUSE DAMAGE?

"EDCs act via nuclear receptors, nonnuclear steroid hormone receptors (*e.g.*, membrane ERs), nonsteroid receptors (*e.g.*, neurotransmitter receptors such as the serotonin receptor, dopamine receptor, norepinephrine receptor), orphan receptors [*e.g.*, aryl hydrocarbon receptor (AhR)], enzymatic pathways involved in steroid biosynthesis and/or metabolism, and numerous other mechanisms that converge upon endocrine and reproductive systems (1)."

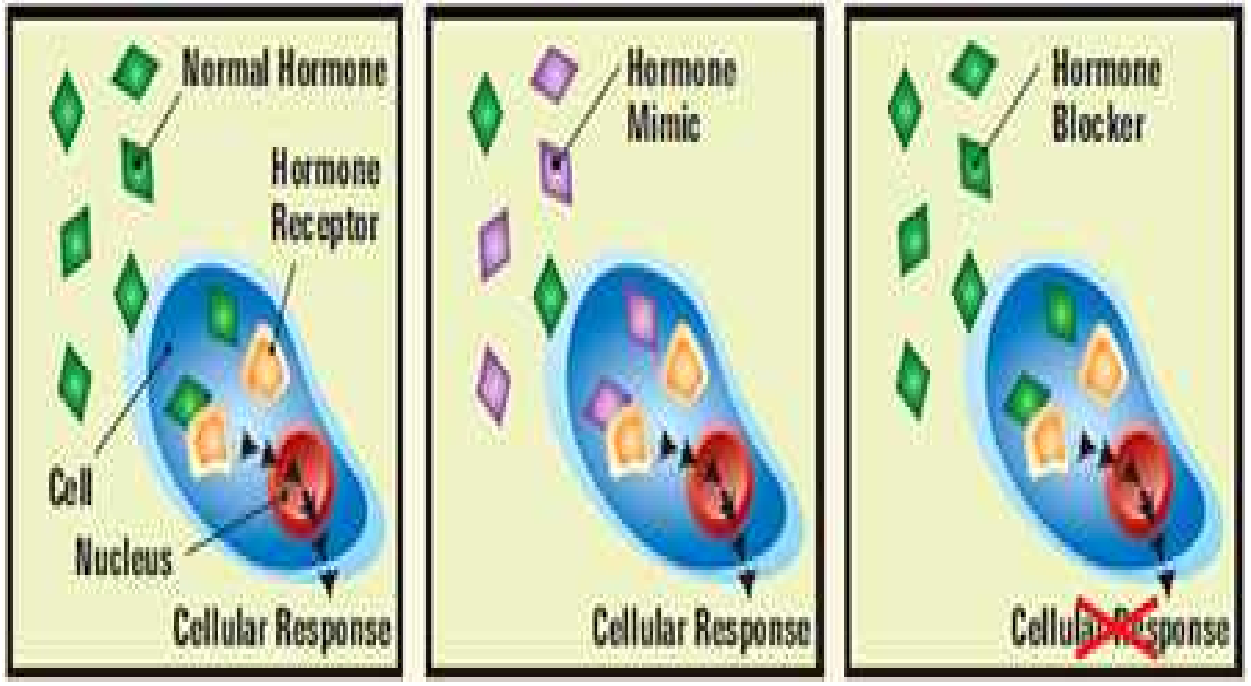
"These chemicals or factors can cause changes in DNA methylation which not only result in changes in estrogen receptor reactivity but also produce a higher ratio of the 4 and 16 hydroxylated estrogen derivatives which are more genotoxic (2,3)."

1. Evanthia Diamanti-Kandarakis, et al. **Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement**. Endocr Rev. 2009 Jun; 30(4): 293–342
2. Latini et al., Mini-Reviews in Medicinal Chemistry, 2010, 10, 846-855
3. Soto, A. M. & Sonnenschein, C. Nat. Rev. Endocrinol. 6, 363–370 (2010).

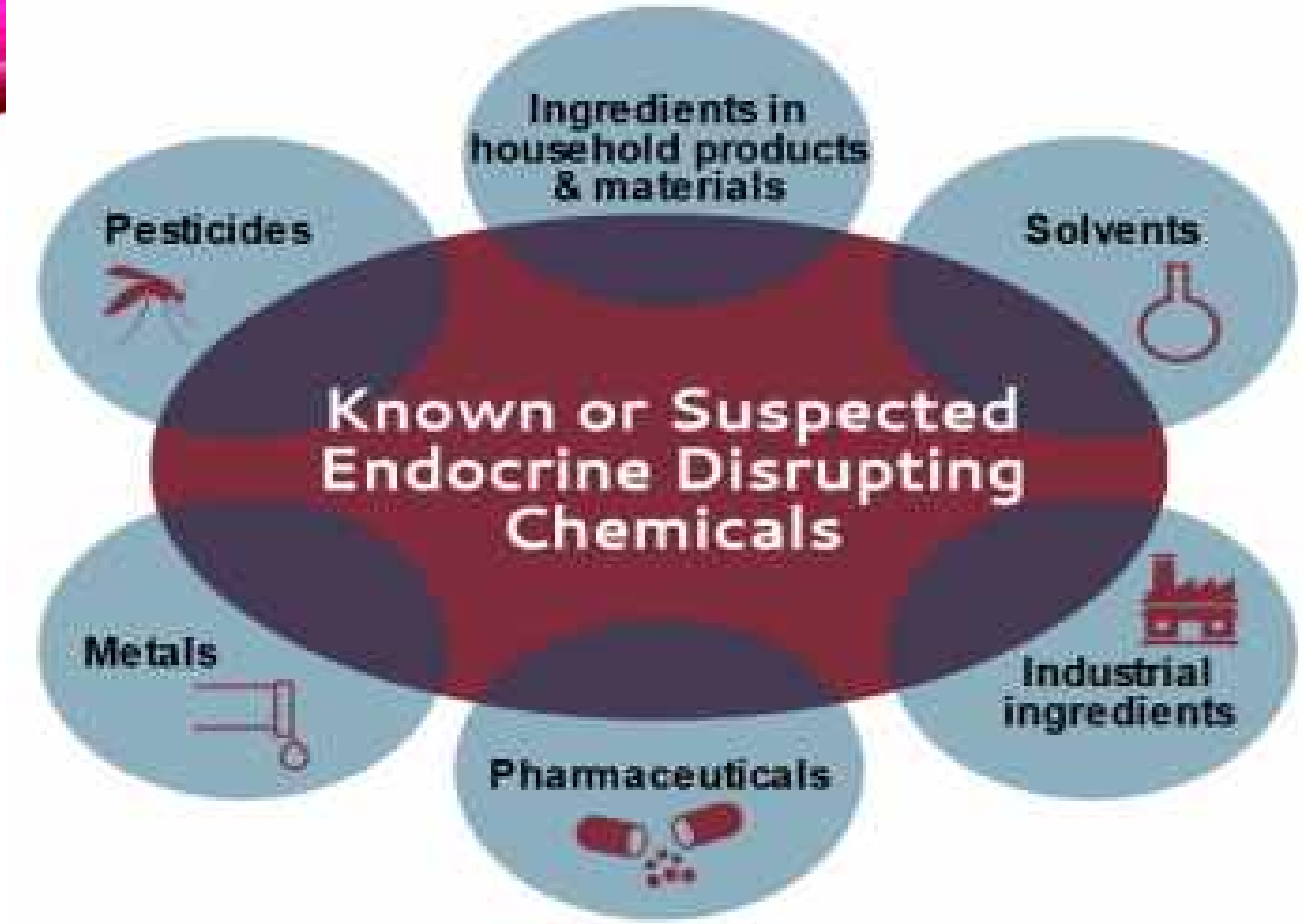




https://epthinktank.eu/2013/03/11/eu-policy-on-endocrine-disruptors/



https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm



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ENDOCRINE DISRUPTORS, FERTILITY AND CANCER

CORRECTED 7 MAY 2010; SEE LAST PAGE

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

Matthew D. Anway, Andrea S. Cupp,* Mehmet Uzumcu,† Michael K. Skinner‡

Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F_1 generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F_1

"The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology."

radiation were the first to be identified through transmission of DNA mutations in the germ line to multiple generations (*2*), often associated with tumor formation. Chemotherapeutic treatments (*3*) and environmental toxins such as endocrine disruptors (*4*) can cause effects in the F_1 generation, but they have not been shown to affect the F_2 generation. Although no effects have been shown to be transgenerational, the potential impact of such transgenerational effects of endocrine disruptors has been discussed (*5*).

Epigenetic alterations that could lead to transgenerational transmission of specific genetic traits have recently been identified (*1*, *6*). A transgenerational phenotype or ge-

sex determination and testis development occur between embryonic days 12 and 15 (E12 to E15) in the rat (after midgestation in the human) and are initiated by the differentiation of precursor Sertoli cells in response to the testis-determining factor Sry. Aggregation of the precursor Sertoli cells, PGCs, and migrating mesonephros cells (precursor peritubular myoid cells) promotes testis morphogenesis and cord formation (*10*, *11*). During the period of gonadal sex determination, the fetal testis contains steroid receptors and is a target for endocrine agents. The androgen receptor (AR) and estrogen receptor–β (ERβ) are present in Sertoli cells, precursor peritubular myoid cells, and germ cells at the time of cord formation (E14) (*12*, *13*). Al-

original gestating mother (F_0) of the F_1 generation received a transient endocrine disruptor treatment. Control groups of animals were bred in a similar manner after vehicle treatment (dimethylsulfoxide buffer alone injected) of the F_0 gestating mother. Analysis of cellular apoptosis demonstrated a greater than two-fold increase in spermatogenic cell apoptosis in the vinclozolin treatment animals for the F_1 to F_4 generations (Fig. 1A). Sperm numbers were reduced minimally, 20%, and sperm forward motility was reduced about 25 to 35% for vinclozolin generation animals (Fig. 1, B and C). More than 90% of all males analyzed from all generations had the germ cell defect of increased spermatogenic cell apoptosis. Therefore, the frequency of the phenotype

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" both vinclozolin and methoxychlor induced transgenerational defects in spermatogenic capacity and sperm viability."

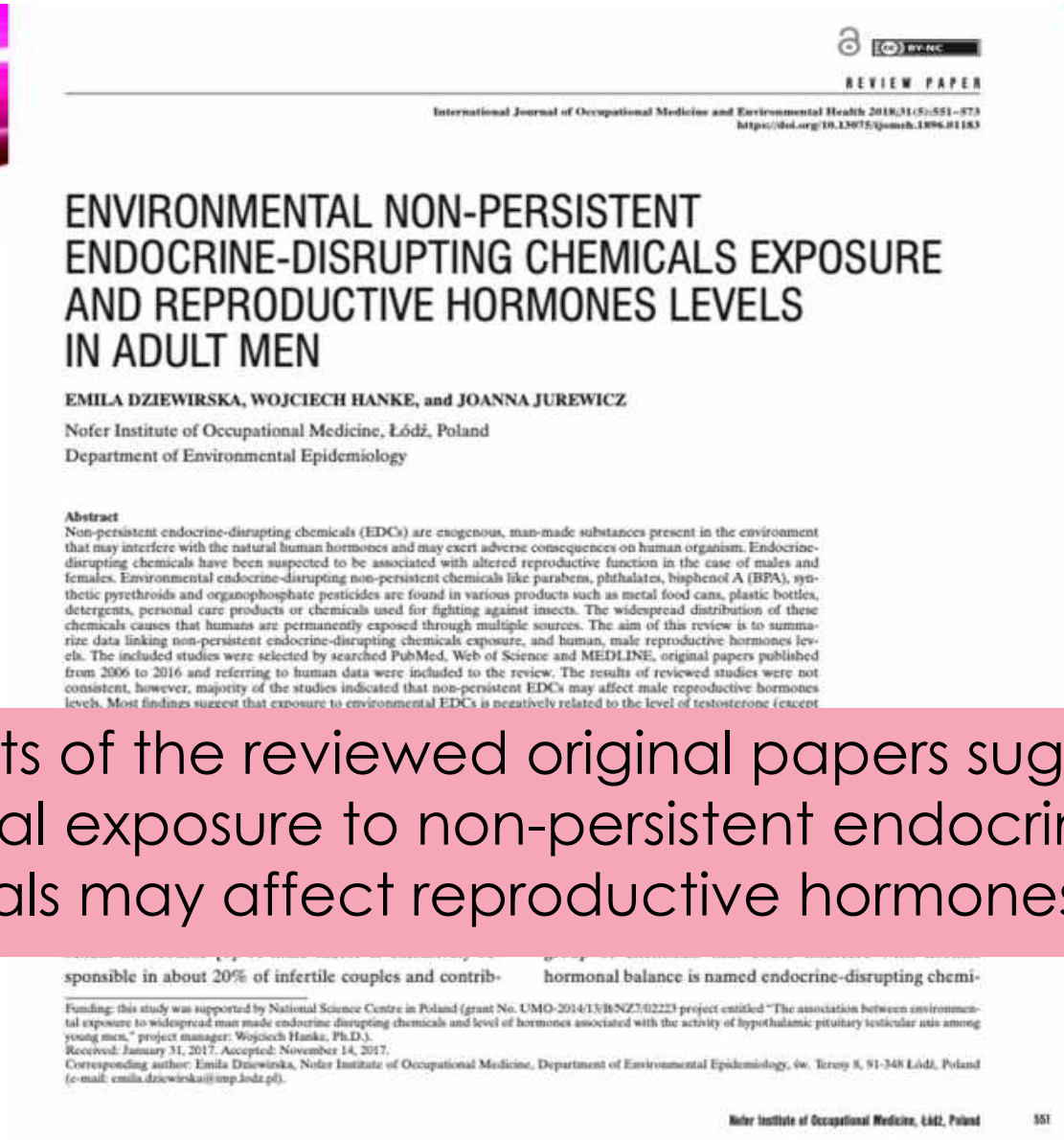
Treatments, such as irradiation and chemotherapy, and compounds, such as environmental toxins, pose a threat to the integrity of the genome. Studies have shown that these agents can result in genetic or developmental defects in the offspring or F_1 generation from an exposed gestating mother. The ability of an external agent to induce a transgenerational effect requires stable chromosomal alterations or an epigenetic phenomenon such as DNA methylation (*1*). In the present study, transgenerational refers to a germline transmission to multiple generations, minimally to the F_2 generation. Transgenerational effects of irradiation were the first to be identified through transmission of DNA mutations in the germ line to multiple generations (*2*), often associated with tumor formation. Chemotherapeutic treatments (*3*) and environmental toxins such as endocrine disruptors (*4*) can cause effects in the F_1 generation, but they have not been shown to affect the F_2 generation. Although no effects have been shown to be transgenerational, the potential impact of such transgenerational effects of endocrine disruptors has been discussed (*5*).

netic trait requires a permanent reprogramming of the germ line. During mammalian germ cell development the methylation state of the genome is reprogrammed. As primordial germ cells (PGCs) migrate down the genital ridge, a demethylation starts and is complete on colonization in the early gonad (*7*, *8*). Germ cells in the gonad then undergo remethylation in a sex-specific manner during gonadal sex determination (*9*). Although demethylation may not require the gonadal somatic cells, remethylation of the germ line appears to be dependent on association with the somatic cells in the gonads (*7*). Gonadal sex determination and testis development occur between embryonic days 12 and 15 (E12 to E15) in the rat (after midgestation in the human) and are initiated by the differentiation of precursor Sertoli cells in response to the testis-determining factor Sry. Aggregation of the precursor Sertoli cells, PGCs, and migrating mesonephros cells (precursor peritubular myoid cells) promotes testis morphogenesis and cord formation (*10*, *11*). During the period of gonadal sex determination, the fetal testis contains steroid receptors and is

tional transmission of an altered phenotype or genetic trait.

The estrogenic and antiandrogenic endocrine disruptors used in the current study are methoxychlor and vinclozolin, respectively. Vinclozolin is a commonly used fungicide in the wine industry that is metabolized into more active (i.e., higher affinity binding to androgen receptor) compounds (*14*). Methoxychlor is used as a pesticide to replace DDT and is metabolized into active compounds with the ERα agonist, the ERβ antagonist, and antiandrogenic activity (*15*–*17*). Vinclozolin or methoxychlor exposure in the late embryonic or early postnatal period influences sexual differentiation, gonad formation, and reproductive functions in the F_1 generation (*14*, *18*, *19*). Transient exposure (daily intraperitoneal injec-

tween E15 and E20 had no effect on the F_1 generation testis (*20*, *21*). These observations were extended in the present study by treating the gestating mother with vinclozolin. F_1 generation male rats were mated with F_1 generation females from different litters. Subsequent breeding continued for four generations with sufficient numbers of animals to avoid sibling inbreeding. Adult males from F_1, F_2, F_3, and F_4 generations between postnatal days PND60 and PND180 were killed. Testes were isolated for histological examination, and caudal epididymal sperm were collected for sperm counts and motility measurements. Only the original gestating mother (F_0) of the F_1 generation received a transient endocrine disruptor treatment. Control groups of animals were bred in a similar manner after vehicle treatment (dimethylsulfoxide buffer alone injected) of the F_0 gestating mother. Analysis of cellular apoptosis demonstrated a greater than two-fold increase in spermatogenic cell apoptosis in the vinclozolin treatment animals for the F_1 to F_4 generations (Fig. 1A). Sperm numbers were reduced minimally, 20%, and sperm forward motility was reduced about 25 to 35%



REVIEW PAPER

International Journal of Occupational Medicine and Environmental Health 2018;31(5):551–573
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ENVIRONMENTAL NON-PERSISTENT ENDOCRINE-DISRUPTING CHEMICALS EXPOSURE AND REPRODUCTIVE HORMONES LEVELS IN ADULT MEN

EMILA DZIEWIRSKA, WOJCIECH HANKE, and JOANNA JUREWICZ

Nofer Institute of Occupational Medicine, Łódź, Poland
Department of Environmental Epidemiology

Abstract

Non-persistent endocrine-disrupting chemicals (EDCs) are exogenous, man-made substances present in the environment that may interfere with the natural human hormones and may exert adverse consequences on human organism. Endocrine-disrupting chemicals have been suspected to be associated with altered reproductive function in the case of males and females. Environmental endocrine-disrupting non-persistent chemicals like parabens, phthalates, bisphenol A (BPA), synthetic pyrethroids and organophosphate pesticides are found in various products such as metal food cans, plastic bottles, detergents, personal care products or chemicals used for fighting against insects. The widespread distribution of these chemicals causes that humans are permanently exposed through multiple sources. The aim of this review is to summarize data linking non-persistent endocrine-disrupting chemicals exposure, and human, male reproductive hormones levels. The included studies were selected by searched PubMed, Web of Science and MEDLINE, original papers published from 2006 to 2016 and referring to human data were included to the review. The results of reviewed studies were not consistent, however, majority of the studies indicated that non-persistent EDCs may affect male reproductive hormones levels. Most findings suggest that exposure to environmental EDCs is negatively related to the level of testosterone (except

"The results of the reviewed original papers suggest that environmental exposure to non-persistent endocrine-disrupting chemicals may affect reproductive hormones levels."

sponsible in about 20% of infertile couples and contrib- hormonal balance is named endocrine-disrupting chemi-

Funding: this study was supported by National Science Centre in Poland (grant No. UMO-2014/13/B/NZ7/02223 project entitled "The association between environmental exposure to widespread man made endocrine disrupting chemicals and level of hormones associated with the activity of hypothalamic pituitary testicular axis among young men," project manager: Wojciech Hanke, Ph.D.).
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Corresponding author: Emila Dziewirska, Nofer Institute of Occupational Medicine, Department of Environmental Epidemiology, św. Teresy 8, 91-348 Łódź, Poland (e-mail: emila.dziewirska@imp.lodz.pl).

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

Urinary concentrations of parabens and reproductive parameters in young men

Evdochia Adoamnei [a], Jaime Mendiola [a,b,c,*], Miriam Moñino-García [a], Fernando Vela-Soria [c,d], Luz M. Iribarne-Durán [c,d], Mariana F. Fernández [c,d], Nicolás Olea [c,d], Niels Jørgensen [e], Shanna H. Swan [f], Alberto M. Torres-Cantero [a,b,c,g]

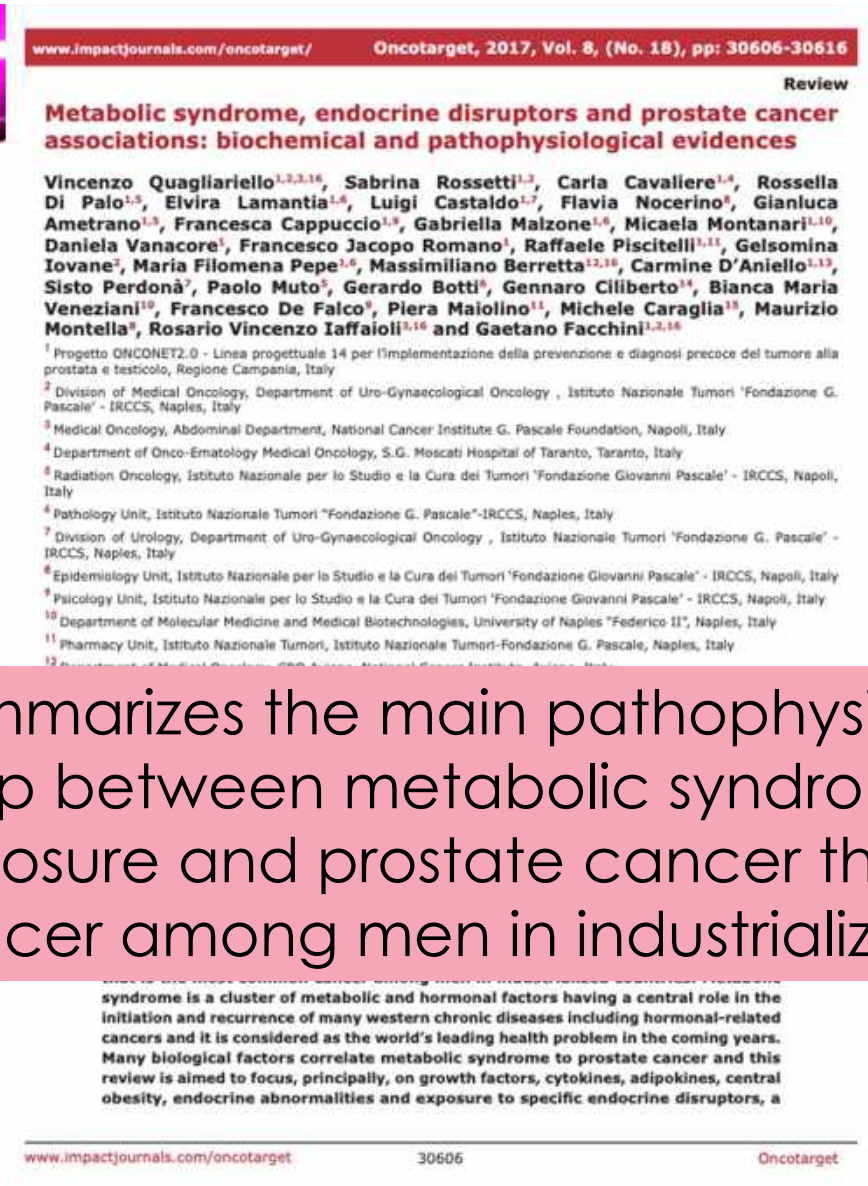
[a] Division of Preventive Medicine and Public Health, Department of Public Health Sciences, University of Murcia School of Medicine, Murcia, Spain
[b] Health Research Methodology Group, Biomedical Research Institute of Murcia (IMIB-Arrixaca), El Palmar, Murcia, Spain
[c] CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[d] Instituto de Investigación Biosanitaria (Ibs. GRANADA), Hospitales Universitarios de Granada, Departamentos de Radiología y Medicina Física, Universidad de Granada, Granada, Spain
[e] Department of Growth and Reproduction, International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, Denmark
[f] Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[g] Department of Preventive Medicine, "Virgen de la Arrixaca" University Clinical Hospital, El Palmar, Murcia, Spain

HIGHLIGHTS

- Urinary paraben concentrations were quantified to estimate environmental exposure
- Semen quality and serum reproductive hormone levels were evaluated
- No associations between parabens and any of the reproductive parameters were observed
- Urinary paraben concentrations may not adversely impact male reproductive function

GRAPHICAL ABSTRACT

"….no associations between urinary concentrations of MP, PP or BP and conventional semen quality parameters, but urinary BP concentration was positively associated with sperm DNA damage."



www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 18), pp: 30606-30616

Review

Metabolic syndrome, endocrine disruptors and prostate cancer associations: biochemical and pathophysiological evidences

Vincenzo Quagliariello[1,2,3,16], Sabrina Rossetti[1,2], Carla Cavaliere[1,4], Rossella Di Palo[1,5], Elvira Lamantia[1,6], Luigi Castaldo[1,7], Flavia Nocerino[8], Gianluca Ametrano[1,9], Francesca Cappuccio[1,9], Gabriella Malzone[1,6], Micaela Montanari[1,10], Daniela Vanacore[1], Francesco Jacopo Romano[1], Raffaele Piscitelli[1,11], Gelsomina Iovane[2], Maria Filomena Pepe[1,6], Massimiliano Berretta[12,16], Carmine D'Aniello[1,13], Sisto Perdonà[7], Paolo Muto[5], Gerardo Botti[6], Gennaro Ciliberto[14], Bianca Maria Veneziani[10], Francesco De Falco[9], Piera Maiolino[11], Michele Caraglia[15], Maurizio Montella[8], Rosario Vincenzo Iaffaioli[3,16] and Gaetano Facchini[1,2,16]

[1] Progetto ONCONET2.0 - Linea progettuale 14 per l'implementazione della prevenzione e diagnosi precoce del tumore alla prostata e testicolo, Regione Campania, Italy

[2] Division of Medical Oncology, Department of Uro-Gynaecological Oncology , Istituto Nazionale Tumori 'Fondazione G. Pascale' - IRCCS, Naples, Italy

[3] Medical Oncology, Abdominal Department, National Cancer Institute G. Pascale Foundation, Napoli, Italy

[4] Department of Onco-Ematology Medical Oncology, S.G. Moscati Hospital of Taranto, Taranto, Italy

[5] Radiation Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione Giovanni Pascale' - IRCCS, Napoli, Italy

[6] Pathology Unit, Istituto Nazionale Tumori "Fondazione G. Pascale"-IRCCS, Naples, Italy

[7] Division of Urology, Department of Uro-Gynaecological Oncology , Istituto Nazionale Tumori 'Fondazione G. Pascale' - IRCCS, Naples, Italy

[8] Epidemiology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione Giovanni Pascale' - IRCCS, Napoli, Italy

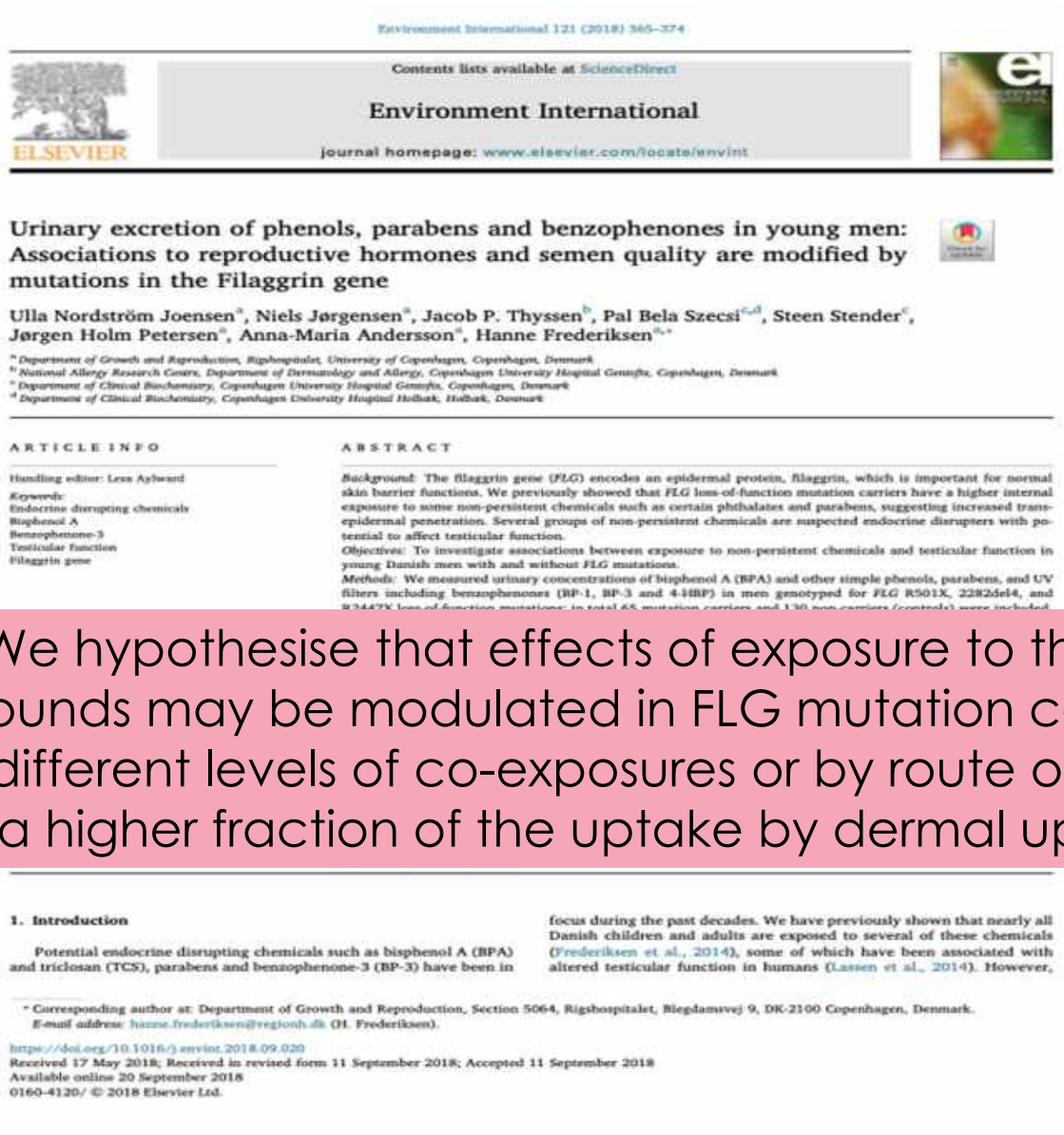
[9] Psicology Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori 'Fondazione Giovanni Pascale' - IRCCS, Napoli, Italy

[10] Department of Molecular Medicine and Medical Biotechnologies, University of Naples "Federico II", Naples, Italy

[11] Pharmacy Unit, Istituto Nazionale Tumori, Istituto Nazionale Tumori-Fondazione G. Pascale, Naples, Italy

syndrome is a cluster of metabolic and hormonal factors having a central role in the initiation and recurrence of many western chronic diseases including hormonal-related cancers and it is considered as the world's leading health problem in the coming years. Many biological factors correlate metabolic syndrome to prostate cancer and this review is aimed to focus, principally, on growth factors, cytokines, adipokines, central obesity, endocrine abnormalities and exposure to specific endocrine disruptors, a

" This review summarizes the main pathophysiological basis of the relationship between metabolic syndrome, endocrine disruptor exposure and prostate cancer that is the most common cancer among men in industrialized countries."



Environment International 121 (2018) 365–374

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Urinary excretion of phenols, parabens and benzophenones in young men: Associations to reproductive hormones and semen quality are modified by mutations in the Filaggrin gene

Ulla Nordström Joensen[a], Niels Jørgensen[a], Jacob P. Thyssen[b], Pal Bela Szecsi[c,d], Steen Stender[c], Jørgen Holm Petersen[a], Anna-Maria Andersson[a], Hanne Frederiksen[a,*]

[a] Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[b] National Allergy Research Centre, Department of Dermatology and Allergy, Copenhagen University Hospital Gentofte, Copenhagen, Denmark
[c] Department of Clinical Biochemistry, Copenhagen University Hospital Gentofte, Copenhagen, Denmark
[d] Department of Clinical Biochemistry, Copenhagen University Hospital Holbæk, Holbæk, Denmark

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Benzophenone-3
Testicular function
Filaggrin gene

ABSTRACT

Background: The filaggrin gene (*FLG*) encodes an epidermal protein, filaggrin, which is important for normal skin barrier functions. We previously showed that *FLG* loss-of-function mutation carriers have a higher internal exposure to some non-persistent chemicals such as certain phthalates and parabens, suggesting increased trans-epidermal penetration. Several groups of non-persistent chemicals are suspected endocrine disrupters with potential to affect testicular function.

Objectives: To investigate associations between exposure to non-persistent chemicals and testicular function in young Danish men with and without *FLG* mutations.

Methods: We measured urinary concentrations of bisphenol A (BPA) and other simple phenols, parabens, and UV filters including benzophenones (BP-1, BP-3 and 4-HBP) in men genotyped for *FLG* R501X, 2282del4, and

"We hypothesise that effects of exposure to these compounds may be modulated in FLG mutation carriers by either different levels of co-exposures or by route of uptake, with a higher fraction of the uptake by dermal uptake."

1. Introduction

Potential endocrine disrupting chemicals such as bisphenol A (BPA) and triclosan (TCS), parabens and benzophenone-3 (BP-3) have been in focus during the past decades. We have previously shown that nearly all Danish children and adults are exposed to several of these chemicals (Frederiksen et al., 2014), some of which have been associated with altered testicular function in humans (Lassen et al., 2014). However,

* Corresponding author at: Department of Growth and Reproduction, Section 5064, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail address: hanne.frederiksen@regionh.dk (H. Frederiksen).

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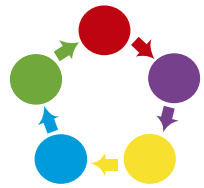
Available online 20 September 2018
0160-4120/

BISPHENOL A (BPA)

THE EDC BPA HAS TRANSGENERATIONAL EFFECTS IN MICE

low-dose BPA (1.2 or 2.4 g/kg body weight)at environmentally relevant levels has been shown to induce transgenerational effects in rats, that is, male offspring prenatally exposed to BPA had reduced sperm counts and sperm motilities, and these phenotypes persisted through to the F3 population

Bernal and Jirtle, 2010



Review > Ceska Gynekol. Winter 2019;84(2):161-165.

Bisphenols in the Pathology of Reproduction

M Ješeta, T Crha, J Žáková, P Ventruba

PMID: 31238688

Abstract

Objective: Bisphenols are one of the most widespread endocrine disruptors that the population of west world countries is exposed to. Objective of this study is to summarize information about influence of bisphenols on reproduction health.

Design: Review article, Setting: Department of Obstetrics and Gynecology, Faculty of Medicine, Masaryk University and University Hospital Brno.

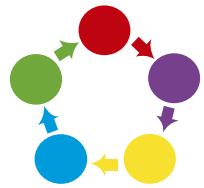
Methods: PubMed was searched for articles in English indexed bisphenol and reproduction up to October 2018.

disorders of men and women.

"Bisphenols are widespread endocrine disruptors that could cause severe fertility disorders of men and women."

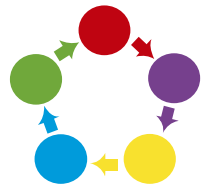
BPA induced changes in gene expression could be transferred across generations

Foster, W.G., Hughes, C.L., 2011. Gene expression in oogenesis and implications for transgenerational effects of environmental toxicants. Biol. Reprod. 84, 2–4.



BPA exposure can affect future generations by altering epigenetic mechanisms.

Soriano, S., Alonso-Magdalena, P., Garcia-Arevalo, M., Novials, A., Muhammed, S.J., Salehi, A., Gustafsson, J.A., Quesada, I., Nadal, A., 2012. Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of langerhans: role of estrogen receptor beta. PLoS One 7, e31109.



nutrients

MDPI

Review

Bisphenol S in Food Causes Hormonal and Obesogenic Effects Comparable to or Worse than Bisphenol A: A Literature Review

Michael Thoene [1,*], Ewa Dzika [1], Slawomir Gonkowski [2] and Joanna Wojtkiewicz [3]

1 Department of Medical Biology, Faculty of Health Sciences, University of Warmia and Mazury in Olsztyn, Żołnierska 14C str., 10-561 Olsztyn, Poland; e.dzika@uwm.edu.pl
2 Department of Clinical Physiology, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn, Oczapowskiego Str. 13, 10-718 Olsztyn, Poland; slawomir.gonkowski@uwm.edu.pl
3 Department of Pathophysiology, School of Medicine, University of Warmia and Mazury, 10-082 Olsztyn, Poland; Joanna.Wojtkiewicz@uwm.edu.pl
* Correspondence: michael.thoene@uwm.edu.pl; Tel.: +89-524-61-16

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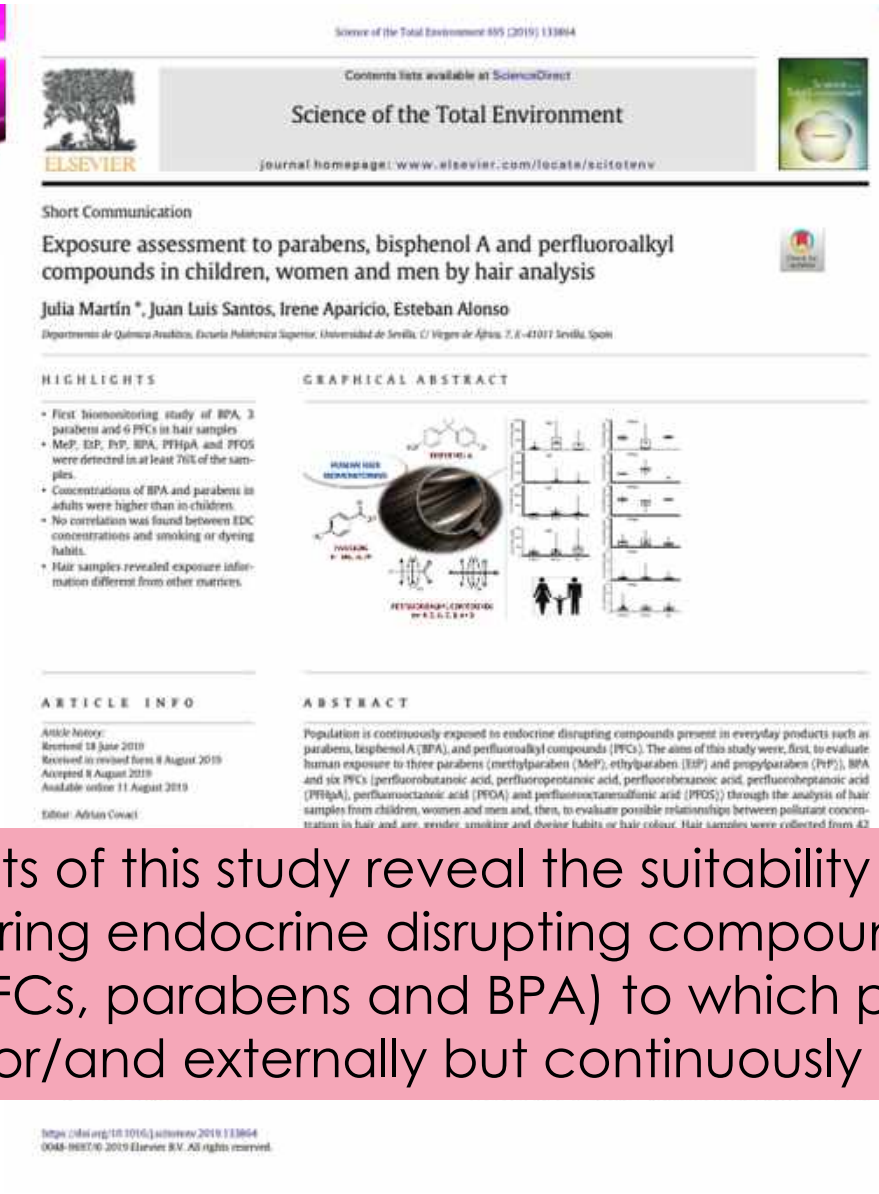
Abstract: In recent years, bisphenol analogues such as bisphenol S (BPS) have come to replace bisphenol A in food packaging and food containers, since bisphenol A (BPA) has been shown to leach into food and water, causing numerous negative health effects. Unfortunately, little or no research was done to determine the safety of these BPA-free products before they were marketed to the public as a healthier alternative. The latest studies have shown that some of these bisphenol analogues may be even more harmful than the original BPA in some situations. This article used a literature survey to investigate the bisphenol analogue BPS and compare it to BPA and other analogues with regards to increased obesity, metabolic disorders, cancer, and reproductive defects; among others. It was found that BPS works via different pathways than does BPA while causing equivalent obesogenic effects, such as activating preadipocytes, and that BPS was correlated with metabolic disorders, such as gestational diabetes, that BPA was not correlated with. BPS was also shown to be more toxic to the reproductive system than BPA and was shown to hormonally promote certain breast cancers at the same rate as BPA. Therefore, a strong argument may be made to regulate BPS in exactly the same manner as BPA.

Keywords: bisphenol analogues; food packaging; obesogenic effects; metabolic disorders

"Therefore, a strong argument may be made to regulate BPS in exactly the same manner as BPA."

of the most well-known EDCs (endocrine disrupting compounds) with pronounced effects on the reproductive system, child development, metabolic disorders, obesity, endocrine disorders, and the nervous system; as well as being implicated in causing DNA damage, oxidative stress, and breast cancer [2–4]. The concern about BPA affecting child development prompted a ban on BPA-containing



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Short Communication

Exposure assessment to parabens, bisphenol A and perfluoroalkyl compounds in children, women and men by hair analysis

Julia Martín *, Juan Luis Santos, Irene Aparicio, Esteban Alonso

Departamento de Química Analítica, Escuela Politécnica Superior, Universidad de Sevilla, C/ Virgen de África, 7, E-41011 Sevilla, Spain

HIGHLIGHTS

- First biomonitoring study of BPA, 3 parabens and 6 PFCs in hair samples
- MeP, EtP, PrP, BPA, PFHpA and PFOS were detected in at least 76% of the samples.
- Concentrations of BPA and parabens in adults were higher than in children.
- No correlation was found between EDC concentrations and smoking or dyeing habits.
- Hair samples revealed exposure information different from other matrices.

GRAPHICAL ABSTRACT

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ABSTRACT

Population is continuously exposed to endocrine disrupting compounds present in everyday products such as parabens, bisphenol A (BPA), and perfluoroalkyl compounds (PFCs). The aims of this study were, first, to evaluate human exposure to three parabens (methylparaben (MeP), ethylparaben (EtP) and propylparaben (PrP)), BPA and six PFCs (perfluorobutanoic acid, perfluoropentanoic acid, perfluorohexanoic acid, perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)) through the analysis of hair samples from children, women and men and, then, to evaluate possible relationships between pollutant concentration in hair and age, gender, smoking and dyeing habits or hair colour. Hair samples were collected from 42

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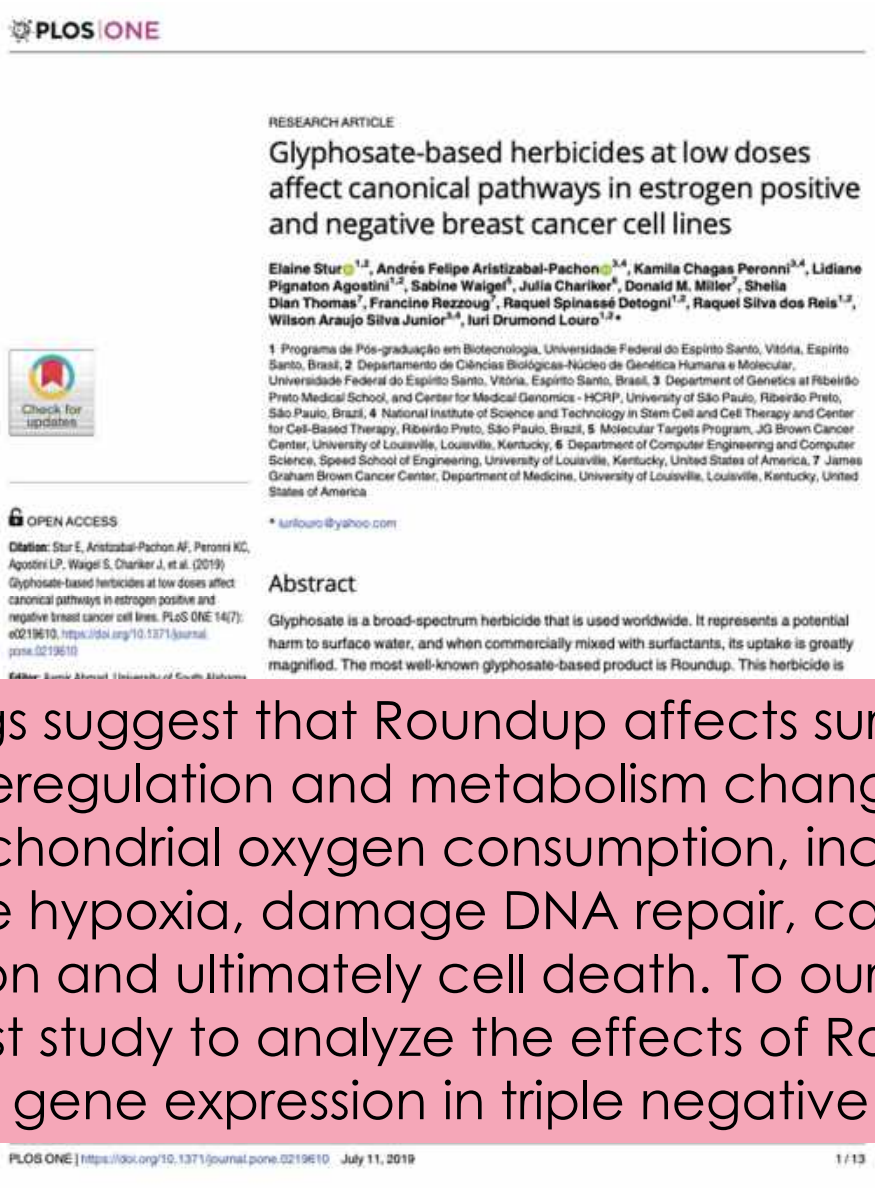
"The results of this study reveal the suitability of hair for biomonitoring endocrine disrupting compounds of high concern (PFCs, parabens and BPA) to which population is internally or/and externally but continuously exposed."

GLYPHOSAPTE



PLOS ONE

RESEARCH ARTICLE

Glyphosate-based herbicides at low doses affect canonical pathways in estrogen positive and negative breast cancer cell lines

Elaine Stur[1,2], Andrés Felipe Aristizabal-Pachon[3,4], Kamila Chagas Peronni[3,4], Lidiane Pignaton Agostini[1,2], Sabine Waigel[4], Julia Chariker[4], Donald M. Miller[7], Shelia Dian Thomas[7], Francine Rezzoug[7], Raquel Spinassé Detogni[1,2], Raquel Silva dos Reis[1,2], Wilson Araujo Silva Junior[3,4], Iuri Drumond Louro[1,2]*

1 Programa de Pós-graduação em Biotecnologia, Universidade Federal do Espírito Santo, Vitória, Espírito Santo, Brasil, 2 Departamento de Ciências Biológicas-Núcleo de Genética Humana e Molecular, Universidade Federal do Espírito Santo, Vitória, Espírito Santo, Brasil, 3 Department of Genetics at Ribeirão Preto Medical School, and Center for Medical Genomics - HCRP, University of São Paulo, Ribeirão Preto, São Paulo, Brazil, 4 National Institute of Science and Technology in Stem Cell and Cell Therapy and Center for Cell-Based Therapy, Ribeirão Preto, São Paulo, Brazil, 5 Molecular Targets Program, JG Brown Cancer Center, University of Louisville, Louisville, Kentucky, 6 Department of Computer Engineering and Computer Science, Speed School of Engineering, University of Louisville, Kentucky, United States of America, 7 James Graham Brown Cancer Center, Department of Medicine, University of Louisville, Louisville, Kentucky, United States of America

* iurilouro@yahoo.com

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Abstract

Glyphosate is a broad-spectrum herbicide that is used worldwide. It represents a potential harm to surface water, and when commercially mixed with surfactants, its uptake is greatly magnified. The most well-known glyphosate-based product is Roundup. This herbicide is

"Our findings suggest that Roundup affects survival due to cell cycle deregulation and metabolism changes that may alter mitochondrial oxygen consumption, increase ROS levels, induce hypoxia, damage DNA repair, cause mutation accumulation and ultimately cell death. To our knowledge, this is the first study to analyze the effects of Roundup and AMPA on gene expression in triple negative BC cells."

Accepted Manuscript

TITLE: Prepubertal subchronic exposure to soy milk and glyphosate leads to endocrine disruption

Jessica Nardi, Patricia Bonamigo Moras, Carina Koeppe, Eliane Dallegrave, Mirna Bainy Leal, Luciana Grazziotin Rossato-Grando

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"Animals receiving soy milk supplemented with 100 mg/kg glyphosate showed decrease in round spermatids and increase in abnormal sperm morphology, compared to control."

Perinatal exposure to glyphosate and a glyphosate-based herbicide affect spermatogenesis in mice.

Thu Ha Pham[1], Lohann Derian[1], Christine Kervarrec[1], Pierre-Yves Kernanec[1], Bernard Jégou[1], Fatima Smagulova[1] and Aurore Gely-Pernot[1#].

[1] Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR_S 1085, F-35000 Rennes, France

Correspondence should be addressed at Irset-Inserm UMR_S 1085, 9 avenue du Pr Léon Bernard, 35000 Rennes, France. E-mail: aurore.gely-pernot@ehesp.fr

Key words: Glyphosate, Roundup, spermatogenesis, reproduction, differentiation

"Our data demonstrate that glyphosate and GBHs could cause endocrine-disrupting effects on male reproduction at low doses."

Manservisi et al. Environmental Health (2019) 18:15
https://doi.org/10.1186/s12940-019-0453-y

Environmental Health

RESEARCH Open Access

The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on development and endocrine system

Fabiana Manservisi[1,2†], Corina Lesseur[3†], Simona Panzacchi[1], Daniele Mandrioli[1,4], Laura Falcioni[1], Luciano Bua[1], Marco Manservigi[1], Marcella Spinaci[2], Giovanna Galeati[2], Alberto Mantovani[5], Stefano Lorenzetti[5], Rossella Miglio[6], Anderson Martino Andrade[7], David Møbjerg Kristensen[8], Melissa J. Perry[9], Shanna H. Swan[3], Jia Chen[3] and Fiorella Belpoggi[1*]

Abstract

Background: Glyphosate-based herbicides (GBHs) are broad-spectrum herbicides that act on the shikimate pathway in bacteria, fungi, and plants. The possible effects of GBHs on human health are the subject of an intense public debate for both its potential carcinogenic and non-carcinogenic effects, including potential effects on the endocrine system The present pilot study examine whether exposure to GBHs at the dose of glyphosate considered to be "safe" (the US Acceptable Daily Intake - ADI - of 1.75 mg/kg bw/day), starting from in utero life, affect the development and endocrine system across different life stages in Sprague Dawley (SD) rats.

Methods: Glyphosate alone and Roundup Bioflow, a commercial brand of GBHs, were administered in drinking water at 1.75 mg/kg bw/day to F0 dams starting from the gestational day (GD) 6 (in utero) up to postnatal day (PND) 120. After weaning, offspring were randomly distributed in two cohorts: 8 M + 8F/group animals belonging

"The present pilot study demonstrate that GBHs exposure, from prenatal period to adulthood, induced endocrine effects and altered reproductive developmental parameters in male and female SD rats. In particular, it was associated with androgen-like effects, including a statistically significant increase of AGDs in both males and females, delay of FE and increased testosterone in female. Hormonal status imbalances were more pronounced in Roundup-treated rats after prolonged exposure."

Accepted Manuscript

Title: Phthalates impact human health: Epidemiological evidences and plausible mechanism of action

Authors: Sailas Benjamin, Eiji Masai, Naofumi Kamimura, Kenji Takahashi, Robin C. Anderson, Panichikkal Abdul Faisal

PII: S0304-3894(17)30457-0
DOI: http://dx.doi.org/doi:10.1016/j.jhazmat.2017.06.036
Reference: HAZMAT 18657

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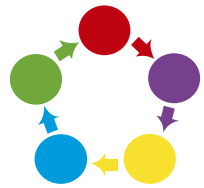
Revised date: 8-1-2017

"Thus, it sirens that the combined effect of various EDCs impacting human health would remain as an ever burning 'health burden' to all the nations, as if an immersed Himalayan iceberg in the ocean, unless and until we melt it down completely with conscious effort and coordinated determination."

ENDOCRINE DISRUPTORS AND INSULIN RESISTANCE



PERSPECTIVES IN DIABETES

The Paradox of Progress: Environmental Disruption of Metabolism and the Diabetes Epidemic

Brian A. Neel[1] and Robert M. Sargis[2]

As the tide of chemicals born of the Industrial Age has arisen to engulf our environment, a drastic change has come about in the nature of the most serious public health problems.

Rachel Carson, *Silent Spring*, 1962

Worldwide rates of diabetes and other metabolic diseases have exploded over the last several decades. Globally, more than 170 million individuals currently suffer from diabetes, and this number is projected to reach a staggering 366 million by 2030 (1). This scourge results in significant individual morbidity and mortality while contributing to the economic fragility of healthcare systems across the globe. In the U.S. alone, annual costs associated with diabetes are estimated to be $174 billion (2). As such, every effort must be made to understand the factors underlying this emerging metabolic disaster in order to mitigate its deleterious impact on the individual and society. Recently, an expanding body of scientific evidence has begun to

disrupting chemical (EDC) as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis, reproduction, development, and/or behavior" (4). Putative EDCs include structurally diverse chemicals including organic pollutants, heavy metals, pharmaceuticals, and phytochemicals, with humans exposed through agricultural goods and consumer products, as well as water and air contaminated with industrial waste (Fig. 1). Early studies of EDCs focused on identifying chemicals with the capacity to modulate sex steroid and thyroid hormone signaling; however, recent work suggests that some chemicals may disturb signaling pathways critical for energy homeostasis (5). Despite the potential importance of EDCs in the pathogenesis of metabolic diseases, the contribution of synthetic chemical exposure to the diabetes epidemic remains largely unrecognized and underappreciated even though U.S. diabetes rates have increased in concordance with the national production of synthetic organic chemicals (Fig. 2). While such correlations are crude, emerging data supports a biologically plausible causative link between diabetes and chemical exposure. Here, we present data suggesting a role for some synthetic chemicals in the pathogenesis of diabetes that merits comprehensive efforts to address the contribution of environmental pollutants to this burgeoning metabolic catastrophe.

mental evidence demonstrating that certain environmental pollutants induce adipogenesis and weight gain in experimental models, led to the environmental obesogen hypothesis that posits a causative role for synthetic chemicals in the pathogenesis of obesity (rev. in 8).

While environmental obesogens have rightfully received much discussion, it is important to recognize that obesity per se may not lead to abnormalities in glucose homeostasis. An important distinction in obesity research is the differentiation between metabolically deleterious obesity

"This paradox of progress now mandates a reassessment of how our consumption habits negatively impact our metabolic health in order to devise effective strategies to limit the significant individual and societal toll of diabetes."

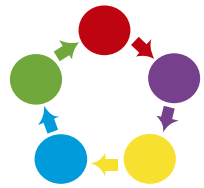


TABLE 1
Epidemiological data linking EDC exposure to diabetes

Reference	EDC	Population	Association with diabetes	
Morgan et al., Arch Environ Contam Toxicol 1980;9:349–382	Pesticides	2,620 pesticide exposed workers from 1971–1977	Cause-of-death questionnaires addressed to survivors indicated possible association between DDT exposure and diabetes	
Lai et al., Am J Epidemiol 1994;139:484–492	Arsenic	891 Taiwanese residents exposed to arsenic in 1988	Abnormal OGTT, medical histories of diagnosed diabetes, and use of diabetes treatments significantly associated with arsenic exposure	Dose-response relationship between arsenic exposure and diabetes prevalence
Henriksen et al., Epidemiology 1997;8:252–258	TCDD	989 Air Force veterans of Operation Ranch Hand exposed to TCDD	Glucose abnormalities, diabetes diagnosis, and use of diabetic medications associated with TCDD exposure	Significant hyperinsulinemia in exposed nondiabetic subjects
Pesatori et al., Occup Environ Med 1998;55:126–131	TCDD	Large Italian cohort (>230,000) localized in the exposure zones of the 1976 Seveso accident	Mortality study using Poisson regression to assess relative risk determined substantial TCDD exposure correlated to increased diabetes mortality in women	
Vena et al., Environ Health Perspect 1998;106:645–653	TCDD, HCD	International study of 36 cohorts from 12 countries (1939–1992) (>25,000)	Job record data and company questionnaires with biological and environmental measurements suggested possible correlation of TCDD exposure with diabetes	Strongest association found when first exposure was 10–19 years previous to assessment and with duration of exposure of 10–19 years
Calvert et al., Occup Environ Med 1999;56:270–276	TCDD	281 former workers at two U.S. chemical plants	Cross-sectional study significantly associated individuals with the highest serum lipid–adjusted TCDD concentrations with higher serum glucose levels	
Cranmer et al., Toxicol Sci 2000;56:431–436	TCDD	69 individuals in Jacksonville, AR, living within 25 miles of the Vertac waste site	Higher fasting plasma insulin levels associated with individuals in the top 10% of TCDD concentrations (>15 ppt)	No associations with TCDD and glucose levels, obesity, or total lipids
Bertazzi et al., Am J Epidemiol 2001;153:1031–1044	TCDD	15-year follow-up to the 1976 Seveso accident	Mortality study associated an increase in reported diabetes with TCDD exposure in women	
Beard et al., Environ Health Perspect 2001;111:724–730	Pesticides	1999 Australian pesticide sprayers employed from 1935–1996	Mortality study and surviving morbidity questionnaire determined increased mortality due to diabetes associated with pesticide exposure	Diabetes more commonly self-reported with occupational herbicide use
Fierens et al., Biomarkers 2003;8:529–534	17 PCDD/Fs, dioxins, 4 PCBs, 12 PCB markers	257 environmentally exposed Belgians	Quantification of serum fat from a population-based study determined significantly increased levels of dioxins, PCBs, and PCB markers in diabetic patients	Diabetes risk significantly increased for individuals in the top decile of dioxin concentrations
Glynn et al., Environ Health Perspect 2003;111:349–355	7 PCBs, 5 OC pesticides	205 Swedish women	Association study of lifestyle/medical factors and serum PCB levels indicated increased prevalence of diabetes with higher serum PCB concentrations	Serum PCB concentrations also associated with age, body, BMI, diet, and location of residence

Continued on facing page

The Paradox of Progress: Environmental Disruption of Metabolism and the Diabetes Epidemic

Brian A. Neel[1] and Robert M. Sargis[2]

The Paradox of Progress: Environmental Disruption of Metabolism and the Diabetes Epidemic

Brian A. Neel[1] and Robert M. Sargis[2]

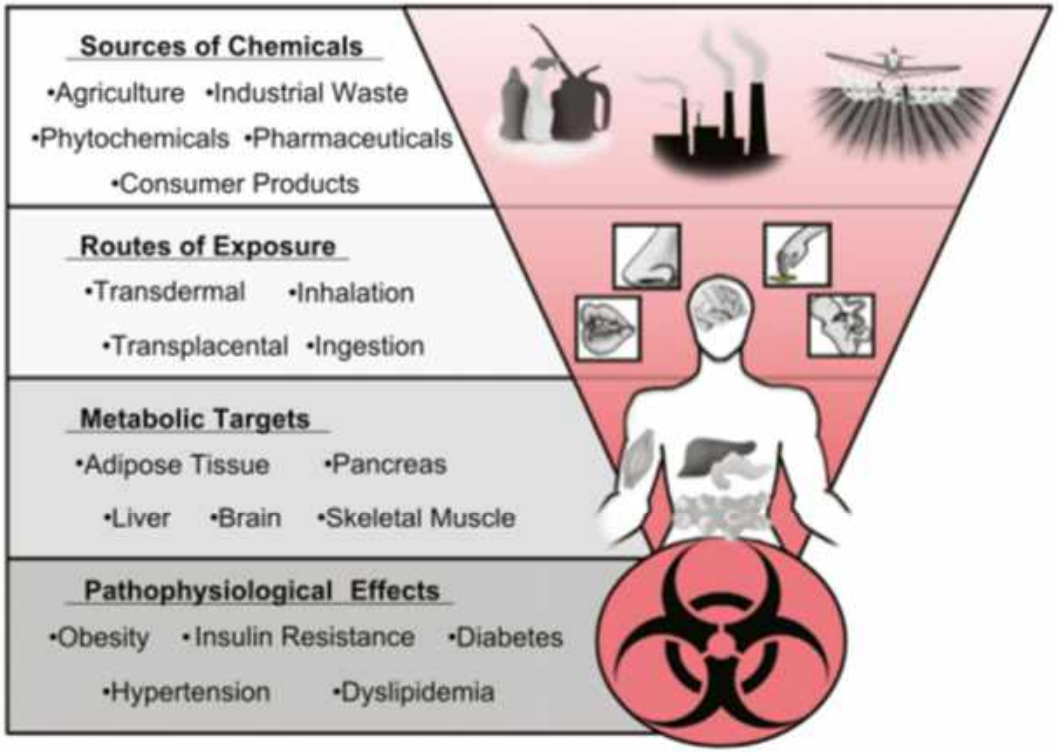


FIG. 1. Sources and targets of metabolic disruptors.

Review

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1205502.

Evaluation of the Association between Persistent Organic Pollutants (POPs) and Diabetes in Epidemiological Studies: A National Toxicology Program Workshop Review

Kyla W. Taylor,[1] Raymond F. Novak,[2] Henry A. Anderson,[3] Linda S. Birnbaum,[4] Chad Blystone,[5] Michael DeVito,[5] David Jacobs,[6] Josef Köhrle,[7] Duk-Hee Lee,[8] Lars Rylander,[9] Anna Rignell-Hydbom,[9] Rogelio Tornero-Velez,[10] Mary E. Turyk,[11] Abee L. Boyles,[1] Kristina A. Thayer,[1] and Lars Lind[12]

[1]Office of Health Assessment and Translation, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; [2]Shriners Hospitals for Children International, Tampa, Florida, USA; [3]Wisconsin Division of Public Health, Bureau of Environmental Health, Madison, Wisconsin, USA; [4]National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; [5]Toxicology Branch, Division of National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; [6]Division of Epidemiology & Community Health, University of Minnesota School of Public Health, Minneapolis, Minnesota, USA; [7]Institute of Experimental Endocrinology, Charité Universitätsmedizin, Humboldt University, Berlin, Germany; [8]Department of Preventative Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea; [9]Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden; [10]National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [11]Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois-Chicago, Chicago, Illinois, USA; [12]Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Background: Diabetes is a major threat to public health in the United States and worldwide. Understanding the role of environmental chemicals in the development or progression of diabetes is an emerging issue in environmental health.

Objective: We assessed the epidemiologic literature for evidence of associations between persistent organic pollutants (POPs) and type 2 diabetes.

Methods: Using a PubMed search and reference lists from relevant studies or review articles, we identified 72 epidemiological studies that investigated associations of persistent organic pollutants (POPs) with diabetes. We evaluated these studies for consistency, strengths and weaknesses of study design (including power and statistical methods), clinical diagnosis, exposure assessment, study population characteristics, and identification of data gaps and areas for future research.

Conclusions: Heterogeneity of the studies precluded conducting a meta-analysis, but the overall evidence is sufficient for a positive association of some organochlorine POPs with type 2 diabetes. Collectively, these data are not sufficient to establish causality. Initial data mining revealed that the strongest positive correlation of diabetes with POPs occurred with organochlorine compounds, such as *trans*-nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), and dioxins and dioxin-like chemicals. There is less indication of an association between other nonorganochlorine POPs, such as perfluoroalkyl acids and brominated compounds, and type 2 diabetes. Experimental data are needed to confirm the causality of these POPs, which will shed new light on the pathogenesis of diabetes. This new information should be considered by governmental bodies involved in the regulation of environmental contaminants.

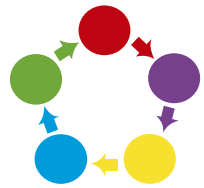
Key words: chemically induced, diabetes, environment, epidemiology, glucose, hormone, insulin, metabolic syndrome, obesity, persistent organic pollutants, pollution, toxicology.

Environ Health Perspect 121:774–783 (2013). http://dx.doi.org/10.1289/ehp.1205502 [Online 7 May 2013]

Diabetes Association 2011; Knowler et al. 2002). Recently, T2D is being diagnosed in individuals earlier in life, including adolescents (NIDDK 2011). Given the number of people impacted by the disease, an estimated 346 million people worldwide (WHO 2011), and the long-term consequences of diabetes in terms of morbidity, mortality, and economic costs, there is considerable interest in understanding the contribution of "nontraditional" risk factors, such as environmental chemicals, to the diabetes epidemic. Environmental exposures that have been linked to diabetes in at least some study populations include persistent organic pollutants (POPs), arsenic, bisphenol A, phthlatates, organotins, nonpersistent pesticides (Thayer et al. 2012), and air pollution (Coogan et al. 2012; Hathout et al. 2006; Krämer et al. 2010; O'Neill et al. 2007; Pearson et al. 2010).

Over the past several years, research addressing the role of environmental chemicals

Address correspondence to K.W. Taylor, National Toxicology Program, P.O. Box 12233, MD K2–04,



in T2D has rapidly expanded. The February 2011 Diabetes Strategic Plan (NIDDK 2011) acknowledged the growing science base in this area and cited the need to understand more about the role of environmental exposures as part of future research and prevention strategies. To help develop such a research strategy, the National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences (NIEHS) organized a state-of-the-science workshop in January 2011 titled "Role of Environmental Chemicals in the Development of Diabetes and Obesity" (NTP 2011). The objective of this workshop was to examine the literature for evidence of associations between certain chemicals and obesity or diabetes. Epidemiological studies of associations between diabetes and POPs, particularly the halogenated POPs, were considered at the workshop, along with studies of diabetes in association with arsenic, maternal smoking during pregnancy, bisphenol A, phthalates, organotins, and non-persistent pesticides (Thayer et al. 2012). A wide variety of chemicals were included in the POPs category, including organochlorines [2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), Agent Orange, other non-TCDD polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), and dichlorodiphenyldichloroethane (DDD)]; brominated compounds [polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs)]; and perfluorinated compounds [perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate, and perfluorononanoic acid].

For the present review we evaluated the literature in terms of consistency, strengths and weaknesses (including power and statistical methods) of the clinical diagnosis, exposure assessment, and study population characteristics in order to identify data gaps and areas for future evaluation and research in the area of POPs exposure and diabetes outcomes.

Methods

Literature search. We developed a PubMed (http://www.ncbi.nlm.nih.gov/pubmed) Medical Subject Headings (MeSH)-based and keyword search–based strategy to identify epidemiological studies of POPs exposure (organochlorine, organofluorine, and organobromine compounds) and health outcomes related to T1D, T2D, and childhood obesity [for detailed information on the literature search strategy, see Supplemental Material, pp. 2–3 (http://dx.doi.org/10.1289/ehp.1205502)]. We conducted an initial search on 24 August 2009 and subsequently updated the search through 15 December 2010. Studies of POPs and T2D or diabetes-related outcomes (e.g., metabolic syndrome) in both adults and children were eligible for review. We excluded studies from consideration if they were occupational studies, used death certificates to identify T2D, or did not present original data. Because of time constraints, we formally assessed only studies with T2D as the outcome, excluding studies with metabolic syndrome as the outcome. Our search identified 2,752 publications (after removal of duplicates), 72 of which presented original data on diabetes-related studies (see Supplemental Material, Figure S1). We excluded 28 studies from consideration because the health outcome was not T2D or because the method used to measure exposure or classify T2D was not adequate (see Supplemental Table S1). We considered blood or target tissue levels the most informative exposure measures; however, this information was not always available (e.g., studies of Vietnam veterans). Studies on Vietnam veterans were excluded if they were not specific enough to imply exposure to Agent Orange or TCDD; for example, studies comparing veterans who were in Vietnam with those who were not in Vietnam were excluded because they did not specify exposed versus unexposed veterans. We did not consider occupational studies because exposure may be more targeted depending on the occupation, nor did we consider a study by Anderson-Mahoney et al. (2008) because the population studied comprised plaintiffs involved in a lawsuit filed due to unusually high PFOA levels in drinking water. In addition, we chose to limit the introduction of potential biases that are unique to these studies, such as the healthy worker effect. We also excluded studies that used death certificates to identify diabetes cases because the prevalence of diabetes is underestimated from mortality data. For example, in a U.S.-based study that characterized the sensitivity and specificity of death certificates for diabetes (Cheng et al. 2008), diabetes was listed as a direct or contributing cause of death on only 6.2% of the death certificates for adults who were known to have diabetes.

We identified an additional 17 articles by reviewing the reference lists in the primary literature and review articles, for a total of 43 studies.

Data extraction. NTP Office of Health Assessment and Translation staff extracted the main findings from the included studies [see Supplemental Material, Table S2 (http://dx.doi.org/10.1289/ehp.1205502)]. The identification of the main findings was based on the following strategy:

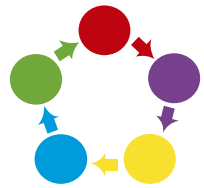
- When a study did not report a statistically significant association (i.e., $p > 0.05$) between POPs exposure and T2D at any exposure level, we extracted the main finding from the highest exposure group compared with the referent group (e.g., fourth quartile vs. first quartile).
- When a study reported a statistically significant association (i.e., $p \leq 0.05$) between POPs exposure and T2D and that association displayed a monotonic dose response, we extracted the main finding based on the lowest exposure group with a statistically significant association (e.g., third quartile vs. first quartile).
- When associations were nonmonotonic in nature, we identified the main findings on a case-by-case basis and considered any statistical trend analyses that might have been conducted, consistency of the overall pattern across exposure groups, and/or the biological significance of the nonmonotonic finding.

POPs represent a toxicologically diverse range of chemicals, all of which are persistent in the body (i.e., have a long half-life) and the environment. Chemicals are broadly divided into categories based on the halogen group (e.g., chlorinated, fluorinated, brominated). Chemicals in the chlorinated group were further divided into common chemical class designations (i.e., dioxins, PCBs, DDT/DDE/DDD). In assessing the PCB studies, we evaluated both total PCBs and PCB153 together because PCB153 is a major contributor to total PCB exposure and is used as an indicator PCB. PCB153 is often used as a surrogate measure for total PCBs because it is less expensive to measure (Cote et al. 2006; Meeker and Hauser 2010). Assessing patterns of association for individual PCBs across studies is particularly challenging because the class contains 209 structures that are not easy to categorize on the basis of structural similarity and/or biological activity. Even the categorization of "dioxin-like" or "nondioxin-like" is not sufficient because both categories of PCBs are linked to diabetes (Glesy and Kannan 1998; Lee et al. 2006, 2010, 2011a). In general, the findings for individual PCB congeners other than PCB153 are less suggestive for an overall association [see Supplemental Material, Figure S2 (http://dx.doi.org/10.1289/ehp.1205502)] (Codru et al. 2007; Everett et al. 2007; Lee et al. 2010; Patel et al. 2010; Turyk et al. 2009a).

Study quality. We categorized studies into groups on the basis of study design and nature of the exposure: *a*) cohort studies with a prospective or nested case–control design, *b*) cross-sectional studies, *c*) case–control studies, *d*) occupational studies, *e*) ecological studies, *f*) studies of maternal exposure, and *g*) studies of Vietnam veterans.

We included a study for consideration if it identified T2D as the outcome and the exposure measure was deemed adequate. Study quality was evaluated by panel members during workshop deliberations. Aspects of study

…the overall evidence is sufficient for a positive association of some …POPs with type 2 diabetes.



Obes Rev. 2013 Sep 2. doi: 10.1111/obr.12086. [Epub ahead of print]

Persistent organic pollutants meet adipose tissue hypoxia: does cross-talk contribute to inflammation during obesity?

Myre M, Imbeault P.

Behavioral and Metabolic Research Unit, School of Human Kinetics, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada.

Abstract

Lipophilic persistent organic pollutants (POPs) accumulate in lipid-rich tissues such as human adipose tissue. This is particularly problematic in individuals with excess adiposity, a physiological state that may be additionally characterized by local adipose tissue hypoxia. Hypoxic patches occur when oxygen diffusion is insufficient to reach all hypertrophic adipocytes. POPs and hypoxia independently contribute to the development of adipose tissue-specific and systemic inflammation often associated with obesity. Inflammation is induced by increased proinflammatory mediators such as tumour necrosis factor-alpha, interleukin-6, and monocyte chemotactic protein-1, as well as reduced adiponectin release, an anti-inflammatory and insulin-sensitizing adipokine. The aryl hydrocarbon receptor (AhR) mediates the cellular response to some pollutants, while hypoxia responses occur through the oxygen-

"POPs and hypoxia independently contribute to the development of adipose tissue-specific and systemic inflammation often associated with obesity".

Environ Res. 2015 Jan 23;137C:419-423. doi: 10.1016/j.envres.2015.01.010. [Epub ahead of print]

Urinary phthalate metabolites are associated with insulin resistance in obese subjects.

Dirinck E[1], Dirtu AC[2], Geens T[2], Covaci A[2], Van Gaal L[3], Jorens PG[4].

Author information

Abstract

Phthalates are potentially involved in the development of type 2 diabetes mellitus. In a cohort of 123 obese subjects, 10 phthalate metabolites were analyzed. An oral glucose tolerance test was performed and various estimates of insulin resistance and beta-cell function were calculated. After adjustment for age, physical activity level, smoking behavior, medication use and body mass index, several phthalate metabolites were linked to markers of glucose tolerance and insulin resistance.

Environ Health Perspect. 2013 Aug;121(8):906-11. doi: 10.1289/ehp.1206113. Epub 2013 May 13.

Diabetes, metabolic syndrome, and obesity in relation to serum dioxin concentrations: the Seveso women's health study.

Warner M, Mocarelli P, Brambilla P, Wesselink A, Samuels S, Signorini S, Eskenazi B.

Center for Environmental Research and Children's Health, School of Public Health, University of California, Berkeley, Berkeley, CA 94720, USA. mwarner@berkeley.edu

Abstract

BACKGROUND: In animal studies, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters glucose transport and increases serum lipid levels and blood pressure. Epidemiologic evidence suggests an association between TCDD and metabolic disease.

OBJECTIVES: On 10 July 1976, a chemical explosion in Seveso, Italy, resulted in the highest known residential exposure to TCDD. Using data from the Seveso Women's Health Study (SWHS), a cohort study of the health of the women, we examined the relation of serum TCDD to diabetes, metabolic syndrome, and obesity > 30 years later.

METHODS: In 1996, we enrolled 981 women who were newborn to 40 years of age in 1976 and resided in the most contaminated areas. Individual TCDD concentration was measured in archived serum that had been collected soon after the explosion. In 2008, 833 women participated in a follow-up study. Diabetes was classified based on self-report or fasting serum glucose and glycated hemoglobin levels. Metabolic syndrome was defined by International Diabetes Federation criteria. Obesity was defined as body mass index ≥ 30 kg/m2.

RESULTS: A 10-fold increase in serum TCDD (log10TCDD) was not associated with diabetes (adjusted hazard ratio = 0.76; 95% CI: 0.45, 1.28) or obesity [adjusted odds ratio (OR) = 0.80; 95% CI: 0.58, 1.10]. Log10TCDD was associated with metabolic syndrome, but only among women who were ≤ 12 years of age at the time of the explosion (adjusted OR = 2.03; 95% CI: 1.25, 3.29; pinteraction = 0.01).

CONCLUSIONS: We found an increased prevalence of metabolic syndrome associated with TCDD, but only among women who were the youngest at the time of the explosion. Continued follow-up of the SWHS cohort will be informative.

Environ Health Perspect. 2016 Oct 7. [Epub ahead of print]

Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL6/J Diet-Induced Obesity Mouse Model.

Duval C[1,2], Teixeira-Clerc F[3,4], Leblanc AF[1,2], Touch S[5,6], Emond C[7], Guerre-Millo M[5,6], Lotersztajn S[3,4,8], Barouki R[1,2,9], Aggerbeck M[1,2], Coumoul X[1,2,10].

Author information

Abstract

BACKGROUND: Exposure to persistent organic pollutants (POPs) has been associated with the progression of chronic liver diseases, yet the contribution of POPs to the development of fibrosis in non-alcoholic fatty liver disease (NAFLD), a condition closely linked to obesity, remains poorly documented.

OBJECTIVES: We investigated the effects of subchronic exposure to low-doses of the POP 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), an aryl hydrocarbon receptor ligand, on NAFLD progression in diet-induced obese C57BL/6J mice.

METHODS: Male C57BL/6J mice were fed either a 10% low fat (LFD) or a 45% high fat (HFD) purified diet during 14 weeks and TCDD-exposure groups were injected once a week with 5 µg/kg TCDD or the vehicle for the last 6 weeks of the diet.

RESULTS: Liver histology and triglyceride levels showed that exposure of HFD fed mice to TCDD worsened hepatic steatosis, as compared to either HFD alone or LFD plus TCDD and the mRNA levels of key genes of hepatic lipid metabolism were strongly altered in co-treated mice. Further, increased liver collagen staining and serum transaminase levels showed that TCDD induced liver fibrosis in the HFD fed mice. TCDD in LFD fed mice increased the expression of several inflammation and fibrosis marker genes with no additional effect from a HFD.

CONCLUSIONS: Exposure to TCDD amplifies the impairment of liver functions observed in mice fed an enriched fat diet as compared to a low fat diet. The results provide new evidence that environmental pollutants promote the development of liver fibrosis in obesity-related NAFLD C57BL/6J in mice.

J Toxicol Environ Health A. 2013;76(12):701-15. doi: 10.1080/15287394.2013.796503.

Chronic Exposure to PCBs (Aroclor 1254) Exacerbates Obesity-Induced Insulin Resistance and Hyperinsulinemia in Mice.

Gray SL, Shaw AC, Gagne AX, Chan HM.

a Northern Medical Program, University of Northern British Columbia , Prince George , British Columbia , Canada.

Abstract

Evidence from recent epidemiological studies has emerged implicating exposure to environmental toxicants as a novel risk factor for the development of type 2 diabetes (T2D) and the metabolic syndrome in the general population. Humans and other organisms in high trophic levels of the food chain consume persistent organic pollutants (POP) through their diet. Few experimental studies demonstrating cause and effect are available and evidence for a direct association between accumulation of POP and T2D is preliminary; however, the possibility exists that lipophilic chemicals that accumulate in fatty tissue may disrupt cellular function and metabolic homeostasis. Chronic exposure of diabetes-prone C57B/6 mice to a polychlorinated biphenyl (PCB) mixture (Aroclor 1254,

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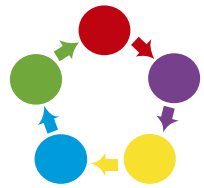
Our results demonstrate a causative association between PCB exposure and obesity-induced insulin resistance and hyperinsulinemia independent of body weight changes.



OPEN ACCESS Freely available online

PLOS ONE

Perinatal Exposure to Perfluorooctane Sulfonate Affects Glucose Metabolism in Adult Offspring

Hin T. Wan, Yin G. Zhao, Pik Y. Leung, Chris K. C. Wong*

Partner State Key Laboratory of Environmental and Biological Analysis, Croucher Institute for Environmental Sciences, Department of Biology, Hong Kong Baptist University, Hong Kong, People's Republic of China

Abstract

Perfluoroalkyl acids (PFAAs) are globally present in the environment and are widely distributed in human populations and wildlife. The chemicals are ubiquitous in human body fluids and have a long serum elimination half-life. The notorious member of PFAAs, perfluorooctane sulfonate (PFOS) is prioritized as a global concerning chemical at the Stockholm Convention in 2009, due to its harmful effects in mammals and aquatic organisms. PFOS is known to affect lipid metabolism in adults and was found to be able to cross human placenta. However the effects of *in utero* exposure to the susceptibility of metabolic disorders in offspring have not yet been elucidated. In this study, pregnant CD-1 mice (F_0) were fed with 0, 0.3 or 3 mg PFOS/kg body weight/day in corn oil by oral gavage daily throughout gestational and lactation periods. We investigated the immediate effects of perinatal exposure to PFOS on glucose metabolism in both maternal and offspring after weaning (PND 21). To determine if the perinatal exposure predisposes the risk for metabolic disorder to the offspring, weaned animals without further PFOS exposure, were fed with either standard or high-fat diet until PND 63. Fasting glucose and insulin levels were measured while HOMA-IR index and glucose AUCs were reported. Our data illustrated the first time the effects of the environmental equivalent dose of PFOS exposure on the disturbance of glucose metabolism in F_1 pups and F_1 adults at PND 21 and 63, respectively. Although the biological effects of PFOS on the elevated levels of fasting serum glucose and insulin levels were observed in both pups and adults of F_1, the phenotypes of insulin resistance and glucose intolerance were only evident in the F_1 adults. The effects were exacerbated under HFD, highlighting the synergistic action at postnatal growth on the development of metabolic disorders.

Citation: Wan HT, Zhao YG, Leung PY, Wong CKC (2014) Perinatal Exposure to Perfluorooctane Sulfonate Affects Glucose Metabolism in Adult Offspring. PLoS ONE 9(1): e87137. doi:10.1371/journal.pone.0087137

Eur Rev Med Pharmacol Sci. 2015 Jan;19(1):123-128.

Effect of environmental air pollution on type 2 diabetes mellitus.

Meo SA[1], Memon AN, Sheikh SA, Al Rouq F, Mahmood Usmani A, Hassan A, Arian SA.

Author information

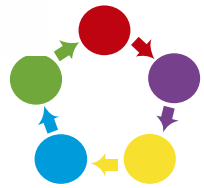
Abstract

OBJECTIVE: Air pollution is a novel risk factor for insulin resistance and occurrence of type 2 diabetes mellitus (T2DM), but the evidence is limited and diverse. Therefore, the aim of this study was to assess the effect of environmental air pollution on incidence of type 2 diabetes mellitus.

METHODS: In this study, we identified 102 published studies through a systematic data base search including ISI-Web of Science, EMBASE and PubMed. We searched the related literature by using the key terms including diabetes mellitus, air pollution, occupational and environmental pollution, gaseous, NO2, particulate matter pollutants PM2.5, and PM10. Studies in which diabetes mellitus, insulin resistance, air pollution, occupational and environmental pollution was discussed were included in the study. No confines on publication status, study design or language of publication were considered. Descriptive and quantitative information were extracted from the selected literature. Finally we included 21 publications and remaining studies were excluded.

RESULTS: Air pollution is a leading cause of insulin resistance and incidence of type 2 diabetes mellitus. The association between air pollution and diabetes is stronger for traffic associated pollutants, gaseous, nitrogen dioxide, tobacco smoke and particulate matter.

CONCLUSIONS: Exposure to air pollutants is significantly associated with increased risk of type 2 diabetes mellitus. It is suggested that, environmental protection officials must take high priority steps to minimize the air pollution, hence to decrease the incidence of type 2 diabetes mellitus.



HEAVY METALS AND INSULIN RESISTANCE

Low-level arsenic exposure reported to be associated with insulin resistance.

NAVAS-ACIEN A, SILBERGELD EK, PASTOR-BARRIUSO R, ET AL. ARSENIC EXPOSURE AND PREVALENCE OF TYPE 2 DIABETES IS US ADULTS. JAMA 2008; 300: 814-22

Yonsei Med J. 2015 Jul;56(4):944-50. doi: 10.3349/ymj.2015.56.4.944.

Blood Mercury and Insulin Resistance in Nondiabetic Koreans (KNHANES 2008-2010).

Kim KN[1], Park SJ[1], Choi B[2], Joo NS[3].

Author information

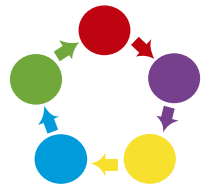
Abstract

PURPOSE: Blood mercury levels are associated with inflammation, and chronic low-grade inflammation is a cause of insulin resistance. This study aimed to investigate the association between serum mercury and insulin resistance.

MATERIALS AND METHODS: Subjects from the 2008-2010 Korean National Health and Nutrition Examination Survey were selected (n=29235) and the relevant data of 5388 subjects (2643 males and 2745 females) were analyzed cross-sectionally. Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was compared according to blood mercury quartiles, and the odds ratio (OR) of having the highest quartile of HOMA-IR according to blood mercury quartiles was calculated.

RESULTS: Blood mercury levels in men and women were 29.4 nmol/L and 20.5 nmol/L, respectively, and fasting blood sugar (FBS), insulin, and HOMA-IR were significantly correlated with blood mercury levels. The correlation was stronger in men than in women. In men, FBS and HOMA-IR showed step-wise increases as the quartiles of blood mercury increased; only HOMA-IR differed significantly in the third and fourth blood mercury quartiles, compared to the first quartile. In women, however, both FBS and HOMA-IR differed significantly in the third and fourth blood mercury quartiles, compared to the first quartile. Among men, the OR of being in the highest HOMA-IR quartile was greatest for the highest blood mercury quartile (OR=1.720, 95% CI; 1.172-2.526), compared with the lowest quartile.

CONCLUSION: In this large population-based study, blood mercury levels were weakly correlated with HOMA-IR and may be a risk factor for insulin resistance in nondiabetic Koreans.



Trends Endocrinol Metab. 2017 Aug;28(8):612-625. doi: 10.1016/j.tem.2017.05.001. Epub 2017 May 29.

Gut Microbiota, Endocrine-Disrupting Chemicals, and the Diabetes Epidemic.

Velmurugan G[1], Ramprasath T[2], Gilles M[3], Swaminathan K[4], Ramasamy S[5].

⊕ Author information

Abstract

Diabetes is rapidly emerging as one of the biggest health concerns worldwide, with profound implications for disability, mortality, and costs. This suddenly escalating rate of diabetes correlates with global industrialization and the production of plastics, pesticides, synthetic fertilizers, electronic waste, and food additives that release endocrine-disrupting chemicals (EDCs) into the environment and the food chain. Emerging evidence indicates an association between exposure of EDCs and diabetes. In humans, these chemicals are also metabolized by the gut microbiota and thereby their toxicodynamics are altered. In this review we highlight studies that focus on the role of gut microbiota in EDC-induced hyperglycemia and dysregulated glucose homeostasis. We also discuss the translational implications of understanding EDC-microbiota interactions for the diagnosis and treatment of diabetes.

On exposure to EDCs, the gut microbiota undergoes a series of changes including microbial dysbiosis and the induction of xenobiotic pathways and associated genes, enzymes, and metabolites that cause biotransformation of EDCs.

Trends Endocrinol Metab. 2017 Aug;28(8):612-625. doi: 10.1016/j.tem.2017.05.001. Epub 2017 May 29.

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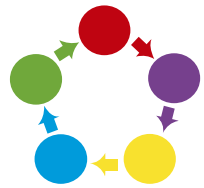
"The microbial products and byproducts of metabolism of EDCs are taken up by the host and affect glucose homeostasis, primarily by influencing hepatic gluconeogenesis."



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"Remediation of EDC-induced microbial changes may be a potent therapeutic option for the control and prevention of diabetes."

Environmental Science and Pollution Research
https://doi.org/10.1007/s11356-019-06663-0

FIFTY YEARS OF PCB RESEARCH: NEW APPROACHES AND DISCOVERIES AND STILL SO MUCH MORE TO LEARN

PCB126 blocks the thermogenic beiging response of adipocytes

Francoise A. Gourronc[1] · Gary H. Perdew[2] · Larry W. Robertson[3] · Aloysius J. Klingelhutz[1]

Received: 29 January 2019 / Accepted: 1 October 2019

Abstract
Subcutaneous white adipose tissue is capable of becoming thermogenic in a process that is referred to as "beiging." Beiging is associated with activation of the uncoupling protein, UCP1, and is known to be important for preventing adipose hypertrophy and development of insulin resistance. Polychlorinated biphenyls (PCBs) accumulate in fat, and it is hypothesized that disruption of adipogenesis and adipocyte function by PCBs may be causative in the development of obesity and diabetes. We developed immortal human subcutaneous preadipocytes that, when differentiated, are capable of beiging. Preadipocytes that were treated with polychlorinated biphenyl congener 126 (PCB126), followed by differentiation, were suppressed for their ability to activate UCP1 upon β-adrenergic stimulation with norepinephrine (NE), demonstrating a block in the beiging response. Treatment of preadipocytes with another known endogenous AhR agonist, indoxyl sulfate (IS), followed by differentiation also blocked the NE-stimulated upregulation of UCP1. Knockdown of the aryl hydrocarbon receptor (AhR) caused the preadipocytes to be refractory to PCB126 and IS effects. The chemical AhR antagonist, CH223191, was effective at preventing the effects of PCB126 but not IS, indicating AhR ligand specificity of CH223191. Repression of NE-induced UCP1 upregulation was also observed when already-differentiated mature adipocytes were treated with PCB126 but not IS. These results indicate that exposure of preadipocytes to endogenous (IS) or exogenous (PCB126) AhR agonists is effective at blocking them from becoming functional adipocytes that are capable of the beiging response. Mature adipocytes may have differential responses. This finding suggests a mechanism by which dioxin-like PCBs such as PCB126 could lead to disruption in energy homeostasis, potentially leading to obesity and diabetes.

Keywords PCB126 · Adipocytes · Indoxyl sulfate · Fat · AhR · Diabetes

Abbreviations
PCB126 polychlorinated biphenyl congener 126

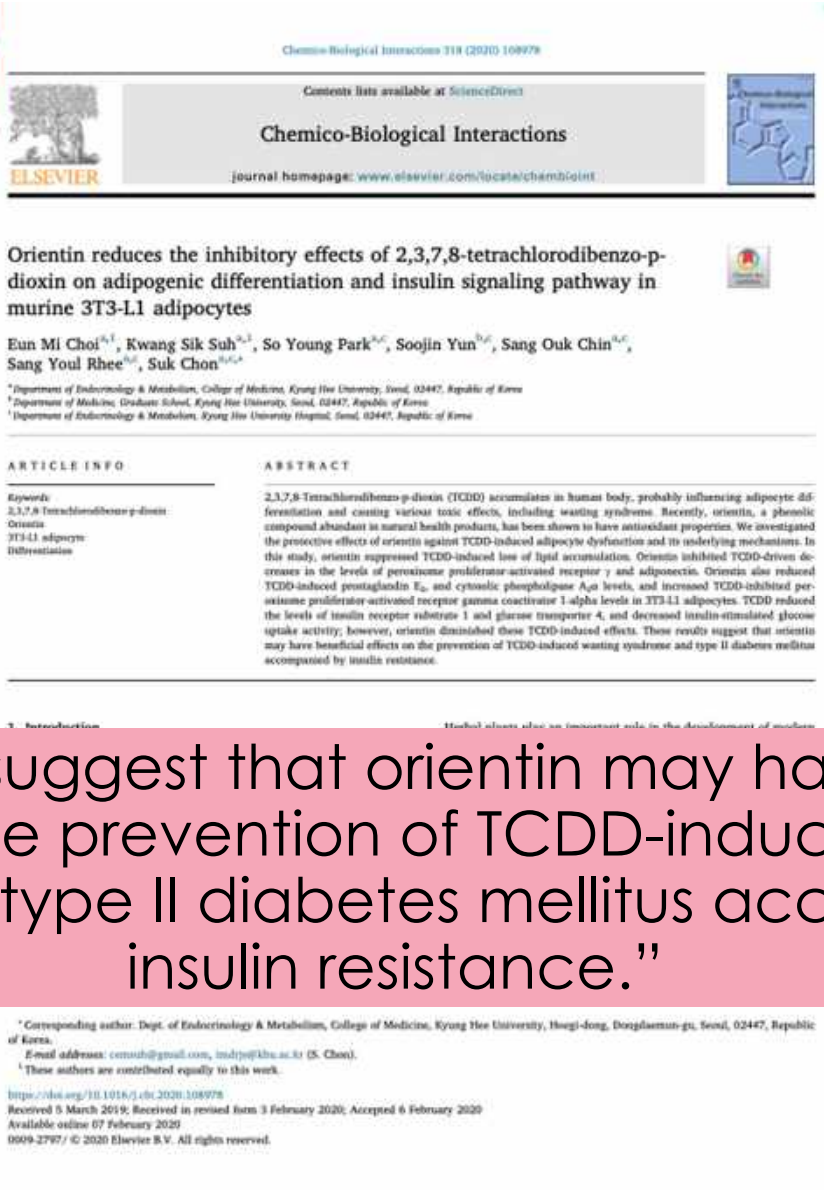
Introduction

State University, University Park 16802, PA, USA
[3] Department of Occupational & Environmental Health, College of Public Health, University of Iowa, Iowa City, IA 52242, USA

preadipocytes, which themselves originate from mesenchymal stem cells. Disruption of adipogenesis can result in stress

Published online: 12 November 2019

"This finding suggests a mechanism by which dioxin-like PCBs such as PCB126 could lead to disruption in energy homeostasis, potentially leading to obesity and diabetes."



Chemico-Biological Interactions 318 (2020) 108978

Contents lists available at ScienceDirect

Chemico-Biological Interactions

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

Orientin reduces the inhibitory effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on adipogenic differentiation and insulin signaling pathway in murine 3T3-L1 adipocytes

Eun Mi Choi[a,1], Kwang Sik Suh[a,1], So Young Park[a,c], Soojin Yun[b,c], Sang Ouk Chin[a,c], Sang Youl Rhee[b,c], Suk Chon[a,c,*]

[a] Department of Endocrinology & Metabolism, College of Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea
[b] Department of Medicine, Graduate School, Kyung Hee University, Seoul, 02447, Republic of Korea
[c] Department of Endocrinology & Metabolism, Kyung Hee University Hospital, Seoul, 02447, Republic of Korea

ARTICLE INFO

Keywords:
2,3,7,8-Tetrachlorodibenzo-p-dioxin
Orientin
3T3-L1 adipocyte
Differentiation

ABSTRACT

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) accumulates in human body, probably influencing adipocyte differentiation and causing various toxic effects, including wasting syndrome. Recently, orientin, a phenolic compound abundant in natural health products, has been shown to have antioxidant properties. We investigated the protective effects of orientin against TCDD-induced adipocyte dysfunction and its underlying mechanisms. In this study, orientin suppressed TCDD-induced loss of lipid accumulation. Orientin inhibited TCDD-driven decreases in the levels of peroxisome proliferator-activated receptor γ and adiponectin. Orientin also reduced TCDD-induced prostaglandin E_2, and cytosolic phospholipase $A_2\alpha$ levels, and increased TCDD-inhibited peroxisome proliferator-activated receptor gamma coactivator 1-alpha levels in 3T3-L1 adipocytes. TCDD reduced the levels of insulin receptor substrate 1 and glucose transporter 4, and decreased insulin-stimulated glucose uptake activity; however, orientin diminished these TCDD-induced effects. These results suggest that orientin may have beneficial effects on the prevention of TCDD-induced wasting syndrome and type II diabetes mellitus accompanied by insulin resistance.

* Corresponding author. Dept. of Endocrinology & Metabolism, College of Medicine, Kyung Hee University, Hoegi-dong, Dongdaemun-gu, Seoul, 02447, Republic of Korea.
E-mail addresses: [illegible] (S. Chon).
[1] These authors are contributed equally to this work.

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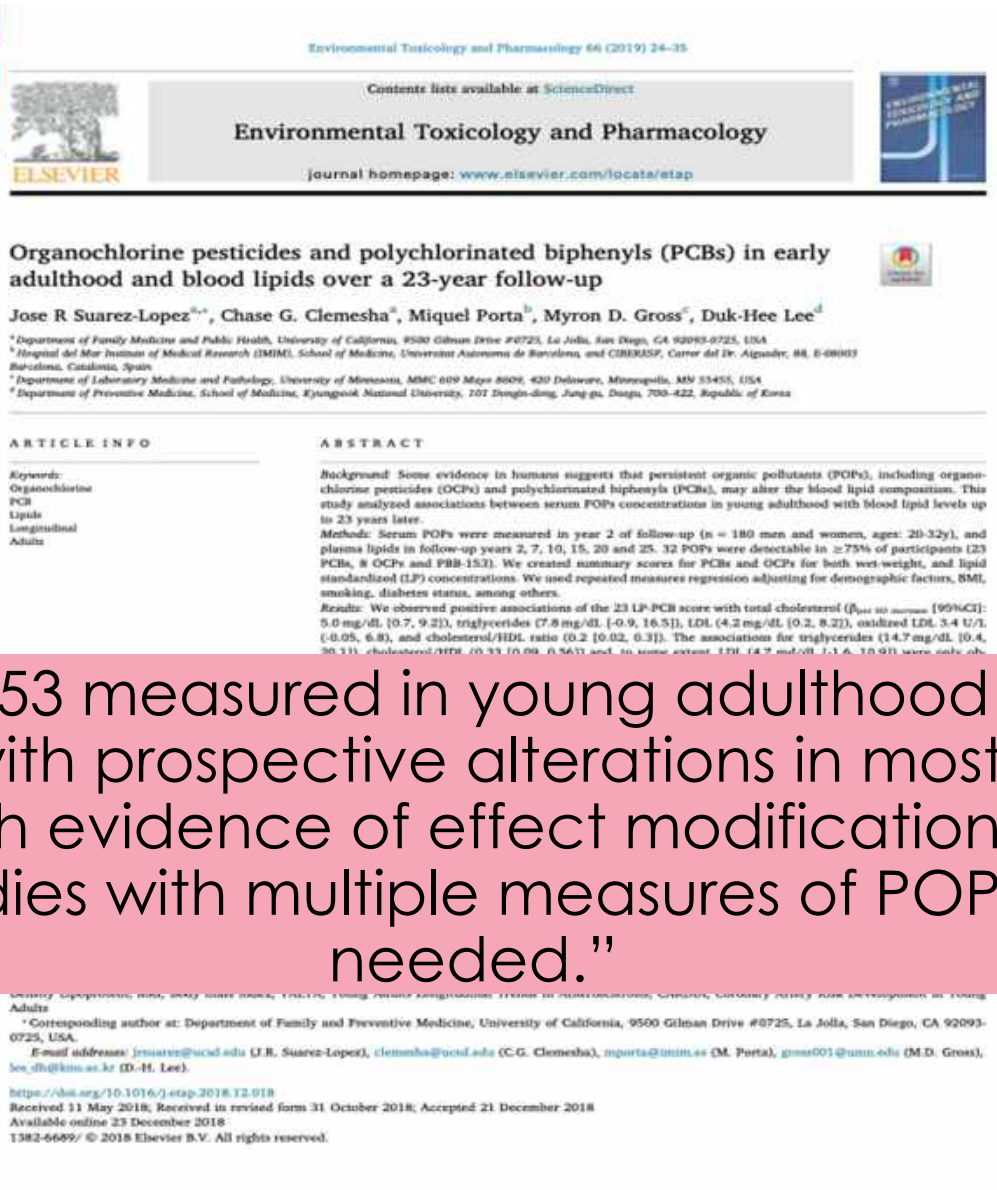
Received 5 March 2019; Received in revised form 3 February 2020; Accepted 6 February 2020
Available online 07 February 2020

"These results suggest that orientin may have beneficial effects on the prevention of TCDD-induced wasting syndrome and type II diabetes mellitus accompanied by insulin resistance."



Environmental Toxicology and Pharmacology 66 (2019) 24–35

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

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

Organochlorine pesticides and polychlorinated biphenyls (PCBs) in early adulthood and blood lipids over a 23-year follow-up

Jose R Suarez-Lopez[a,*], Chase G. Clemesha[a], Miquel Porta[b], Myron D. Gross[c], Duk-Hee Lee[d]

[a] Department of Family Medicine and Public Health, University of California, 9500 Gilman Drive #0725, La Jolla, San Diego, CA 92093-0725, USA
[b] Hospital del Mar Institute of Medical Research (IMIM), School of Medicine, Universitat Autonoma de Barcelona, and CIBERESP, Carrer del Dr. Aiguader, 88, E-08003 Barcelona, Catalonia, Spain
[c] Department of Laboratory Medicine and Pathology, University of Minnesota, MMC 609 Mayo 8609, 420 Delaware, Minneapolis, MN 55455, USA
[d] Department of Preventive Medicine, School of Medicine, Kyungpook National University, 101 Dongin-dong, Jung-gu, Daegu, 700-422, Republic of Korea

ARTICLE INFO

Keywords:
Organochlorine
PCB
Lipids
Longitudinal
Adults

ABSTRACT

Background: Some evidence in humans suggests that persistent organic pollutants (POPs), including organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), may alter the blood lipid composition. This study analyzed associations between serum POPs concentrations in young adulthood with blood lipid levels up to 23 years later.

Methods: Serum POPs were measured in year 2 of follow-up (n = 180 men and women, ages: 20-32y), and plasma lipids in follow-up years 2, 7, 10, 15, 20 and 25. 32 POPs were detectable in ≥75% of participants (23 PCBs, 8 OCPs and PBB-153). We created summary scores for PCBs and OCPs for both wet-weight, and lipid standardized (LP) concentrations. We used repeated measures regression adjusting for demographic factors, BMI, smoking, diabetes status, among others.

Results: We observed positive associations of the 23 LP-PCB score with total cholesterol ($\beta_{per\ SD\ increase}$ [95%CI]: 5.0 mg/dL [0.7, 9.2]), triglycerides (7.8 mg/dL [-0.9, 16.5]), LDL (4.2 mg/dL [0.2, 8.2]), oxidized LDL 3.4 U/L (-0.05, 6.8), and cholesterol/HDL ratio (0.2 [0.02, 0.3]). The associations for triglycerides (14.7 mg/dL [0.4, 29.1]), cholesterol/HDL (0.33 [0.09, 0.56]) and, to some extent, LDL (4.2 mg/dL [-1.6, 10.0]) were only ob-

"PCBs and PBB-153 measured in young adulthood were positively associated with prospective alterations in most blood lipid components, with evidence of effect modification by BMI. Further longitudinal studies with multiple measures of POPs overtime are needed."

Adults

* Corresponding author at: Department of Family and Preventive Medicine, University of California, 9500 Gilman Drive #0725, La Jolla, San Diego, CA 92093-0725, USA.
E-mail addresses: jrsuarez@ucsd.edu (J.R. Suarez-Lopez), clemesha@ucsd.edu (C.G. Clemesha), mporta@imim.es (M. Porta), grosz001@umn.edu (M.D. Gross), lee_dh@knu.ac.kr (D.-H. Lee).

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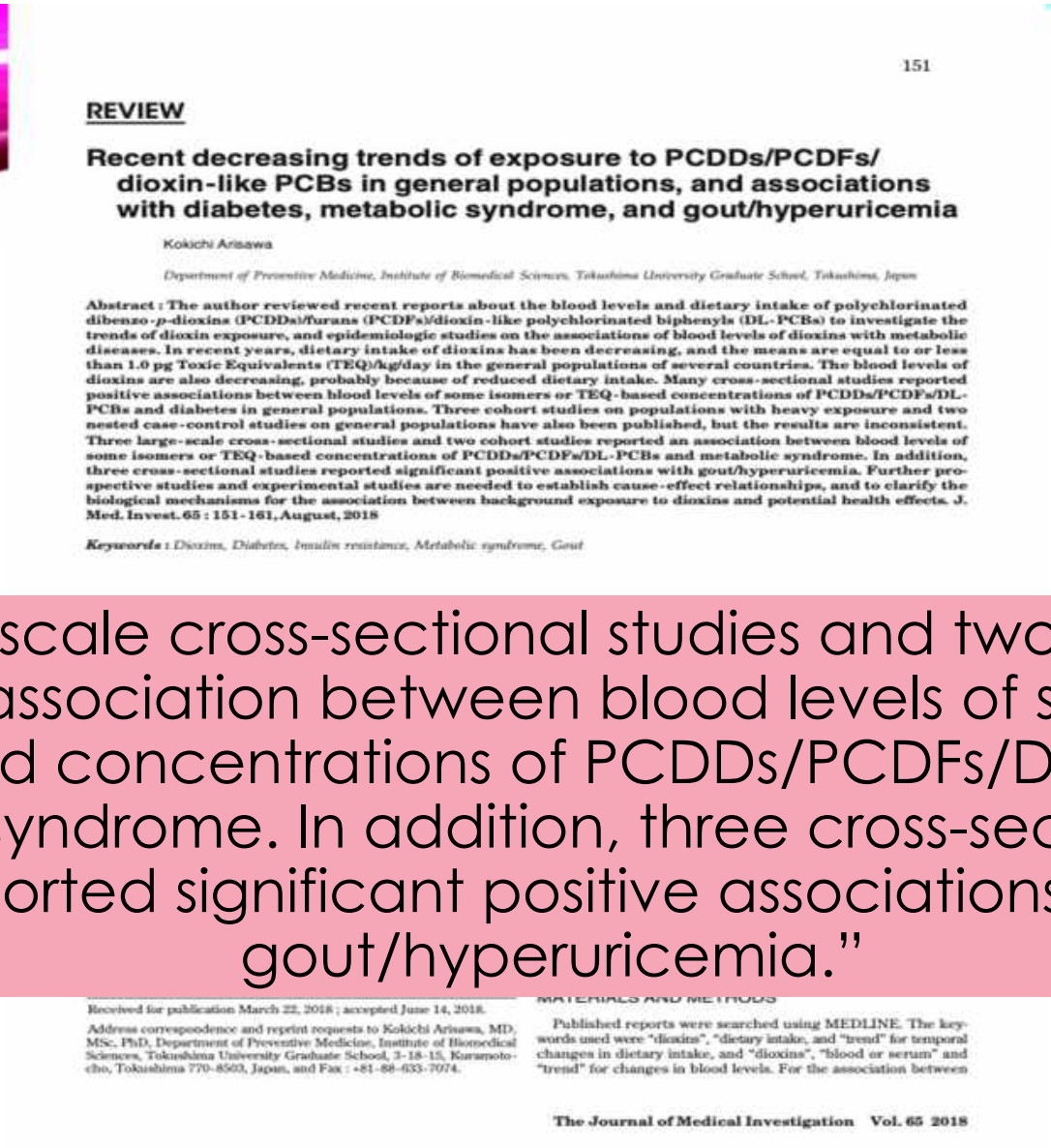

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REVIEW

Recent decreasing trends of exposure to PCDDs/PCDFs/ dioxin-like PCBs in general populations, and associations with diabetes, metabolic syndrome, and gout/hyperuricemia

Kokichi Arisawa

Department of Preventive Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan

Abstract : The author reviewed recent reports about the blood levels and dietary intake of polychlorinated dibenzo-*p*-dioxins (PCDDs)/furans (PCDFs)/dioxin-like polychlorinated biphenyls (DL-PCBs) to investigate the trends of dioxin exposure, and epidemiologic studies on the associations of blood levels of dioxins with metabolic diseases. In recent years, dietary intake of dioxins has been decreasing, and the means are equal to or less than 1.0 pg Toxic Equivalents (TEQ)/kg/day in the general populations of several countries. The blood levels of dioxins are also decreasing, probably because of reduced dietary intake. Many cross-sectional studies reported positive associations between blood levels of some isomers or TEQ-based concentrations of PCDDs/PCDFs/DL-PCBs and diabetes in general populations. Three cohort studies on populations with heavy exposure and two nested case-control studies on general populations have also been published, but the results are inconsistent. Three large-scale cross-sectional studies and two cohort studies reported an association between blood levels of some isomers or TEQ-based concentrations of PCDDs/PCDFs/DL-PCBs and metabolic syndrome. In addition, three cross-sectional studies reported significant positive associations with gout/hyperuricemia. Further prospective studies and experimental studies are needed to establish cause-effect relationships, and to clarify the biological mechanisms for the association between background exposure to dioxins and potential health effects. J. Med. Invest. 65 : 151-161, August, 2018

Keywords *: Dioxins, Diabetes, Insulin resistance, Metabolic syndrome, Gout*

"Three large-scale cross-sectional studies and two cohort studies reported an association between blood levels of some isomers or TEQ-based concentrations of PCDDs/PCDFs/DL-PCBs and metabolic syndrome. In addition, three cross-sectional studies reported significant positive associations with gout/hyperuricemia."

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Address correspondence and reprint requests to Kokichi Arisawa, MD, MSc, PhD, Department of Preventive Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan, and Fax : +81-88-633-7074.

MATERIALS AND METHODS

Published reports were searched using MEDLINE. The keywords used were "dioxins", "dietary intake, and "trend" for temporal changes in dietary intake, and "dioxins", "blood or serum" and "trend" for changes in blood levels. For the association between

Diabetes, Cardiovascular Disorders and 2,3,7,8-Tetrachlorodibenzo-p-Dioxin Body Burden in Czech Patients 50 Years After the Intoxication

Tomas Pelcl [1], Jan Skrha Jr [1], Martin Prazny [1], Stepanka Vlckova [2], Zdenka Fenclova [2], Tomas Navratil [3], Jan Malik [1], Pavel Diblik [4], Vit Zikan [1], Daniela Pelclova [2]

Affiliations + expand

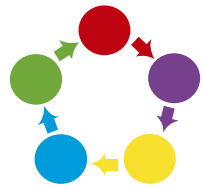
PMID: 29569337 DOI: 10.1111/bcpt.13013

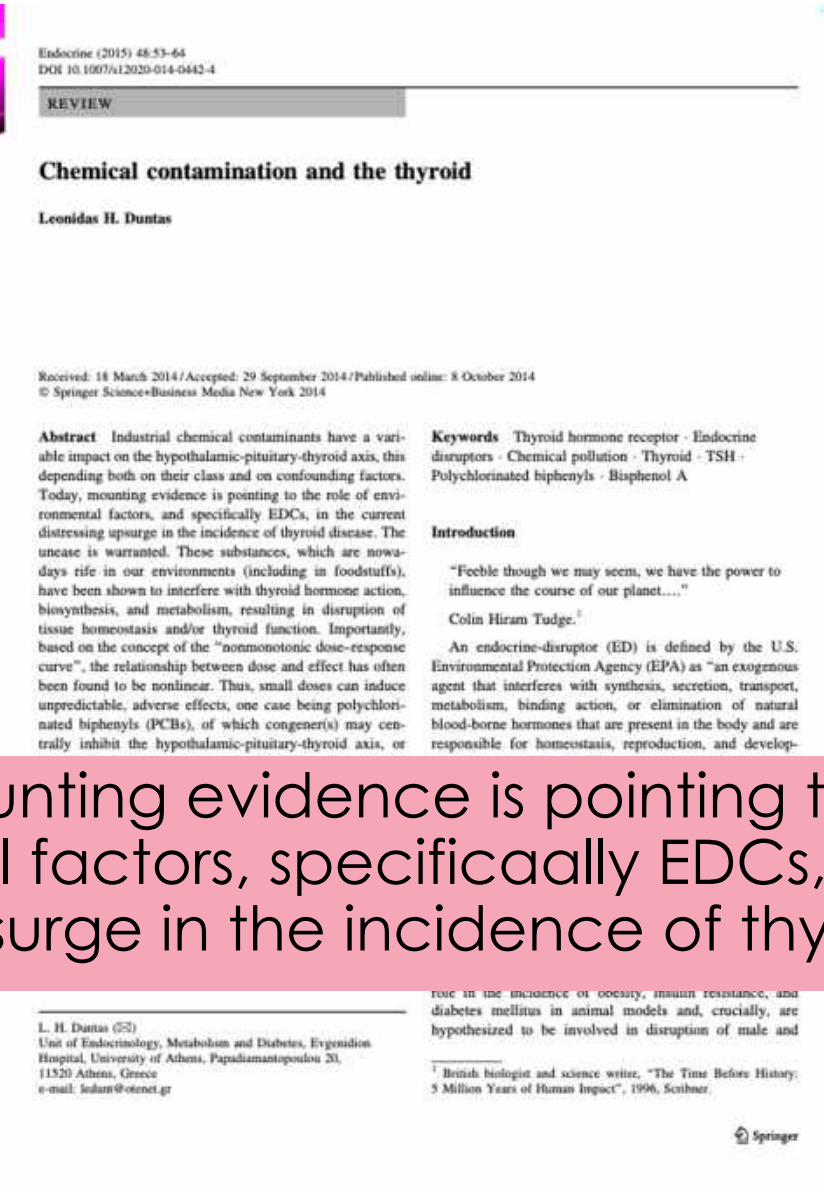
Abstract

The correlation between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication and the parameters of metabolic impairment was examined in the last eight male survivors of 80 workers exposed to TCDD during the production of herbicides in a chemical factory in 1965-1967. Their median TCDD blood level was 112 (46-390) pg/g lipids, and the median TCDD body deposit was 3.9 (0.8-11.7) µg. This puts these patients into the most severely intoxicated group of subjects, according to back-calculated levels of TCDD. The median TCDD blood level in eight controls was 12 pg/g (<0.10 to 22.2 pg/g). Markers of metabolic impairment - diabetes, dyslipidaemia, arterial hypertension, carotid artery plaque, skin microvascular hypertension angiopathy (50% versus 14%). All eight patients (100% versus 43%) developed plaques in carotid arteries, six had stenosis >50% and two had a carotid intervention (stenting or endarterectomy). Total cholesterol levels decreased compared to the earlier study this patient group in 2008, most likely due to a more intensive use of lipid-lowering drugs. Several metabolic parameters were higher (diabetes as much as 3.5-fold) in the group of severely TCDD-intoxicated subjects than in a general population of comparable age. This suggests that TCDD plays a role in the development of metabolic impairment and vascular changes.

"This suggests that TCDD plays a role in the development of metabolic impairment and vascular changes."

THYROID AND ENDOCRINE DISRUPTION





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REVIEW

Chemical contamination and the thyroid

Leonidas H. Duntas

Received: 18 March 2014 / Accepted: 29 September 2014 / Published online: 8 October 2014

Abstract Industrial chemical contaminants have a variable impact on the hypothalamic-pituitary-thyroid axis, this depending both on their class and on confounding factors. Today, mounting evidence is pointing to the role of environmental factors, and specifically EDCs, in the current distressing upsurge in the incidence of thyroid disease. The unease is warranted. These substances, which are nowadays rife in our environments (including in foodstuffs), have been shown to interfere with thyroid hormone action, biosynthesis, and metabolism, resulting in disruption of tissue homeostasis and/or thyroid function. Importantly, based on the concept of the "nonmonotonic dose–response curve", the relationship between dose and effect has often been found to be nonlinear. Thus, small doses can induce unpredictable, adverse effects, one case being polychlorinated biphenyls (PCBs), of which congener(s) may centrally inhibit the hypothalamic-pituitary-thyroid axis, or

Keywords Thyroid hormone receptor · Endocrine disruptors · Chemical pollution · Thyroid · TSH · Polychlorinated biphenyls · Bisphenol A

Introduction

"Feeble though we may seem, we have the power to influence the course of our planet…."

Colin Hiram Tudge.[1]

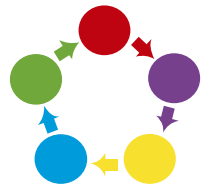
An endocrine-disruptor (ED) is defined by the U.S. Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and develop-

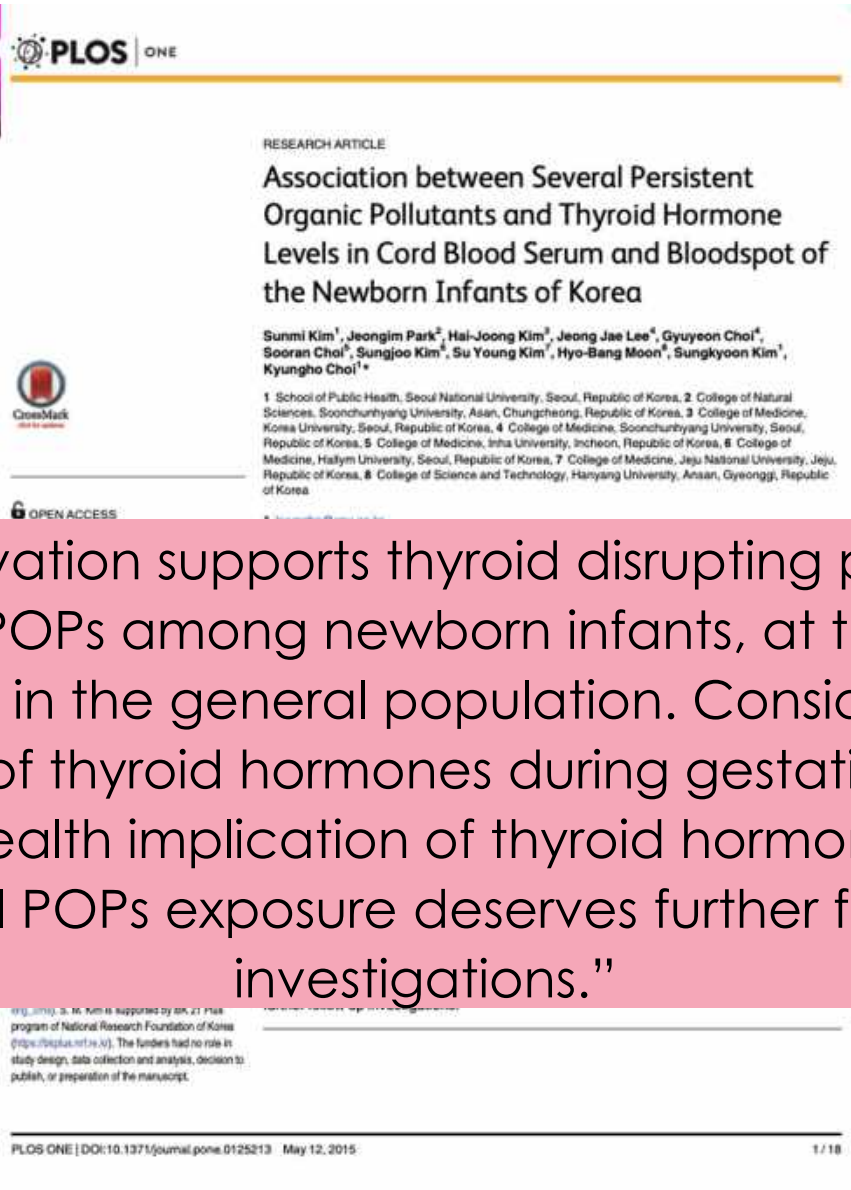
role in the incidence of obesity, insulin resistance, and diabetes mellitus in animal models and, crucially, are hypothesized to be involved in disruption of male and

L. H. Duntas (✉)
Unit of Endocrinology, Metabolism and Diabetes, Evgenidion Hospital, University of Athens, Papadiamantopoulou 20, 11520 Athens, Greece
e-mail: leduni@otenet.gr

[1] British biologist and science writer, "The Time Before History: 5 Million Years of Human Impact", 1996, Scribner.

"Today, mounting evidence is pointing to the role of environmental factors, specificaally EDCs, in the current distressing upsurge in the incidence of thyroid disease."





PLOS | ONE

RESEARCH ARTICLE

Association between Several Persistent Organic Pollutants and Thyroid Hormone Levels in Cord Blood Serum and Bloodspot of the Newborn Infants of Korea

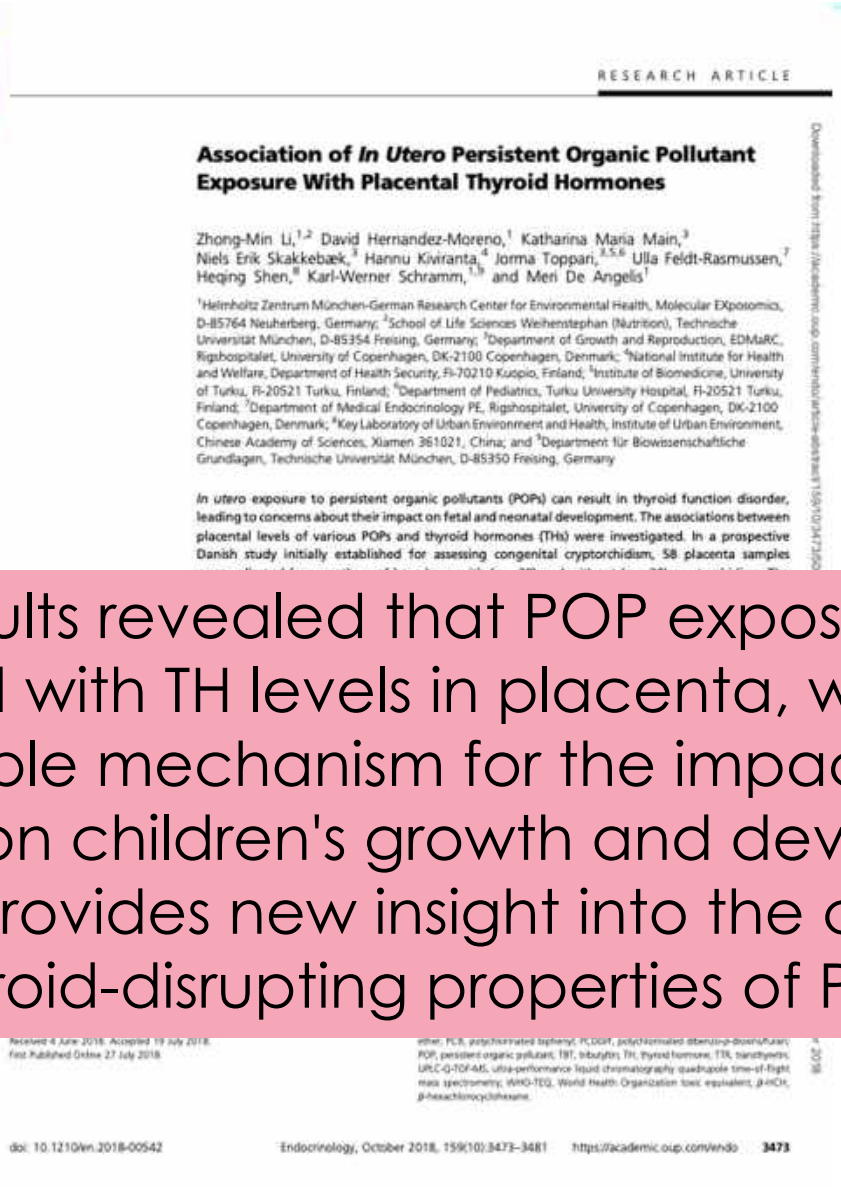
Sunmi Kim[1], Jeongim Park[2], Hai-Joong Kim[3], Jeong Jae Lee[4], Gyuyeon Choi[4], Sooran Choi[5], Sungjoo Kim[6], Su Young Kim[7], Hyo-Bang Moon[8], Sungkyoon Kim[1], Kyungho Choi[1]*

1 School of Public Health, Seoul National University, Seoul, Republic of Korea, 2 College of Natural Sciences, Soonchunhyang University, Asan, Chungcheong, Republic of Korea, 3 College of Medicine, Korea University, Seoul, Republic of Korea, 4 College of Medicine, Soonchunhyang University, Seoul, Republic of Korea, 5 College of Medicine, Inha University, Incheon, Republic of Korea, 6 College of Medicine, Hallym University, Seoul, Republic of Korea, 7 College of Medicine, Jeju National University, Jeju, Republic of Korea, 8 College of Science and Technology, Hanyang University, Ansan, Gyeonggi, Republic of Korea

OPEN ACCESS

program of National Research Foundation of Korea (https://beptus.nrf.re.kr). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

"our observation supports thyroid disrupting potential of several POPs among newborn infants, at the levels occurring in the general population. Considering the importance of thyroid hormones during gestation and early life stages, health implication of thyroid hormone effects by low level POPs exposure deserves further follow up investigations."



RESEARCH ARTICLE

Association of *In Utero* Persistent Organic Pollutant Exposure With Placental Thyroid Hormones

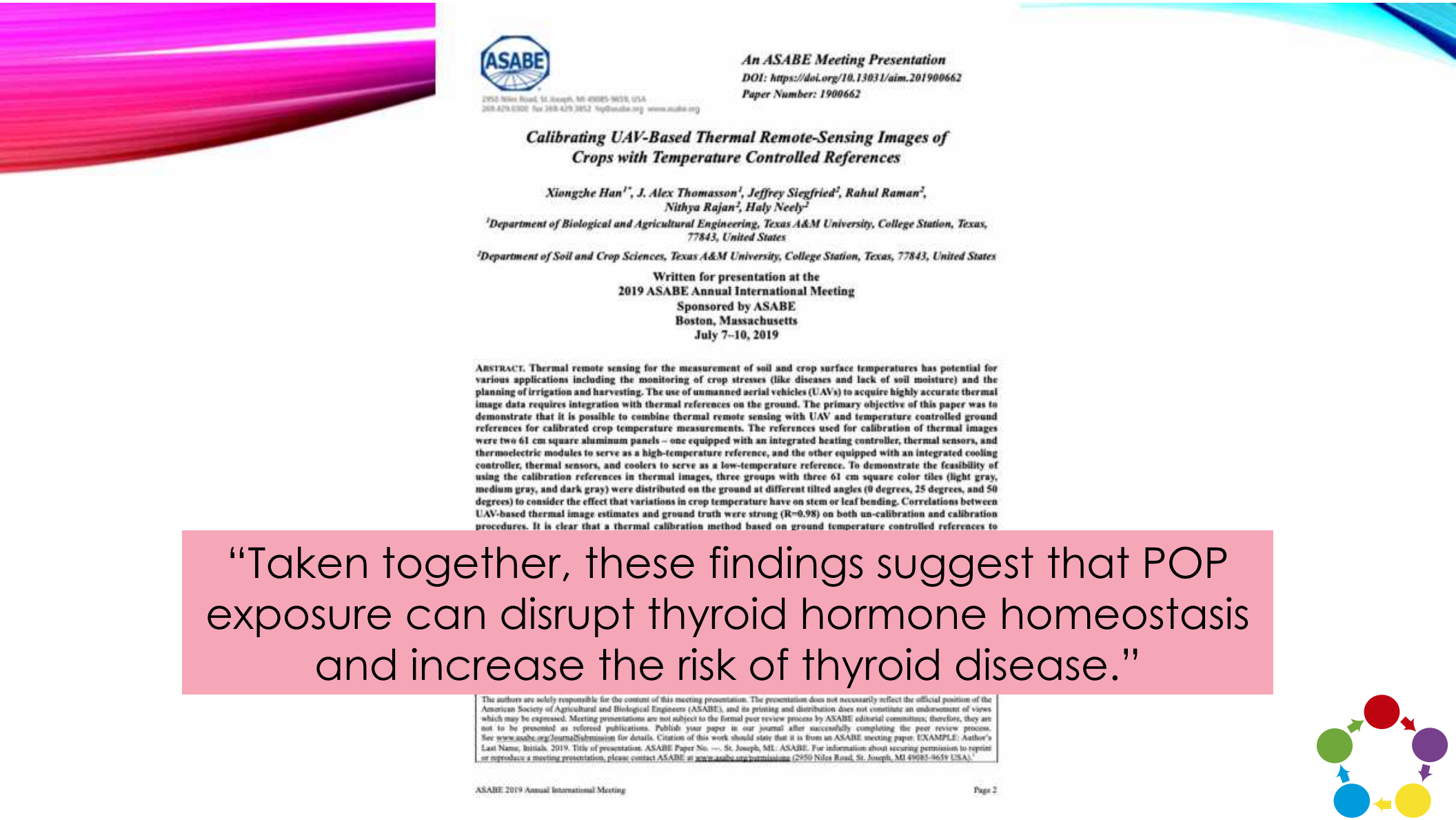
Zhong-Min Li,[1,2] David Hernandez-Moreno,[1] Katharina Maria Main,[3] Niels Erik Skakkebæk,[3] Hannu Kiviranta,[4] Jorma Toppari,[3,5,6] Ulla Feldt-Rasmussen,[7] Heqing Shen,[8] Karl-Werner Schramm,[1,9] and Meri De Angelis[1]

[1]Helmholtz Zentrum München-German Research Center for Environmental Health, Molecular EXposomics, D-85764 Neuherberg, Germany; [2]School of Life Sciences Weihenstephan (Nutrition), Technische Universität München, D-85354 Freising, Germany; [3]Department of Growth and Reproduction, EDMaRC, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark; [4]National Institute for Health and Welfare, Department of Health Security, FI-70210 Kuopio, Finland; [5]Institute of Biomedicine, University of Turku, FI-20521 Turku, Finland; [6]Department of Pediatrics, Turku University Hospital, FI-20521 Turku, Finland; [7]Department of Medical Endocrinology PE, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark; [8]Key Laboratory of Urban Environment and Health, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen 361021, China; and [9]Department für Biowissenschaftliche Grundlagen, Technische Universität München, D-85350 Freising, Germany

In utero exposure to persistent organic pollutants (POPs) can result in thyroid function disorder, leading to concerns about their impact on fetal and neonatal development. The associations between placental levels of various POPs and thyroid hormones (THs) were investigated. In a prospective Danish study initially established for assessing congenital cryptorchidism, 58 placenta samples

doi: 10.1210/en.2018-00542 Endocrinology, October 2018, 159(10):3473–3481 https://academic.oup.com/endo 3473

"These results revealed that POP exposures were associated with TH levels in placenta, which may be a possible mechanism for the impacts of POP exposures on children's growth and development. This study provides new insight into the complexity of thyroid-disrupting properties of POPs"



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2950 Niles Road, St. Joseph, MI 49085-9659, USA
269.429.0300 fax 269.429.3852 hq@asabe.org www.asabe.org

An ASABE Meeting Presentation
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Paper Number: 1900662

Calibrating UAV-Based Thermal Remote-Sensing Images of Crops with Temperature Controlled References

Xiongzhe Han[1], J. Alex Thomasson[1], Jeffrey Siegfried[2], Rahul Raman[2], Nithya Rajan[2], Haly Neely[2]*

[1]Department of Biological and Agricultural Engineering, Texas A&M University, College Station, Texas, 77843, United States

[2]Department of Soil and Crop Sciences, Texas A&M University, College Station, Texas, 77843, United States

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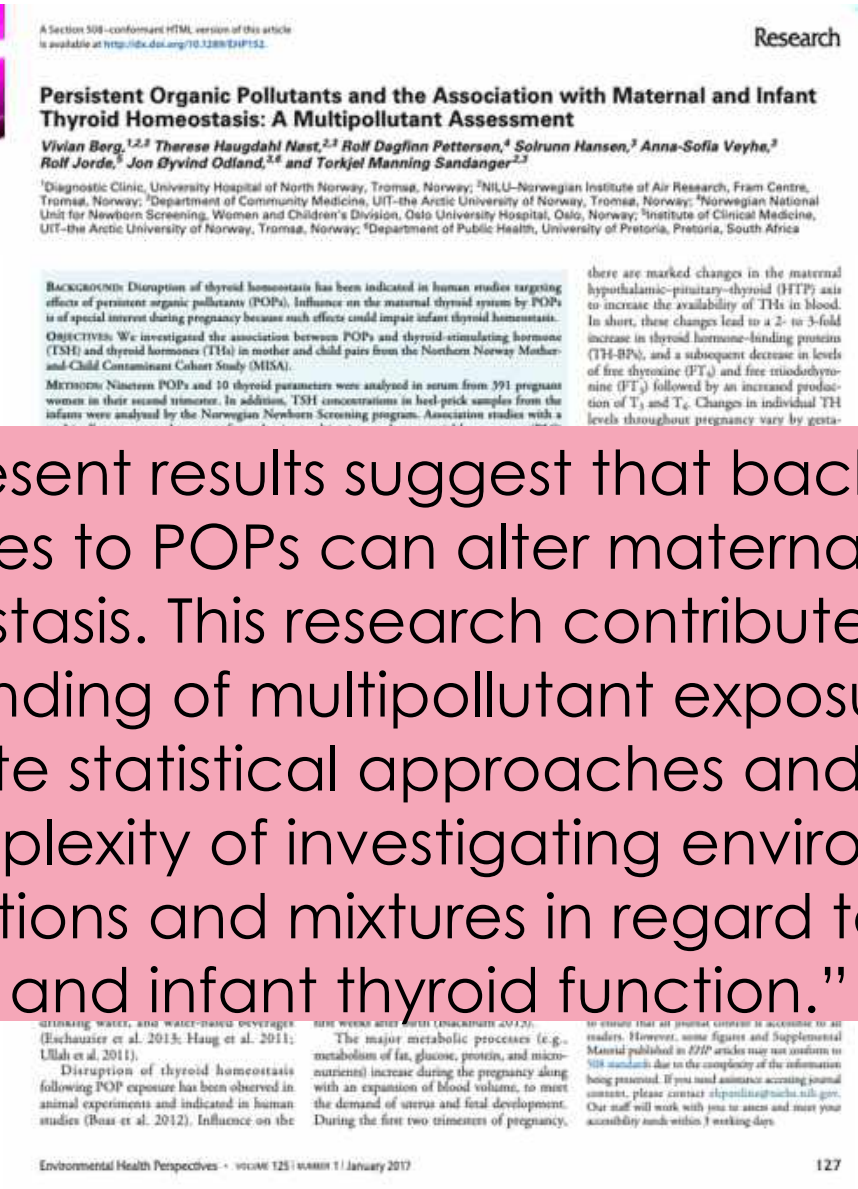
2019 ASABE Annual International Meeting
Sponsored by ASABE
Boston, Massachusetts
July 7–10, 2019

ABSTRACT. **Thermal remote sensing for the measurement of soil and crop surface temperatures has potential for various applications including the monitoring of crop stresses (like diseases and lack of soil moisture) and the planning of irrigation and harvesting. The use of unmanned aerial vehicles (UAVs) to acquire highly accurate thermal image data requires integration with thermal references on the ground. The primary objective of this paper was to demonstrate that it is possible to combine thermal remote sensing with UAV and temperature controlled ground references for calibrated crop temperature measurements. The references used for calibration of thermal images were two 61 cm square aluminum panels – one equipped with an integrated heating controller, thermal sensors, and thermoelectric modules to serve as a high-temperature reference, and the other equipped with an integrated cooling controller, thermal sensors, and coolers to serve as a low-temperature reference. To demonstrate the feasibility of using the calibration references in thermal images, three groups with three 61 cm square color tiles (light gray, medium gray, and dark gray) were distributed on the ground at different tilted angles (0 degrees, 25 degrees, and 50 degrees) to consider the effect that variations in crop temperature have on stem or leaf bending. Correlations between UAV-based thermal image estimates and ground truth were strong (R=0.98) on both un-calibration and calibration procedures. It is clear that a thermal calibration method based on ground temperature controlled references to**

"Taken together, these findings suggest that POP exposure can disrupt thyroid hormone homeostasis and increase the risk of thyroid disease."



A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/EHP152.

Research

Persistent Organic Pollutants and the Association with Maternal and Infant Thyroid Homeostasis: A Multipollutant Assessment

Vivian Berg,[1,2,3] Therese Haugdahl Nøst,[2,3] Rolf Dagfinn Pettersen,[4] Solrunn Hansen,[3] Anna-Sofia Veyhe,[3] Rolf Jorde,[5] Jon Øyvind Odland,[2,6] and Torkjel Manning Sandanger[2,3]

[1]Diagnostic Clinic, University Hospital of North Norway, Tromsø, Norway; [2]NILU–Norwegian Institute of Air Research, Fram Centre, Tromsø, Norway; [3]Department of Community Medicine, UiT–the Arctic University of Norway, Tromsø, Norway; [4]Norwegian National Unit for Newborn Screening, Women and Children's Division, Oslo University Hospital, Oslo, Norway; [5]Institute of Clinical Medicine, UiT–the Arctic University of Norway, Tromsø, Norway; [6]Department of Public Health, University of Pretoria, Pretoria, South Africa

Background: Disruption of thyroid homeostasis has been indicated in human studies targeting effects of persistent organic pollutants (POPs). Influence on the maternal thyroid system by POPs is of special interest during pregnancy because such effects could impair infant thyroid homeostasis.

Objectives: We investigated the association between POPs and thyroid-stimulating hormone (TSH) and thyroid hormones (THs) in mother and child pairs from the Northern Norway Mother-and-Child Contaminant Cohort Study (MISA).

Methods: Nineteen POPs and 10 thyroid parameters were analyzed in serum from 391 pregnant women in their second trimester. In addition, TSH concentrations in heel-prick samples from the infants were analyzed by the Norwegian Newborn Screening program. Association studies with a

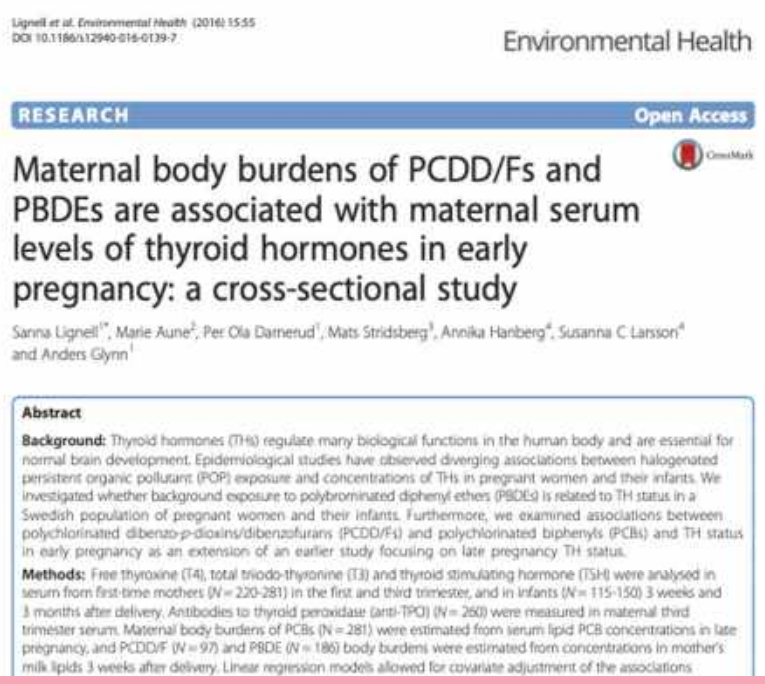
there are marked changes in the maternal hypothalamic–pituitary–thyroid (HTP) axis to increase the availability of THs in blood. In short, these changes lead to a 2- to 3-fold increase in thyroid hormone–binding proteins (TH-BPs), and a subsequent decrease in levels of free thyroxine (FT_4) and free triiodothyronine (FT_3) followed by an increased production of T_3 and T_4. Changes in individual TH levels throughout pregnancy vary by gesta-

"The present results suggest that background exposures to POPs can alter maternal thyroid homeostasis. This research contributes to the understanding of multipollutant exposures using multivariate statistical approaches and highlights the complexity of investigating environmental concentrations and mixtures in regard to maternal and infant thyroid function."

drinking water, and water-based beverages (Eschauzier et al. 2013; Haug et al. 2011; Ullah et al. 2011).

Disruption of thyroid homeostasis following POP exposure has been observed in animal experiments and indicated in human studies (Boas et al. 2012). Influence on the

The major metabolic processes (e.g., metabolism of fat, glucose, protein, and micronutrients) increase during the pregnancy along with an expansion of blood volume, to meet the demand of uterus and fetal development. During the first two trimesters of pregnancy,



Lignell et al. Environmental Health (2016) 15:55
DOI 10.1186/s12940-016-0139-7

Environmental Health

RESEARCH Open Access

Maternal body burdens of PCDD/Fs and PBDEs are associated with maternal serum levels of thyroid hormones in early pregnancy: a cross-sectional study

Sanna Lignell[1*], Marie Aune[2], Per Ola Darnerud[1], Mats Stridsberg[3], Annika Hanberg[4], Susanna C Larsson[4] and Anders Glynn[1]

Abstract

Background: Thyroid hormones (THs) regulate many biological functions in the human body and are essential for normal brain development. Epidemiological studies have observed diverging associations between halogenated persistent organic pollutant (POP) exposure and concentrations of THs in pregnant women and their infants. We investigated whether background exposure to polybrominated diphenyl ethers (PBDEs) is related to TH status in a Swedish population of pregnant women and their infants. Furthermore, we examined associations between polychlorinated dibenzo-*p*-dioxins/dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) and TH status in early pregnancy as an extension of an earlier study focusing on late pregnancy TH status.

Methods: Free thyroxine (T4), total triiodo-thyronine (T3) and thyroid stimulating hormone (TSH) were analysed in serum from first-time mothers ($N = 220$-281) in the first and third trimester, and in infants ($N = 115$-150) 3 weeks and 3 months after delivery. Antibodies to thyroid peroxidase (anti-TPO) ($N = 260$) were measured in maternal third trimester serum. Maternal body burdens of PCBs ($N = 281$) were estimated from serum lipid PCB concentrations in late pregnancy, and PCDD/F ($N = 97$) and PBDE ($N = 186$) body burdens were estimated from concentrations in mother's milk lipids 3 weeks after delivery. Linear regression models allowed for covariate adjustment of the associations

"Our results suggest that maternal PCDD/F and BDE-153 body burdens influence maternal TH status in early pregnancy, which is a critical period when maternal TH status influences fetal development."

* Correspondence: sanna.lignell@slv.se
[1]Risk Benefit Assessment Department, National Food Agency, Box 622SE-751 26 Uppsala, Sweden
Full list of author information is available at the end of the article

ENVIRONMENTAL Science & Technology

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Ecotoxicology and Public Health

Persistent Organic Pollutants in Human Breast Milk and Associations with Maternal Thyroid Hormone Homeostasis

Zhong-Min Li, Michael Albrecht, Hermann Fromme, Karl-Werner Schramm, and Meri De Angelis

Environ. Sci. Technol., **Just Accepted Manuscript** • DOI: 10.1021/acs.est.9b06054 • Publication Date (Web): 21 Dec 2019

"Multipollutant analysis using principal component analysis and hierarchical clustering revealed inverse associations of PBDEs (BDE-28, -47, -99, -100, -154, -183, and -197) with TT4 and TrT3. These results indicate that POPs at low levels might be related to reduced THs. This study shows that human breast milk might be an appropriate specimen to evaluate the thyroid disruption of POPs."

Science of the Total Environment 466–467 (2014) 706–715

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

Association between thyroid function and selected organochlorine pesticides: Data from NHANES 2001–2002☆

Ram B. Jain *

3061 Albemarle Way, Lawrenceville, GA 30044, United States

HIGHLIGHTS

- Effect of selected organochlorine pesticides on thyroid function was assessed.
- TSH levels were positively associated with the levels of trans-nonachlor.
- TT4 levels were negatively associated with the levels of trans-nonachlor.
- For selected 60+ year old males, TSH had a positive association with p,p′-DDE.

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p,p′-DDE
Smoking

ABSTRACT

Exposure to organochlorine pesticides (OCP) has been shown to be associated with adverse thyroid function. The impact of exposure to selected OCPs on total serum thyroxine (TT4) and thyroid stimulating hormone (TSH) was evaluated by analyzing data from the 2001–2002 National Health and Nutrition Examination Survey. Oxychlordane, p,p′-DDE, trans-nonachlor, and heptachlor epoxide were selected for analysis. Regression models with logs of TSH and TT4 as dependent variables and OCP exposure, race/ethnicity, iodine and smoking status, total lipids and others as independent variables were fitted. TSH levels increased ($p < 0.05$) with increase in trans-nonachlor exposure for 20–39 year old iodine deficient males. TSH levels were higher when oxychlordane exposure was low than when the exposure was medium or high for 20–39 year old iodine deficient females ($p < 0.05$). For iodine deficient females, TT4 levels were lower when p,p′-DDE exposure was low than when it was medium ($p < 0.05$). For non-Hispanic blacks (NHB), TT4 levels decreased with increase in exposure to heptachlor epoxide ($p < 0.05$). For iodine replete males, TSH levels increased with increase in trans-nonachlor exposure ($p < 0.05$). For iodine replete females, (i) Mexican Americans (MA) had higher TSH levels when the exposure to oxychlordane was medium than when the exposure was low; (ii) for 60+ years old, there was a positive association between TSH and heptachlor epoxide levels; and (iii) TT4 levels had an inverse association with trans-nonachlor and oxychlordane. In general though not always, (i) TSH and TT4 levels were lowest for the 20–39 years old and highest for the 60+ years old ($p <= 0.05$), (ii) TSH and TT4 levels for iodine deficient males and females were lowest for NHB, highest for MA, and in-between for non-Hispanic white, and (iii) non-smokers had higher TSH and TT4 levels than smokers and in general, statistically significantly so.

1. Introduction

Thyroid gland is one of the largest endocrine glands in the human body. Principal hormones produced by thyroid are triiodothyronine (T3) and thyroxine (T4). According to a document by the American Thyroid Association (http://thyroid.org/wp-content/uploads/patients/brochures/CAM_brochure.pdf), thyroid hormones help the body use energy, stay warm, and keep the brain, heart, muscles, and other organs working as they should. These two hormones, T3 and T4, regulate the rate of metabolism. Tyrosines and iodine are two principal "raw materials" necessary to synthesize T3 and T4 (http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/synthesis.html). Thus, inadequate iodine uptake may perturb thyroid homeostasis which is maintained by a multi-loop feedback system called the hypothalamic–pituitary–thyroid axis. There are many factors that affect thyroid homeostasis. At the local level (Konturek and Barczynski, 2012), thyroid homeostasis is affected by growth stimulators like epidermal growth factor, transforming growth factor alpha, insulin growth factors, fibroblast growth factors, hepatocyte growth factor, platelet-derived growth factor, and transforming growth factor beta. In a review article, Miller et al. (2009) have identified 8 classes of chemicals that can disrupt thyroid homeostasis. These include iodine transport chemicals like perchlorate, nitrates and thiocyanates; synthesis inhibitors like

☆ No funds were provided to the author for conducting this research. All data used in this work are available free of charge from www.cdc.gov/nchs.

* Tel.: +1 678 431 9728.
E-mail address: jain.ram.b@gmail.com.

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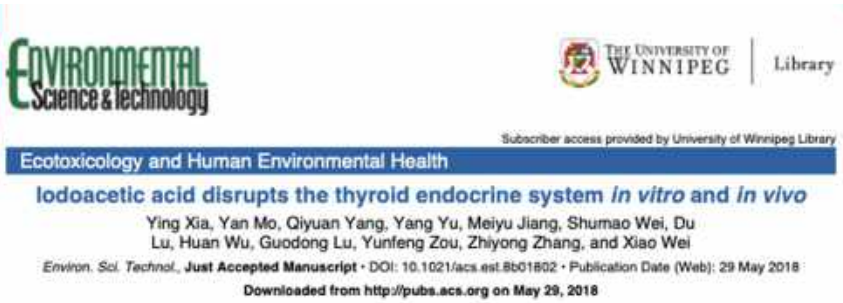

"IAA exposure decreased T3 levels but increased the weights of hypothalamus and the levels of thyrotropin releasing hormone and thyrotropin. In addition, IAA induced the formation of smaller and more depleted follicles or even vacuolization in the thyroid. These results suggested that IAA potentially disrupts the thyroid endocrine system both in vitro and in vivo."

Bulletin of Environmental Contamination and Toxicology
https://doi.org/10.1007/s00128-018-2359-8

Chronic PFOS Exposure Disrupts Thyroid Structure and Function in Zebrafish

Jiangfei Chen[1] · Lidan Zheng[1] · Linjie Tian[1] · Nengzhuang Wang[1] · Lei Lei[1] · Yanbo Wang[2] · Qiaoxiang Dong[1] · Changjiang Huang[1] · Dongren Yang[1]

Received: 12 February 2018 / Accepted: 12 May 2018

Abstract
Perfluorooctane sulfonic acid (PFOS), as a potential endocrine disrupting chemical, is widely detected in the environment, wildlife and human. Currently few studies have documented the effects of chronic PFOS exposure on thyroid in aquatic organisms and the underlying mechanisms are largely unknown. The present study assessed the effect of chronic PFOS exposure on thyroid structure and function using zebrafish model. Zebrafish at 8 h post fertilization (hpf) were exposed to PFOS (250 μg/l) until 120 d post fertilization (dpf). Thyroid hormone (T_3 and T_4) level, thyroid morphology and thyroid function related gene expression were evaluated in zebrafish at 120 dpf. Our findings demonstrated that chronic PFOS exposure altered thyroid hormone level, thyroid follicular cell structure and thyroid hormone related gene expression, suggesting the validity of zebrafish as an alternative model for PFOS chronic toxicity screening.

Keywords Zebrafish · PFOS · Thyroid hormone · Thyroid morphology · Gene expression

"Our findings demonstrated that chronic PFOS exposure altered thyroid hormone level, thyroid folicular cell structure and thyroid hormone related gene expression, suggesting the validity of zebrafish as na alternative model for PFOS chronic toxicity screening."

Jiangfei Chen, Lidan Zheng and Linjie Tian have contributed equally to this work.

✉ Changjiang Huang
cjhuang5711@163.com

✉ Dongren Yang
yangdongren@yahoo.com

[1] Institute of Environmental Safety and Human Health, Wenzhou Medical University, Wenzhou 325035, China

[2] Zhejiang Gongshang University, Hangzhou 310035, China

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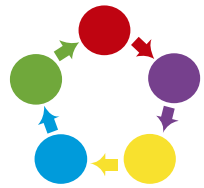
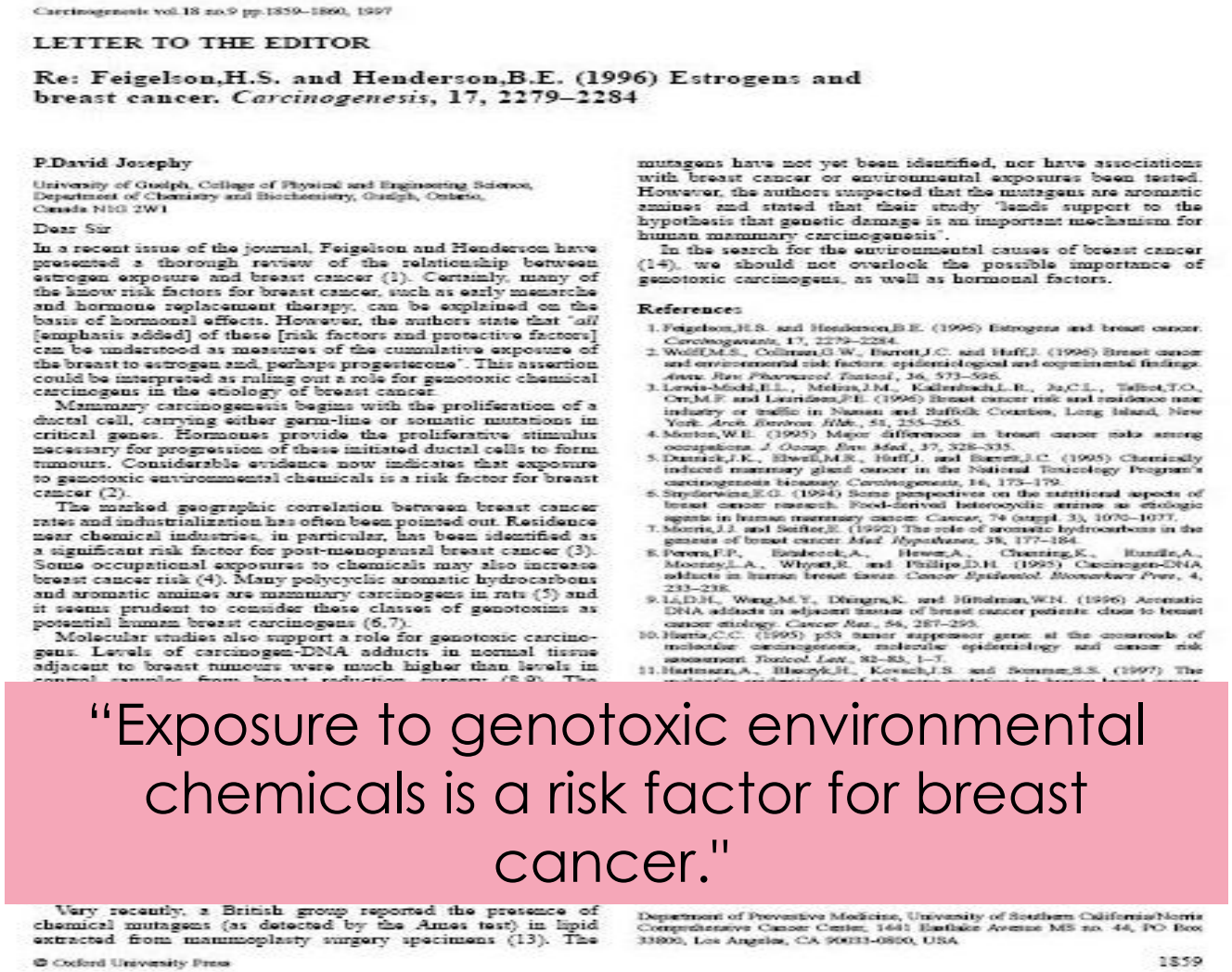
et al. 2016; Cui et al. 2017; Wang et al. 2011a). For example, it has been reported that acute waterborne exposure to PFOS (0-400 μg/l) during 1–15 d post fertilization (dpf) causes disruption of the hypothalamic -pituitary-thyroid (HPT) axis in zebrafish larvae by altering gene expression in the HPT axis (Shi et al. 2009). Although it has been demonstrated that acute exposure to PFOS disrupts thyroid function, adverse effect of chronic exposure at the relative low level of PFOS has not been well studied, especially the effects of PFOS on the morphological and molecular changes of thyroid have

ENDOCRINE DISRUPTORS, ESTROGEN METABOLISM & CANCER





Carcinogenesis vol.18 no.9 pp.1859–1860, 1997

LETTER TO THE EDITOR

Re: Feigelson,H.S. and Henderson,B.E. (1996) Estrogens and breast cancer. *Carcinogenesis*, 17, 2279–2284

P.David Josephy

University of Guelph, College of Physical and Engineering Science, Department of Chemistry and Biochemistry, Guelph, Ontario, Canada N1G 2W1

Dear Sir

In a recent issue of the journal, Feigelson and Henderson have presented a thorough review of the relationship between estrogen exposure and breast cancer (1). Certainly, many of the know risk factors for breast cancer, such as early menarche and hormone replacement therapy, can be explained on the basis of hormonal effects. However, the authors state that "*all* [emphasis added] of these [risk factors and protective factors] can be understood as measures of the cumulative exposure of the breast to estrogen and, perhaps progesterone". This assertion could be interpreted as ruling out a role for genotoxic chemical carcinogens in the etiology of breast cancer.

Mammary carcinogenesis begins with the proliferation of a ductal cell, carrying either germ-line or somatic mutations in critical genes. Hormones provide the proliferative stimulus necessary for progression of these initiated ductal cells to form tumours. Considerable evidence now indicates that exposure to genotoxic environmental chemicals is a risk factor for breast cancer (2).

The marked geographic correlation between breast cancer rates and industrialization has often been pointed out. Residence near chemical industries, in particular, has been identified as a significant risk factor for post-menopausal breast cancer (3). Some occupational exposures to chemicals may also increase breast cancer risk (4). Many polycyclic aromatic hydrocarbons and aromatic amines are mammary carcinogens in rats (5) and it seems prudent to consider these classes of genotoxins as potential human breast carcinogens (6,7).

Molecular studies also support a role for genotoxic carcinogens. Levels of carcinogen-DNA adducts in normal tissue adjacent to breast tumours were much higher than levels in

Very recently, a British group reported the presence of chemical mutagens (as detected by the Ames test) in lipid extracted from mammoplasty surgery specimens (13). The mutagens have not yet been identified, nor have associations with breast cancer or environmental exposures been tested. However, the authors suspected that the mutagens are aromatic amines and stated that their study 'lends support to the hypothesis that genetic damage is an important mechanism for human mammary carcinogenesis'.

In the search for the environmental causes of breast cancer (14), we should not overlook the possible importance of genotoxic carcinogens, as well as hormonal factors.

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Department of Preventive Medicine, University of Southern California/Norris Comprehensive Cancer Center, 1441 Eastlake Avenue MS no. 44, PO Box 33800, Los Angeles, CA 90033-0800, USA

"Exposure to genotoxic environmental chemicals is a risk factor for breast cancer."

Steroids. 2014 Aug 26. pii: S0039-128X(14)00196-2. doi: 10.1016/j.steroids.2014.08.003. [Epub ahead of print]

Estrogen metabolites and breast cancer.

Santen RJ[1], Yue W[2], Wang JP[2].

Author information

Abstract

Epidemiologic studies link several factors related to estrogen production in women to an increased risk of breast cancer. These include early menarche, late menopause, obesity, use of post-menopausal hormone therapy, and plasma estradiol levels. Two possible mechanisms have been proposed to explain the increased risk: (1) estrogen receptor (ER) mediated stimulation of breast cell proliferation with a concomitant enhanced rate of mutations and (2) metabolism of estradiol to genotoxic metabolites with a resulting increase in DNA mutations. The metabolism of estradiol can cause DNA damage in two ways: (a) formation of estradiol-adenine - guanine adducts which are released from the DNA backbone leaving depurinated sites which undergo error prone DNA repair and mutations and (b) generation of oxygen free radicals resulting from redox cycling of 4-OH estradiol to the 3-4 estradiol quinone and back conversion to 4-OH estradiol. If one or both pathways are operative, sufficient numbers of mutations accumulate over a long period of time to induce neoplastic transformation. Our studies are based on the hypothesis that both receptor-mediated and genotoxic pathways contribute to breast cancer. We initially demonstrated that MCF-7 breast cancer cells and normal breast tissue in aromatase transfected mice contain the enzymes necessary to convert estradiol to the estradiol DNA adducts. We then utilized a highly reductionist model to separately analyze the effect of estrogen receptor alpha (ER) on tumor formation and the effects of estrogen depletion by

...this data supports the role of estradiol metabolism as one of the components in the development of experimental breast cancer.

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Environ Int. 2016 Dec 28. pii: S0160-4120(16)30449-4. doi: 10.1016/j.envint.2016.12.010. [Epub ahead of print]

Environmental impact of estrogens on human, animal and plant life: A critical review.

Adeel M[1], Song X[2], Wang Y[2], Francis D[2], Yang Y[3].

⊕ Author information

Abstract

BACKGROUND: Since the inception of global industrialization, steroidal estrogens have become an emerging and serious concern. Worldwide, steroid estrogens including estrone, estradiol and estriol, pose serious threats to soil, plants, water resources and humans. Indeed, estrogens have gained notable attention in recent years, due to their rapidly increasing concentrations in soil and water all over the world. Concern has been expressed regarding the entry of estrogens into the human food chain which in turn relates to how plants take up and metabolism estrogens.

OBJECTIVES: In this review we explore the environmental fate of estrogens highlighting their release through effluent sources, their uptake, partitioning and physiological effects in the ecological system. We draw attention to the potential risk of intensive modern agriculture and waste disposal systems on estrogen release and their effects on human health. We also highlight their uptake and metabolism in plants.

METHODS: We use MEDLINE and other search data bases for estrogens in the environment from 2005 to the present, with the majority of our sources spanning the past five years. Published acceptable daily intake of estrogens (μg/L) and predicted no effect concentrations (μg/L) are listed from published sources and used as thresholds to discuss reported levels of estrogens in the aquatic and terrestrial environments. Global levels of estrogens from river sources and from Waste Water Treatment Facilities have been mapped, together with transport pathways of estrogens in plants.

RESULTS: Estrogens at polluting levels have been detected at sites close to waste water treatment facilities and in groundwater at various sites globally. Estrogens at pollutant levels have been linked with breast cancer in women and prostate cancer in men. Estrogens also perturb fish physiology and can affect reproductive development in both domestic and wild animals. Treatment of plants with steroid estrogen hormones or their precursors can affect root and shoot development, flowering and germination. However, estrogens can ameliorate the effects

CONCL

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"There is published evidence to establish a causal relationship between estrogens in the environment and breast cancer."

Carcinogenesis. 2001 Jun;22(6):905-11.

Analysis of potential biomarkers of estrogen-initiated cancer in the urine of Syrian golden hamsters treated with 4-hydroxyestradiol.

Todorovic R[1], Devanesan P, Higginbotham S, Zhao J, Gross ML, Rogan EG, Cavalieri EL.

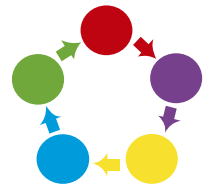
Author information

Abstract

Estrone (E1) and 17beta-estradiol (E2) are metabolized to catechol estrogens (CE), which may be oxidized to semiquinones and quinones (CE-Q). CE-Q can react with glutathione (GSH) and DNA, or be reduced to CE. In particular, CE-3,4-Q react with DNA to form depurinating adducts (N7Gua and N3Ade), which are cleaved from DNA to leave behind apurinic sites. We report the determination of 22 estrogen metabolites, conjugates and adducts in the urine of male Syrian golden hamsters treated with 4-hydroxyestradiol (4-OHE2). After initial purification, urine samples were analyzed by HPLC with multichannel electrochemical detection and by capillary HPLC/tandem mass spectrometry. 4-Hydroxyestrogen-2-cysteine [4-OHE1(E2)-2-Cys] and N-acetylcysteine [4-OHE1(E2)-2-NAcCys] conjugates, as well as the methoxy CE, were identified and quantified by HPLC, whereas the 4-OHE1(E2)-1-N7Gua depurinating adducts and 4-OHE1(E2)-2-SG conjugates could only be

These results provide strong evidence that exposure to 4-OHE1(E2) leads to the formation of DNA adducts. This process is a putative tumor initiating event.

The estrogen metabolites, conjugates and adducts can be used as biomarkers for detecting susceptibility to estrogen-induced cancer.



Ann N Y Acad Sci. 2006 Nov;1089:286-301.

Catechol quinones of estrogens in the initiation of breast, prostate, and other human cancers: keynote lecture.

Cavalieri E[1], Rogan E.

Author information

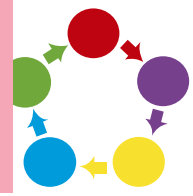
Abstract

Estrogens can be converted to electrophilic metabolites, particularly the catechol estrogen-3,4-quinones, estrone(estradiol)-3,4-quinone [E(1)(E(2))-3,4-Q], which react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone repair of this damage leads to the mutations that initiate breast, prostate, and other types of cancer. The reaction of E(1)(E(2))-3,4-Q with DNA forms the depurinating adducts 4-hydroxyE(1)(E(2))-1-N3adenine [4-OHE(1)(E(2))-1-N3Ade] and 4-OHE(1)(E(2))-1-N7guanine(Gua). These two adducts constitute >99% of the total DNA

"The depurinating adducts that migrate from cells and can be found in body fluids can also serve as biomarkers of cancer risk.

In fact, a higher level of estrogen-DNA adducts has been found in the urine of men with prostate cancer and in women with breast cancer compared to healthy controls.

This unifying mechanism of the origin of cancer and other diseases suggests preventive strategies based on the level of depurinating DNA adducts that generate the first critical step in the initiation of diseases".



Biochim Biophys Acta. 2006 Aug;1766(1):63-78. Epub 2006 Apr 19.

Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention.

Cavalieri E[1], Chakravarti D, Guttenplan J, Hart E, Ingle J, Jankowiak R, Muti P, Rogan E, Russo J, Santen R, Sutter T.

Author information

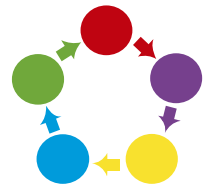
Abstract

Exposure to estrogens is associated with increased risk of breast and other types of human cancer. Estrogens are converted to metabolites, particularly the catechol estrogen-3,4-quinones (CE-3,4-Q), that can react with DNA to form depurinating adducts. These adducts are released from DNA to generate apurinic sites. Error-prone base excision repair of this damage may lead to the mutations that can initiate breast, prostate and other types of cancer. The reaction of CE-3,4-Q with DNA forms the depurinating adducts 4-hydroxyestrone(estradiol) [4-OHE1(E2)-1-N3Ade and 4-OHE1(E2)-1-N7Gua. These two adducts constitute more than 99% of the total DNA adducts formed. Increased levels of these quinones and their reaction with DNA occur when estrogen metabolism is unbalanced. Such an imbalance is the result of overexpression of estrogen

depurinating adducts. Initiated cells may be promoted by a number of processes, including hormone receptor stimulated proliferation. These results lay the groundwork for assessing risk and preventing disease.

"In summary, this evidence strongly indicates that estrogens can become endogenous tumor initiators when CE-3,4-Q react with DNA to form specific depurinating adducts".

"Initiated cells may be promoted by a number of processes…. including hormone receptor stimulated proliferation. These results lay the groundwork for assessing risk and preventing disease."



Int J Environ Res Public Health. 2012 Aug;9(8):2694-714. doi: 10.3390/ijerph9082694. Epub 2012 Jul 31.

Non-genomic effects of xenoestrogen mixtures.

Viñas R[1], Jeng YJ, Watson CS.

Author information

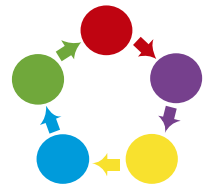
[1]Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, TX 77555, USA. revinas@utmb.edu

Abstract

Xenoestrogens (XEs) are chemicals derived from a variety of natural and anthropogenic sources that can interfere with endogenous estrogens by either mimicking or blocking their responses via non-genomic and/or genomic signaling mechanisms. Disruption of estrogens' actions through the less-studied non-genomic pathway can alter such functional end points as cell proliferation, peptide

Xenoestrogens (XEs) are chemicals derived from a variety of natural and anthropogenic sources that can interfere with endogenous estrogens by either mimicking or blocking their responses via non-genomic and/or genomic signaling mechanisms.

work should focus on carefully studying individual and mixture components across a range of concentrations and cellular pathways in a variety of tissue types.



J Steroid Biochem Mol Biol. 2011 Oct;127(1-2):44-50. doi: 10.1016/j.jsbmb.2011.01.015. Epub 2011 Feb 12.

Endocrine disruption via estrogen receptors that participate in nongenomic signaling pathways.

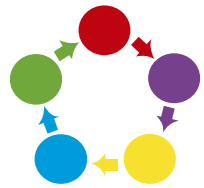
Watson CS[1], Jeng YJ, Guptarak J.

Author information

Abstract

When inappropriate (non-physiologic) estrogens affect organisms at critical times of estrogen sensitivity, disruption of normal endocrine functions can result. Non-physiologic estrogen mimetics (environmental, dietary, and pharmaceutical) can signal rapidly and potently via the membrane versions of estrogen receptors, as can physiologic estrogens. Both physiologic and non-physiologic estrogens activate multiple signaling pathways, leading to altered cellular functions (e.g. peptide release, cell proliferation or death, transport). Xenoestrogens' mimicry of physiologic estrogens is imperfect. When superimposed, xenoestrogens can alter endogenous estrogens' signaling and thereby disrupt normal signaling pathways, leading to malfunctions in many tissue types. Though these xenoestrogen actions occur rapidly via nongenomic signaling pathways, they can be sustained with continuing ligand stimulation, combinations of ligands, and signaling that perpetuates downstream

Xenoestrogens can alter endogenous estrogens' signaling and thereby disrupt normal signaling pathways, leading to malfunctions in many tissue types.



Environ Health Perspect. Jan 2011; 119(1): 104–112.
Published online Sep 22, 2010. doi: 10.1289/ehp.1002512
PMCID: PMC3018487
Research

Combinations of Physiologic Estrogens with Xenoestrogens Alter ERK Phosphorylation Profiles in Rat Pituitary Cells

Yow-Jiun Jeng and Cheryl S. Watson

Abstract

Background Estrogens are potent nongenomic phospho-activators of extracellular-signal–regulated kinases (ERKs). A major concern about the toxicity of xenoestrogens (XEs) is potential alteration of responses to physiologic estrogens when XEs are present simultaneously.

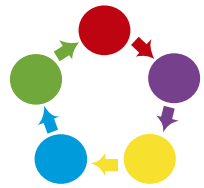
Objectives We examined estrogen-induced ERK activation, comparing the abilities of structurally related XEs (alkylphenols and bisphenol A) to alter ERK responses induced by physiologic concentrations (1 nM) of estradiol (E_2), estrone (E_1), and estriol (E_3).

Methods We quantified hormone/mimetic-induced ERK phosphorylations in the GH_3/B6/F10 rat pituitary cell line using a plate immunoassay, comparing effects with those on cell proliferation and by estrogen receptor subtype-selective ligands.

Results Alone, these structurally related XEs activate ERKs in an oscillating temporal pattern similar (but not identical) to that with physiologic estrogens. The potency of all estrogens was similar (active between femtomolar and nanomolar concentrations). XEs potently disrupted physiologic estrogen

particular estrogens are important (e.g., development, reproductive cycling, pregnancy, menopause).

Xenoestrogens are both imperfect potent estrogens and endocrine disruptors; the more efficacious a XE, the more it disrupts actions of physiologic estrogens.



Published in final edited form as:
Steroids. 2007 February ; 72(2): 124–134.

Xenoestrogens are potent activators of nongenomic estrogenic responses

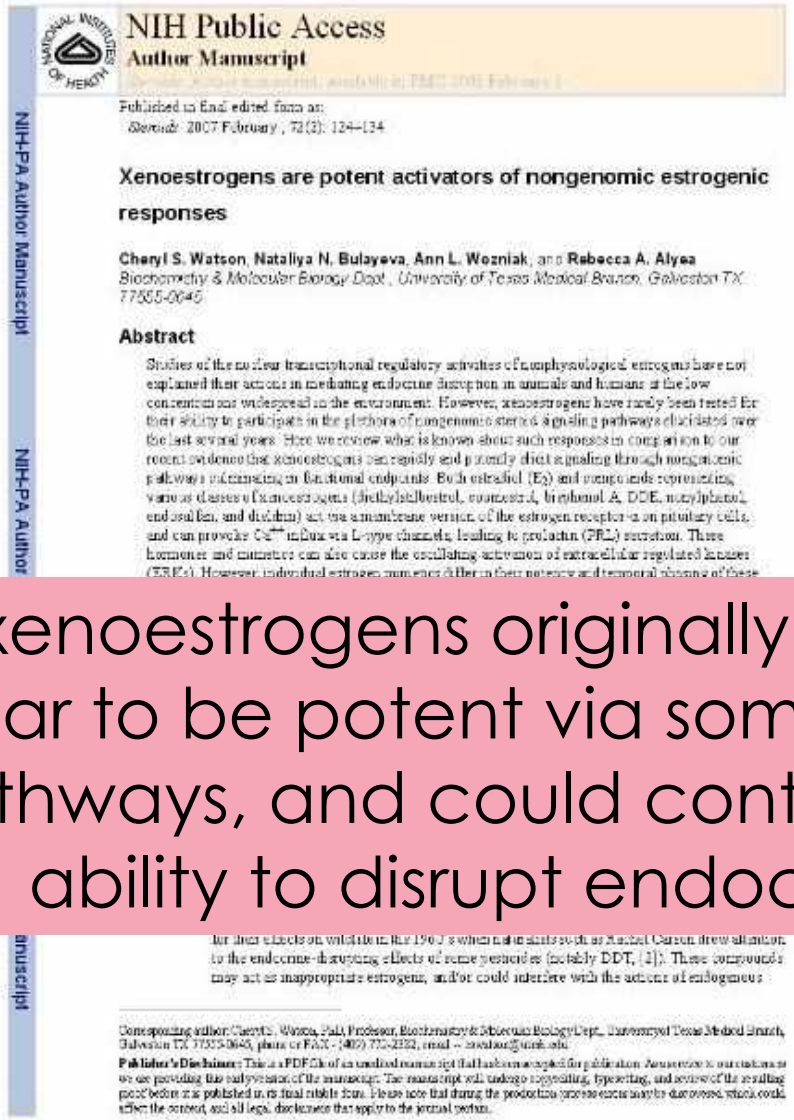
Cheryl S. Watson, **Nataliya N. Bulayeva**, **Ann L. Wozniak**, and **Rebecca A. Alyea**
Biochemistry & Molecular Biology Dept., University of Texas Medical Branch, Galveston TX 77555-0645

Abstract

Studies of the nuclear transcriptional regulatory activities of nonphysiological estrogens have not explained their actions in mediating endocrine disruption in animals and humans at the low concentrations widespread in the environment. However, xenoestrogens have rarely been tested for their ability to participate in the plethora of nongenomic steroid signaling pathways elucidated over the last several years. Here we review what is known about such responses in comparison to our recent evidence that xenoestrogens can rapidly and potently elicit signaling through nongenomic pathways culminating in functional endpoints. Both estradiol (E_2) and compounds representing various classes of xenoestrogens (diethylstilbestrol, coumestrol, bisphenol A, DDE, nonylphenol

estrogenic or antiestrogenic potential of different types of xenoestrogens, and help us to develop strategies for preventing xenoestrogenic disruption of estrogen action in many tissues.

Xenoestrogens can rapidly and potently elicit signaling through nongenomic pathways culminating in functional endpoints.



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Xenoestrogens are potent activators of nongenomic estrogenic responses

Cheryl S. Watson, **Nataliya N. Bulayeva**, **Ann L. Wozniak**, and **Rebecca A. Alyea**
Biochemistry & Molecular Biology Dept., University of Texas Medical Branch, Galveston TX 77555-0645

Abstract

Studies of the nuclear transcriptional regulatory activities of naturally occurring estrogens have not explained their actions in mediating endocrine disruption in animals and humans at the low concentrations widespread in the environment. However, xenoestrogens have rarely been tested for their ability to participate in the plethora of nongenomic steroid signaling pathways elucidated over the last several years. Here we review what is known about such responses in comparison to our recent evidence that xenoestrogens can rapidly and potently affect signaling through nongenomic pathways culminating in functional endpoints. Both estradiol (E_2) and compounds representing various classes of xenoestrogens (diethylstilbestrol, coumestrol, bisphenol A, DDE, nonylphenol, endosulfan, and dieldrin) act via a membrane version of the estrogen receptor-α on pituitary cells, and can provoke Ca^{++} influx via L-type channels, leading to prolactin (PRL) secretion. These hormones and xenoestrogens can also cause the oscillating activation of extracellular regulated kinases (ERKs). However, individual estrogen responses differ in their potency and temporal absence of these

for their effects on wildlife in the 1960's when naturalists such as Rachel Carson drew attention to the endocrine-disrupting effects of some pesticides (notably DDT, [1]). These compounds may act as inappropriate estrogens, and/or could interfere with the actions of endogenous

Corresponding author: Cheryl S. Watson, PhD, Professor, Biochemistry & Molecular Biology Dept., University of Texas Medical Branch, Galveston TX 77555-0645, phone or FAX - (409) 772-2382, email – [redacted]

Many xenoestrogens originally deemed "weak" appear to be potent via some nongenomic signaling pathways, and could contribute to these compounds' ability to disrupt endocrine functions.

Environ Mol Mutagen. 2014 May;55(4):343-53. doi: 10.1002/em.21847. Epub 2014 Jan 24.

Di-(2-ethylhexyl) phthalate and bisphenol A exposure impairs mouse primordial follicle assembly in vitro.

Zhang T[1], Li L, Qin XS, Zhou Y, Zhang XF, Wang LQ, De Felici M, Chen H, Qin GQ, Shen W.

Author information

[1]Laboratory of Germ Cell Biology, Key Laboratory of Animal Reproduction and Germplasm Enhancement in Universities of Shandong, College of Animal Science and Technology, Qingdao Agricultural University, Qingdao, China.

Abstract

Bisphenol-A (BPA) and diethylhexyl phthalate (DEHP) are estrogenic compounds widely used in commercial plastic products. Previous studies have shown that exposure to such compounds have adverse effects on various aspects of mammalian reproduction including folliculogenesis. The objective of this study was to examine the effects of BPA and DEHP exposure on primordial follicle formation. We found that germ cell nest breakdown and primordial follicle assembly were significantly reduced when newborn mouse ovaries were exposed to 10 or 100 μM BPA and DEHP in vitro. Moreover, BPA and DEHP

"Finally, folliculogenesis was severely impaired in BPA and DEHP exposed ovaries after transplantation into the kidney capsules of immunodeficient mice.

In conclusion, BPA and DEHP exposures impair mouse primordial follicle assembly in vitro."

IUBMB Life. 2010 Oct;62(10):746-51. doi: 10.1002/iub.376.

Is bisphenol A a weak carcinogen like the natural estrogens and diethylstilbestrol?

Cavalieri EL[1], Rogan EG.

Author information

[1]Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE 68198-6805, USA. ecavalie@unmc.edu

Abstract

Bisphenol A (BPA) displays weak estrogenic properties and could be a weak carcinogen by a mechanism similar to that of estrone (E(1)), estradiol (E(2)) and the synthetic estrogen diethylstilbestrol, a human carcinogen. A wide variety of scientific evidence supports the hypothesis that certain estrogen metabolites, predominantly catechol estrogen-3,4-quinones, react with

"BPA displays weak estrogenic properties and could be a weak carcinogen by a mechanism similar to that of estrone (E(1)), estradiol (E(2)) and the synthetic estrogen diethylstilbestrol, a human carcinogen…..

The catechol of BPA may alter expression of estrogen-activating and deactivating enzymes, and/or compete with methoxylation of 4-OHE(1)(E(2)) by catechol-O-methyltransferase, thereby unbalancing the metabolism of estrogens to increase formation of E(1)(E(2))-3,4-Q and the depurinating estrogen-DNA adducts leading to cancer initiation.

Thus, exposure to BPA could increase the risk of developing cancer by direct and/or indirect mechanisms".

Proc Natl Acad Sci U S A. 2011 Oct 25;108(43):17732-7. doi: 10.1073/pnas.1115187108. Epub 2011 Oct 17.

Effects of bisphenol A and triclocarban on brain-specific expression of aromatase in early zebrafish embryos.

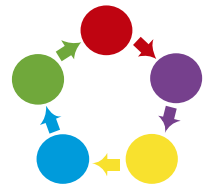
Chung E[1], Genco MC, Megrelis L, Ruderman JV.

Author information

Abstract

Estrogen regulates numerous developmental and physiological processes. Most effects are mediated by estrogen receptors (ERs), which function as ligand-regulated transcription factors. Estrogen also regulates the activity of GPR30, a membrane-associated G protein-coupled receptor. Many different types of environmental contaminants can activate ERs; some can bind GPR30 as well. There is growing concern that exposure to some of these compounds, termed xenoestrogens, is interfering with the behavior and reproductive potential of numerous wildlife species, as well as affecting human health. Here, we investigated how two common, environmentally pervasive chemicals affect the in vivo expression of a known estrogen target gene in the brain of developing zebrafish embryos, aromatase AroB, which converts androgens to estrogens. We confirm that, like estrogen, the well-studied xenoestrogen bisphenol A (BPA, a plastics monomer), induces strong brain-specific overexpression of aromatase. Experiments using ER- and GPR30-selective modulators argue that this induction is largely through nuclear ERs. BPA induces dramatic overexpression of AroB RNA in the same subregions of the developing brain as estrogen. The antibacterial triclocarban (TCC) by itself stimulates AroB expression only slightly, but TCC strongly enhances

Both BPA and TCC have the potential to elevate levels of aromatase and thereby, levels of endogenous estrogens in the developing brain.



PLoS One. 2014 Feb 20;9(2):e88961. doi: 10.1371/journal.pone.0088961. eCollection 2014.

Xenoestrogens alter estrogen receptor (ER) α intracellular levels.

La Rosa P, Pellegrini M, Totta P, Acconcia F, Marino M.

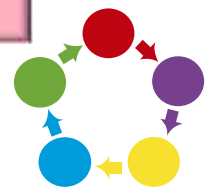
Author information

Abstract

17β-estradiol (E2)-dependent estrogen receptor (ER) α intracellular concentration is a well recognized critical step in the pleiotropic effects elicited by E2 in several target tissues. Beside E2, a class of synthetic and plant-derived chemicals collectively named endocrine disruptors (EDs) or xenoestrogens bind to and modify both nuclear and extra-nuclear ERα activities. However, at the present no information is available on the ability of EDs to hamper ERα intracellular concentration. Here, the effects of bisphenol A (BPA) and naringenin (Nar), prototypes of synthetic and plant-derived ERα ligands, have

"These data demonstrate that ERα intracellular concentration is an important target through which EDs hamper the hormonal milieu of E2 target cells driving cells to different outcomes or mimicking E2 even in the absence of the hormone".

important target through which EDs hamper the hormonal milieu of E2 target cells driving cells to different outcomes or mimicking E2 even in the absence of the hormone.



Mol Cell Endocrinol. 2009 May 25;304(1-2):63-8. doi: 10.1016/j.mce.2009.02.016. Epub 2009 Mar 9.

The pancreatic beta-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes.

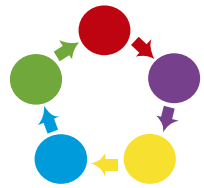
Nadal A[1], Alonso-Magdalena P, Soriano S, Quesada I, Ropero AB.

Author information

Abstract

The estrogen receptor ERalpha is emerging as a key molecule involved in glucose and lipid metabolism. The main functions of pancreatic beta-cells are the biosynthesis and release of insulin, the only hormone that can directly decrease blood glucose levels. Estrogen receptors ERalpha and ERbeta exist in beta-cells. The role of ERbeta is still unknown, yet ERalpha plays an important role in the regulation of insulin biosynthesis, insulin secretion and beta-cell survival. Activation of ERalpha by excess of E2 or the action of an environmental estrogen such as BPA, it will produce an excessive insulin signaling. This may provoke insulin resistance in the liver and muscle, as well as beta-cell exhaustion and therefore, it may contribute to the development of type II diabetes.

"If ER alpha is over stimulated by an excess of E2 or the action of an environmental estrogen such as BPA, it will produce an excessive insulin signaling."



Carcinogenesis vol.25 no.2 pp.289–297, 2004
DOI: 10.1093/carcin/bgg191

Metabolism and DNA binding studies of 4-hydroxyestradiol and estradiol-3,4-quinone *in vitro* and in female ACI rat mammary gland *in vivo*

Kai-Ming Li[1], Rosa Todorovic[1], Prabu Devanesan[1], Sheila Higginbotham[1], Harald Köfeler[2], Ragulan Ramanathan[2], Michael L.Gross[2], Eleanor G.Regan[1] and Ercole L.Cavalieri[1,3]

[1]Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, 986805 Nebraska Medical Center, Omaha, NE 68198-6805 and [2]Department of Chemistry, Washington University, One Brookings Drive, St Louis, MO 63130, USA

[3]To whom correspondence should be addressed
Email: ecavalie@unmc.edu

Studies of estrogen metabolism, formation of DNA adducts, carcinogenicity, cell transformation and mutagenicity have led to the hypothesis that reaction of certain estrogen metabolites, predominantly catechol estrogen-3,4-

which react with DNA to form primarily depurinating adducts. These adducts can generate the critical mutations that initiate cancer (Chakravarti *et al.*, *Oncogene*, 2001, 20, 7945; Chakravarti *et al.*, *Proc. Am. Assoc. Cancer Res.*, 2003, 44, 180).

Introduction

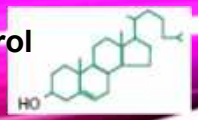
Experiments on estrogen metabolism (1–7), formation of DNA adducts (8–12), carcinogenicity (13–16), cell transformation (17–19) and mutagenicity (20–22) have led to the hypothesis that certain estrogen metabolites, predominantly catechol estrogen-3,4-quinones, react with DNA and can generate

"The most common pathway of conjugation of 4-OHE1(E2) in extrahepatic tissues occurs by O-methylation, which is catalyzed by the ubiquitous catechol-O-methyltransferase (COMT).

This inactivating pathway is in competition with the activation of CE to semiquinones and quinones…..The quinones can be inactivated by formation of glutathione (GSH) conjugates and/or by reduction to CE by quinone reductase.

If, however, these two processes are insufficient, the CE-3,4-quinones can react with DNA to form depurinating adducts (4-OHE1(E2)-1-N3Ade and 4-OHE1(E2)-1-N7Gua)."

ESTROGEN METABOLISM



Cholesterol

Pregnenolone → 17-OH-Pregnenolone → DHEA → Androstenediol

Progesterone → 17-OH-Progesterone → Androstenedione ↔ Testosterone → DHT

Corticosterone → Aldosterone

(Mineralo-corticoids)

Cortisol ↔ Cortisone

(Glucocorticoids)

(Androgens)

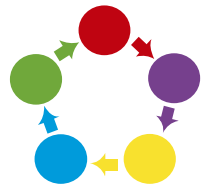
Estrone (E1) ↔ Estradiol (E2)

2-OHE1 → 2-MeOE1

16α-OHE1 → Estriol (E3)

4-OHE1 → 4-MeOE1

(Estrogens)



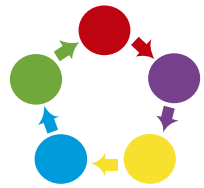
THE METABOLISM OF ESTROGEN

- Unused Estrogen is primarily metabolized in the liver via Phase I and/or Phase II detoxification:

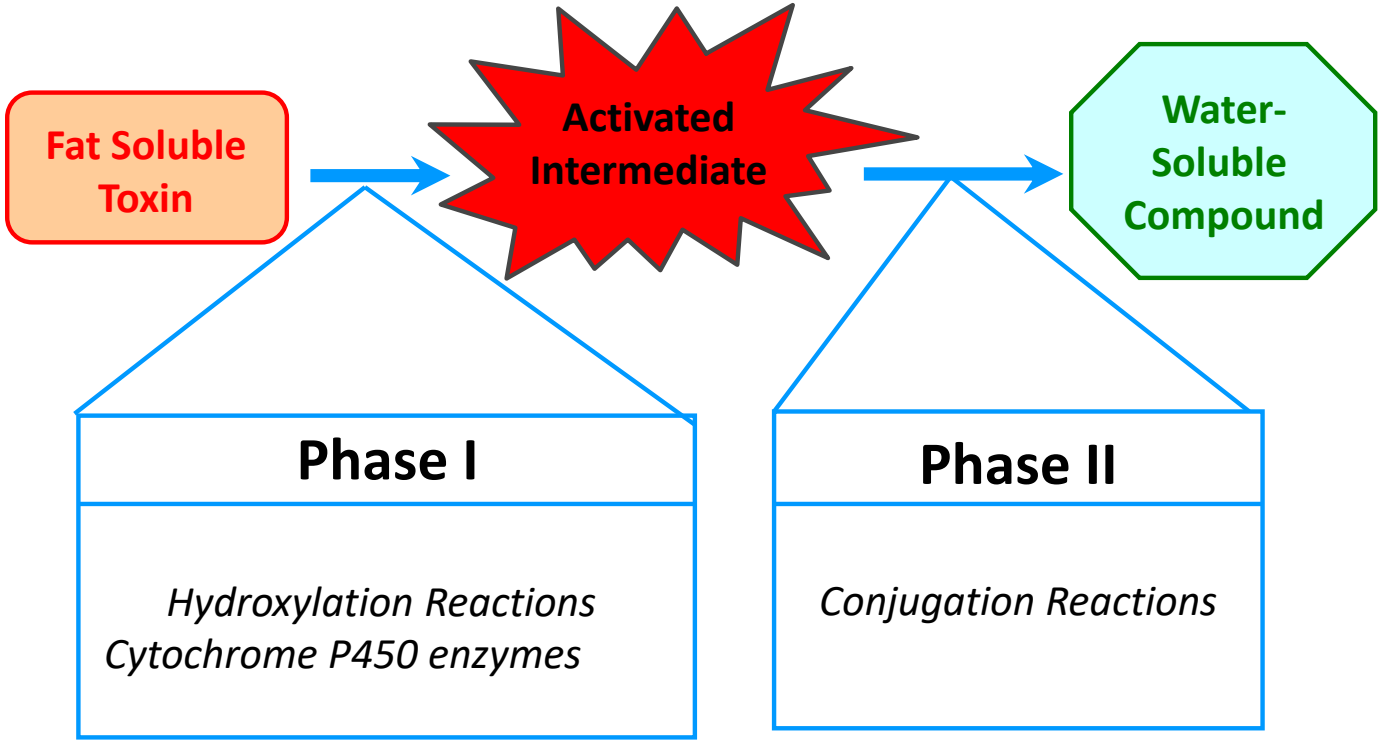
Phase I

- Major Pathway
- Hydroxylation

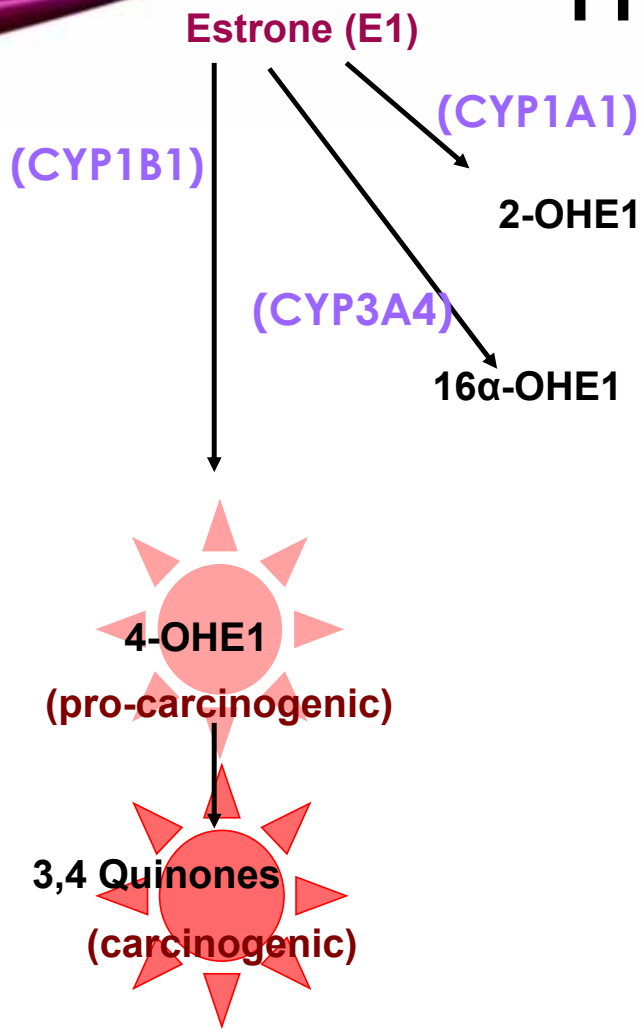
- Phase II
  - Glucuronidation
  - Sulfation
  - Methylation
  - Acetylation



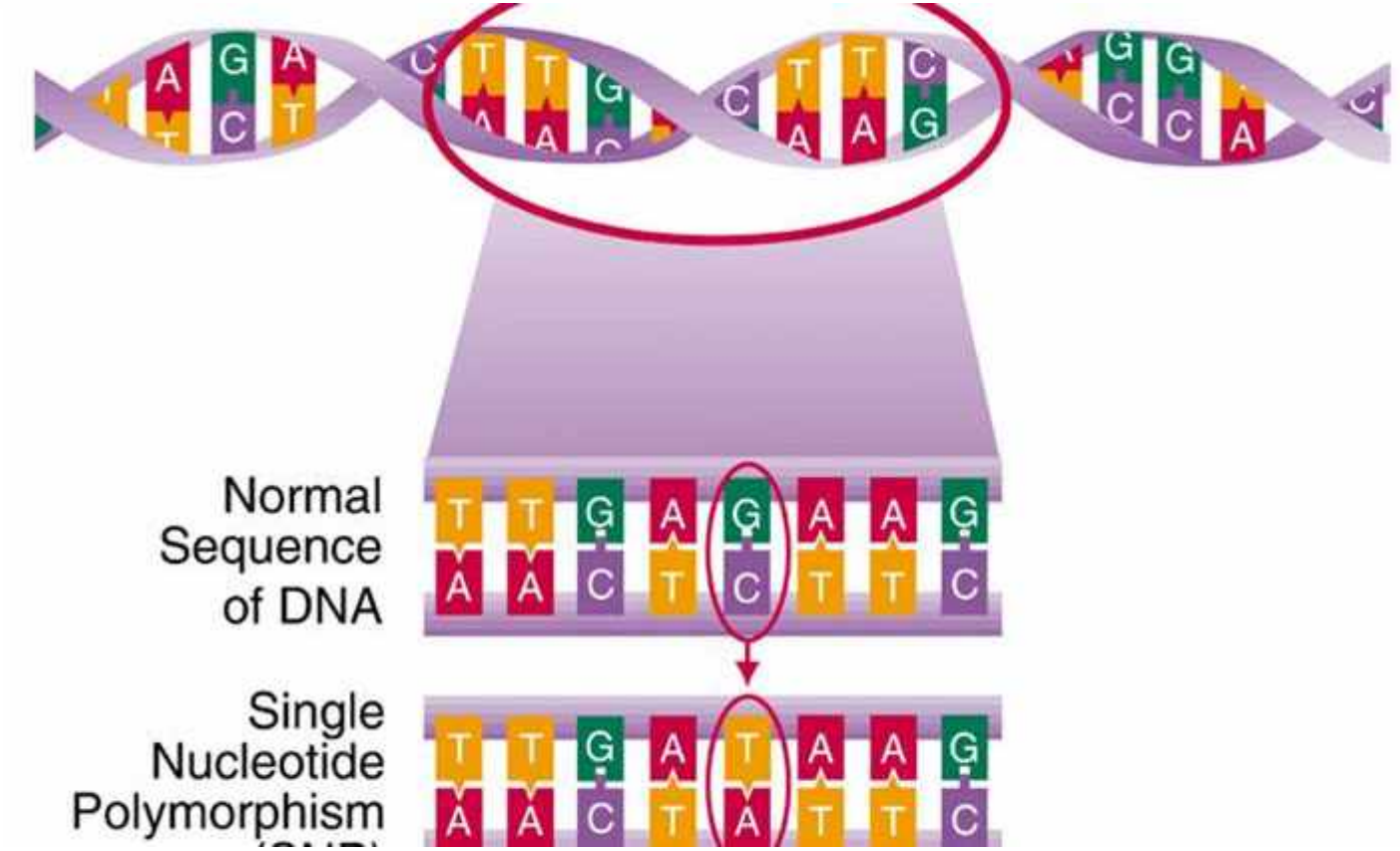
TWO MAJOR PATHWAYS OF DETOXIFICATION

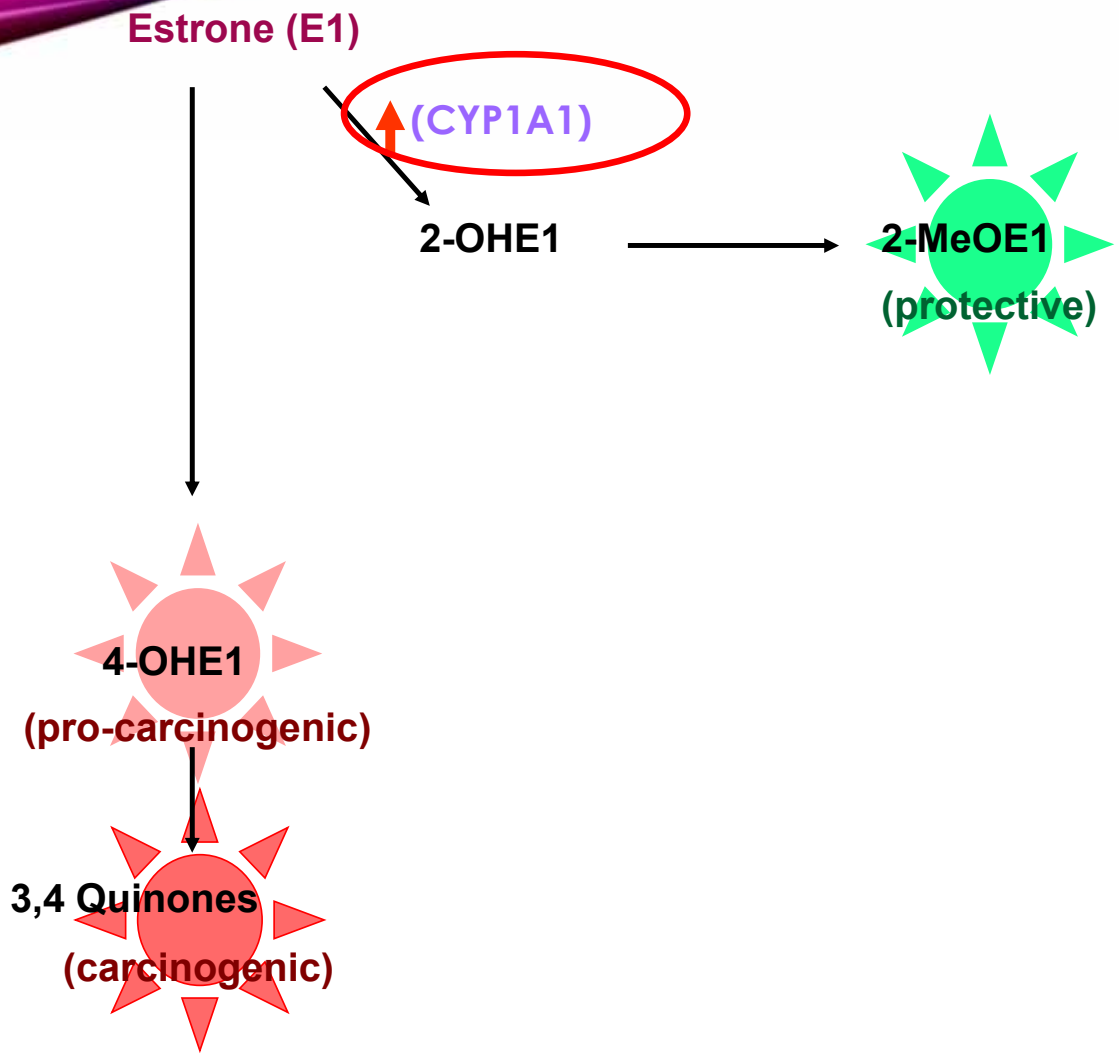


Phase 1 Detoxification



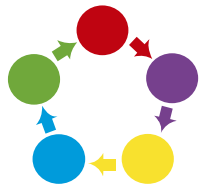
SINGLE NUCLEOTIDE POLYMORPHISM (SNP)



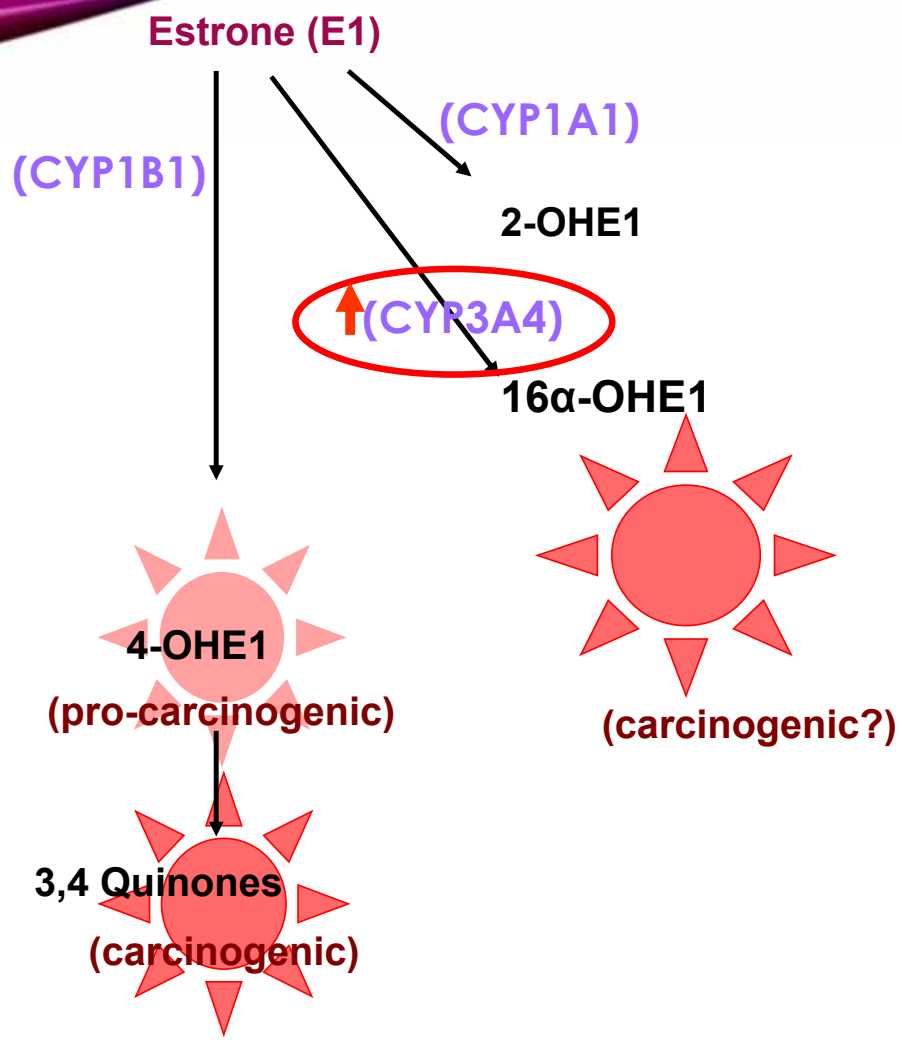

Estrone (E1)
(CYP1A1)
2-OHE1
2-MeOE1
(protective)
4-OHE1
(pro-carcinogenic)
3,4 Quinones
(carcinogenic)

2-HYDROXYESTRONE (2-OHE1)

"2-OHE1metabolite has very little estrogen receptor binding affinity, and has been shown to decrease cell proliferation by 20 to 30% in cultured breast cancer cell lines."

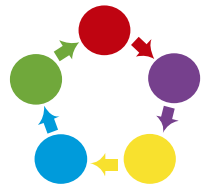


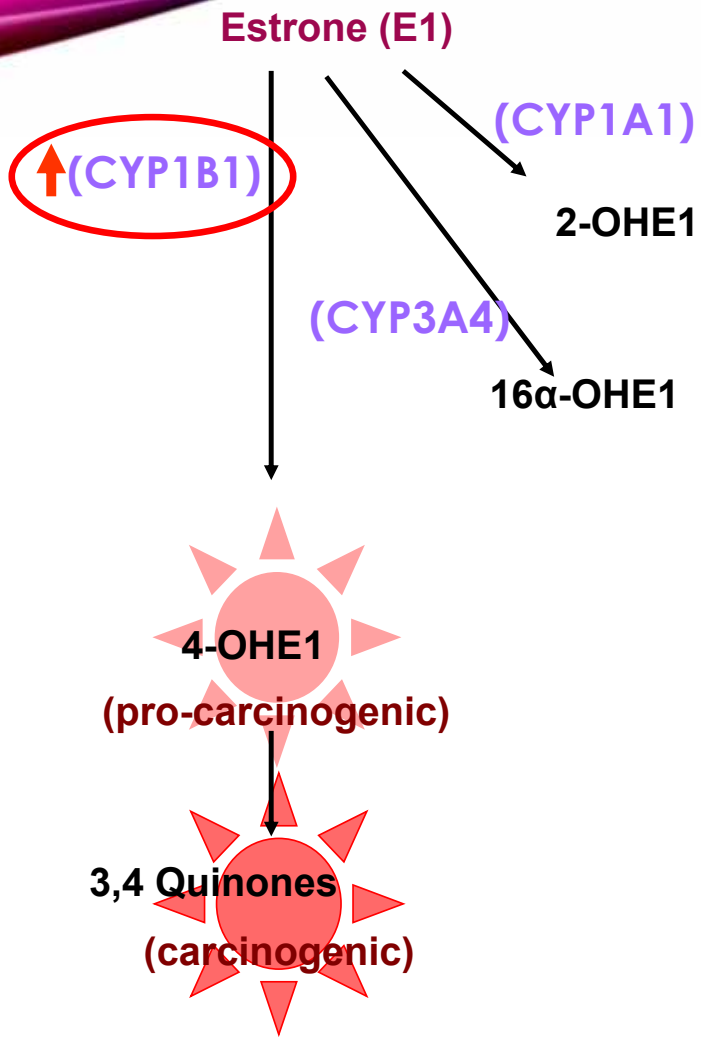
Taioli et al. Comparison of estrogens and estrogen metabolites in human breast tissue and urine. Reproductive Biology and Endocrinology. 2010, 8:93.


Estrone (E1)
(CYP1A1)
(CYP1B1)
2-OHE1
(CYP3A4)
16α-OHE1
4-OHE1
(pro-carcinogenic)
(carcinogenic?)
3,4 Quinones
(carcinogenic)

16A-HYDROXYESTRONE (16A-OHE1)

- Strong estrogenic activity
- Turns on estrogen receptor
- Greater likelihood of estrogen-dependent conditions

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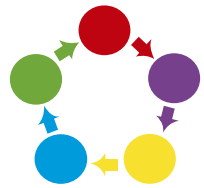
(pro-carcinogenic)
3,4 Quinones
(carcinogenic)

CYTOCHROME P450 1B1 (CYP1B1)

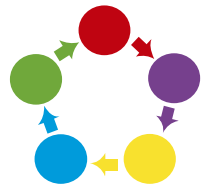
- Polymorphism is associated with FASTER enzyme activity
- Increased production of 4-OH-estrogens and other potentially carcinogenic compounds
- Tendency for lower 2:16aOH-estrone
- Increased risk of breast cancer, especially if xenobiotic exposure (e.g., PAHs), high BMI, equine estrogens, coexisting CYP1A1 SNP



(Han W 2004, Saintot M 2004, Kocabas NA 2002, Rylander-Rudqvist 2003*)*

CYTOCHROME P450 1B1 (CYP1B1)

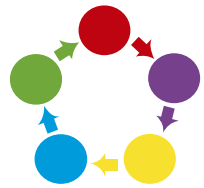
"CYP1B1, which has specific estrogen-4-hydroxylase activity, is present in tissues such as uterus, breast, ovary, and prostate, which often give rise to hormone-responsive cancers"



J Steroid Biochem Mol Biol 2003;86:477–86
Short Review of Pathophysiology of Catechol Estrogen. **Pak J Physiol 2010;6(2)**

4-HYDROXYESTRONE (4-OHE1)

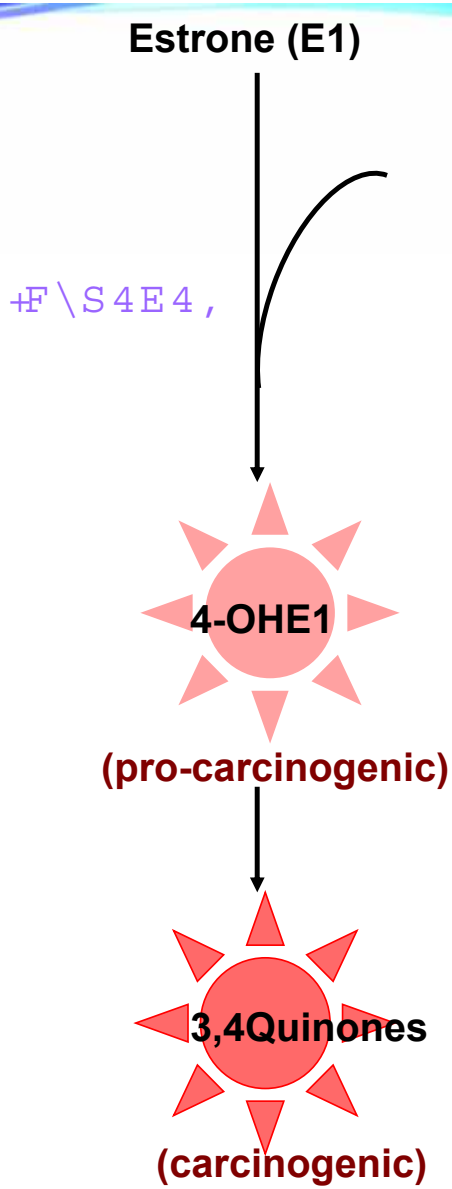
- Very potent
- If not inactivated by COMT, 4-OHE1 can be oxidized to quinones compounds → DNA adduct formation in tissues such as breast
- Increased 4-hydroxylation of estrogen in uterine fibroids *(Reddy VV 1981)*
- Link between CYP1B1 SNP (increased 4-OH-estrogen production) and prostate CA *(Tang YM 2000)*



Conjugated Equine Estrogens

CEEs are preferentially 4-hydroxylated.

(Chang M 1998)

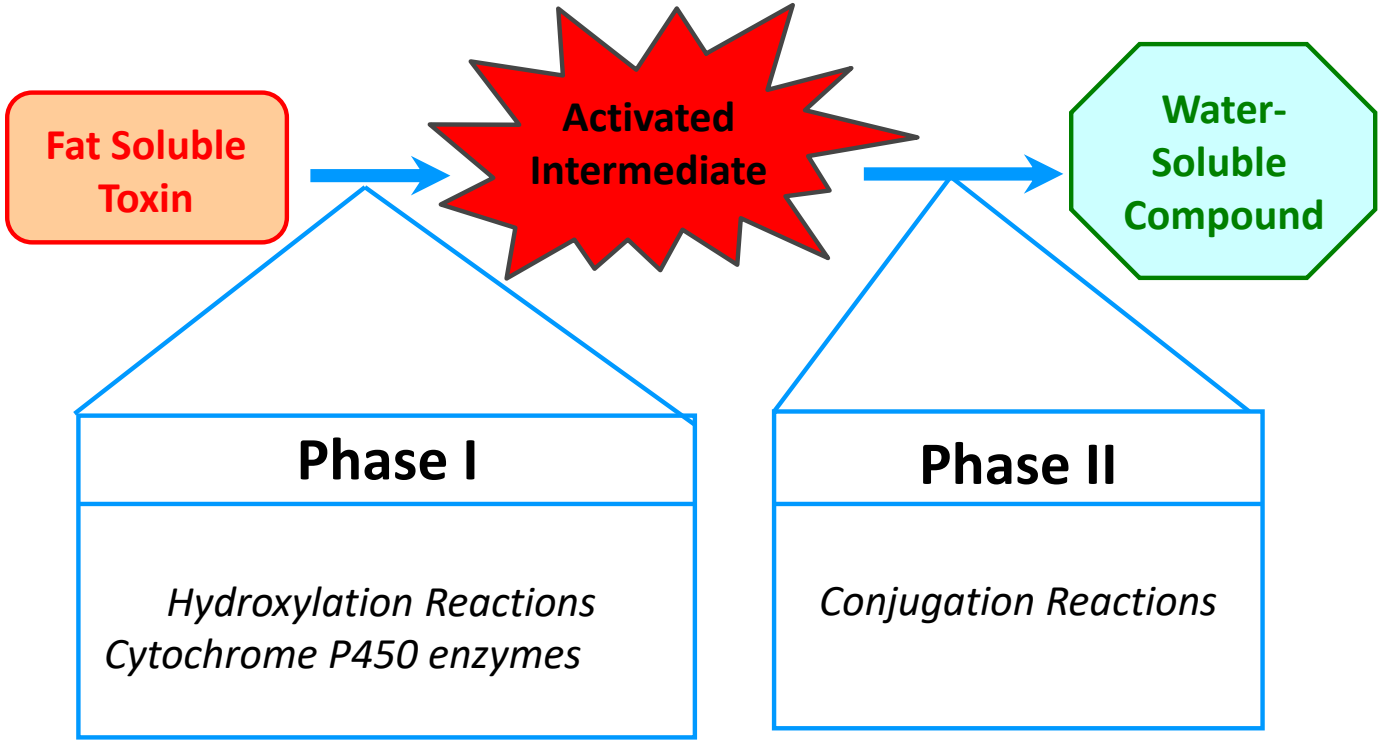


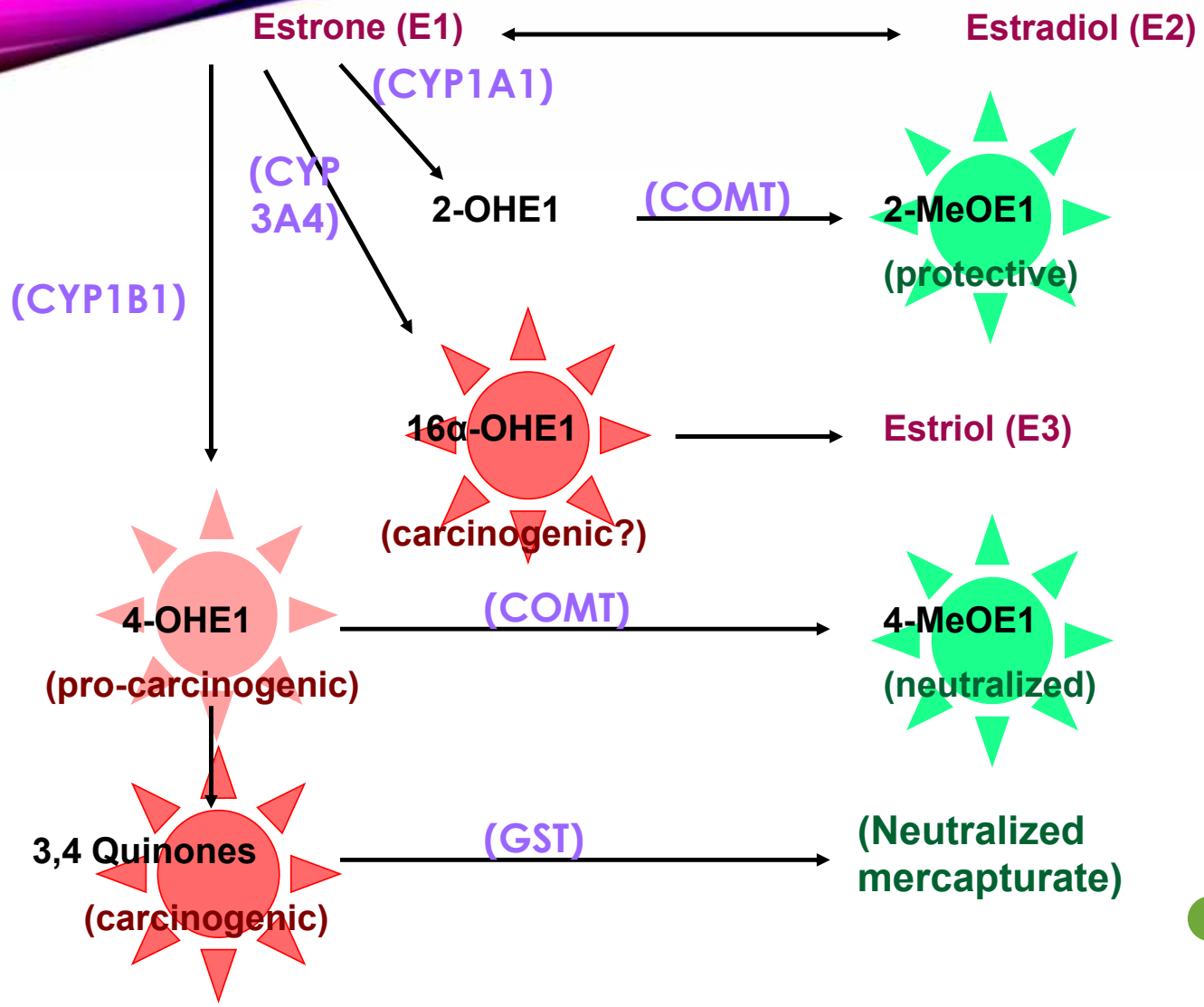
ENDOCRINE DISRUPTORS

- Environmental xenobiotics act as “endocrine disruptors” that modify intercellular communication and function
- Chemicals commonly detected in people include DDT, Polychlorinated biphenyls (PCB's), Bisphenol A, Polybrominated diphenyl ethers (PBDE's)
- May play role in cancer, obesity
- Changes in DNA methylation (epigenetic modification) which can ultimately change ER activity
- Produce a higher ratio of the 4 and 16 hydroxylated estrogen derivatives that are potentially more genotoxic by modifying members of the CYP450 enzyme family

1. Latini et al., Mini-Reviews in Medicinal Chemistry, 2010, 10, 846-855
2. Soto, A. M. & Sonnenschein, C. Nat. Rev. Endocrinol. 6, 363–370 (2010); published online 25 May 2010; doi:10.1038/nrendo.2010.87

TWO MAJOR PATHWAYS OF DETOXIFICATION

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(protective)
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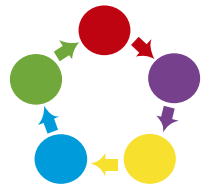
16α-OHE1
Estriol (E3)
(carcinogenic?)
4-OHE1
(pro-carcinogenic)
(COMT)
4-MeOE1
(neutralized)
3,4 Quinones
(carcinogenic)
(GST)
(Neutralized mercapturate)

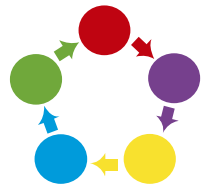
PHASE II SUBSTRATE CLASSES

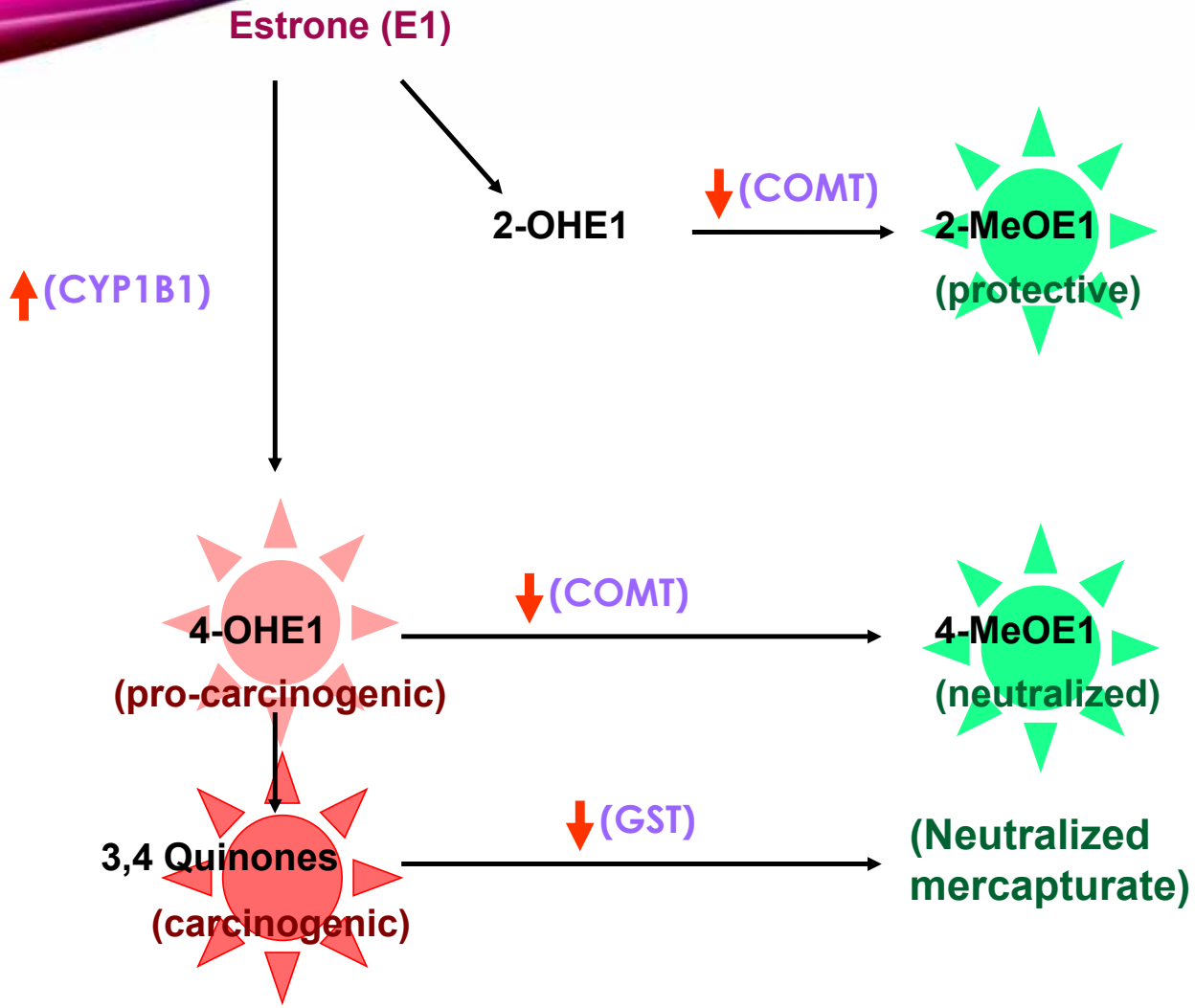
- Sulfation & Glucuronidation
  - many drugs and xenobiotics (esp. phenolic compounds)
  - many steroid hormones and the fat-soluble vitamins
  - bile acids, bilirubin, some neurotransmitters
- Acetylation & Methylation
  - many drugs and some xenobiotics (esp. metals/ minerals)
  - many neurotransmitters
- Amino Acid Conjugation
  - some drugs and xenobiotics (esp. aliphatic compounds)
  - fatty acids and bile acids
- Glutathione Conjugation
  - few drugs but many xenobiotics (esp. toxic metals)
  - small carbon molecules, prostaglandins, and lipid peroxides



ROLE OF METHYLATION

- 2-OHE1 is only protective against cancer when methylated by catechol-O-methyltransferase (COMT)
  - 2-methoxy-estrogens are being researched for therapeutic use in breast cancer and CV disease
- 4-OHE1 is less likely to oxidize to carcinogenic compounds if neutralized by COMT
- 2-MeOE1:2-OHE1 and 4-MeOE1:4-OE1 ratios in urine provide a gauge of methylation capacity in a given patient

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3,4 Quinones
(carcinogenic)
(GST)
(Neutralized
mercapturate)

Int J Cancer. 2018 Sep 5. doi: 10.1002/ijc.31851. [Epub ahead of print]

Estrogen metabolism in menopausal hormone users in the Women's Health Initiative Observational Study: Does it differ between estrogen plus progestin and estrogen alone?

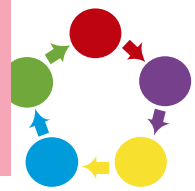
Falk RT[1], Manson JE[2], Barnabei VM[3], Anderson GL[4], Brinton LA[1], Rohan TE[5], Cauley JA[6], Chen C[4], Coburn SB[1], Pfeiffer RM[1], Reding KW[7], Sarto GE[8], Wentzensen N[1], Chlebowski RT[9], Xu X[10], Trabert B[1].

⊕ Author information

Abstract

The WHI found an unexpected reduced breast cancer risk in women using CEE alone. We hypothesized CEE alone induces estrogen hydroxylation along the 2-pathway rather than the competing 16-pathway, a pattern linked to reduced postmenopausal breast cancer risk. 1864 women in a WHIOS case-control study of estrogen metabolism and ovarian and endometrial cancer were studied of whom 609 were current E+P users (351 used CEE+MPA), while 272 used E alone (162 used CEE). Fifteen EM were measured, and analyses conducted for each metabolite, hydroxylation pathway (2-, 4-, or 16-pathway), and ratios of pathway concentrations using inverse probability weighted linear regression. Compared to E+P users, all EM were higher in E alone users (significant for unconjugated estrone, total/conjugated estradiol, total/unconjugated 2-methoxyestrone, 4-methoxyestrone and unconjugated estriol). The relative concentrations of 2- and 4-pathway EM did not differ between the MHT users (2-pathway EM comprised 15% and 4-pathway EM <2% of the total), but 16-pathway EM were lower in E alone users (p=0.036). Ratios of 2- and 4-pathway EM compared to 16-pathway EM were significantly higher in E alone compared to E+P users. Similar but not significant patterns were observed in CEE-alone and CEE+MPA users. Our data suggest that compared to E+P users, women using E alone have more extensive metabolism via the 2- versus the competing 16-pathway. This is consistent with epidemiologic evidence of reduced postmenopausal breast cancer risk associated with

Compared to E+P users, women using E alone have more extensive metabolism via the 2-versus the competing the 16-pathway…and may provide a clue to breast cancer reduction in the CEE alone users in the WHI.



Cancer Epidemiol Biomarkers Prev. 2018 Oct;27(10):1208-1213. doi: 10.1158/1055-9965.EPI-18-0135. Epub 2018 Jul 26.

Estrogen Metabolism in Postmenopausal Women Exposed *In Utero* to Diethylstilbestrol.

Troisi R[1], Hatch EE[2], Palmer JR[3], Titus L[4], Sampson JN[5], Xu X[6], Hoover RN[5].

⊕ Author information

Abstract

Background: Prenatal diethylstilbestrol (DES) exposure is associated with adverse reproductive outcomes and cancer of the breast and vagina/cervix in adult women. DES effects on estrogen metabolism have been hypothesized, but reproductive hormone concentrations and metabolic pathways have not been comprehensively described.**Methods:** Blood samples were provided by 60 postmenopausal women (40 exposed and 20 unexposed) who were participants in the NCI Combined DES Cohort Study, had never used hormone supplements or been diagnosed with cancer, had responded to the most recent cohort study questionnaire, and lived within driving distance of Boston University Medical School (Boston, MA). Parent estrogens and their metabolites were measured by high-performance liquid chromatography-tandem mass spectrometry. Age-adjusted percent changes in geometric means and associated

"These preliminary data suggest that postmenopausal women who were prenatally DES exposed may have relatively less 2 than 16 pathway estrogen metabolism compared with unexposed women. Impact: Lower 2 pathway metabolism has been associated with increased postmenopausal breast cancer risk and could potentially offer a partial explanation for the modest increased risk observed for prenatally DES-exposed women."

Published OnlineFirst April 27, 2014; DOI: 10.1158/1055-9965.EPI-14-0009

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Circulating Estrogen Metabolites and Risk of Breast Cancer in Postmenopausal Women

Alan A. Arslan[1,2,3,4], Karen L. Koenig[2,3], Per Lenner[5], Yelena Afanasyeva[2], Roy E. Shore[8], Yu Chen[2,3,4], Eva Lundin[6], Paolo Toniolo[1,4], Göran Hallmans[7], and Anne Zeleniuch-Jacquotte[2,3,4]

Abstract

Background: It has been hypothesized that predominance of the 2-hydroxylation estrogen metabolism pathway over the 16α-hydroxylation pathway may be inversely associated with breast cancer risk.

Methods: We examined the associations of invasive breast cancer risk with circulating 2-hydroxyestrone (2-OHE1), 16α-hydroxyestrone (16α-OHE1), and the 2-OHE1:16α-OHE1 ratio in a case–control study of postmenopausal women nested within two prospective cohorts: the New York University Women's Health Study (NYUWHS) and the Northern Sweden Mammary Screening Cohort (NSMSC), with adjustment for circulating levels of estrone, and additional analyses by tumor estrogen receptor (ER) status. Levels of 2-OHE1 and 16α-OHE1 were measured using ESTRAMET 2/16 assay in stored serum or plasma samples from 499 incident breast cancer cases and 499 controls, who were matched on cohort, age, and date of blood donation.

Results: Overall, no significant associations were observed between breast cancer risk and circulating levels of 2-OHE1, 16α-OHE1, or their ratio in either cohort and in combined analyses. For 2-OHE1, there was evidence of heterogeneity by ER status in models adjusting for estrone ($P \leq 0.03$). We observed a protective association of 2-OHE1 with ER+ breast cancer [multivariate-adjusted OR for a doubling of 2-OHE1, 0.67 (95% confidence interval [CI], 0.48–0.94; $P = 0.02$)].

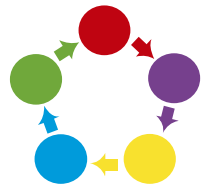
Conclusions: In this study, higher levels of 2-OHE1 were associated with reduced risk of ER+ breast cancer in postmenopausal women after adjustment for circulating estrone.

Impact: These results suggest that taking into account the levels of parent estrogens and ER status is

Higher levels of 2-OH estrone is associated with reduced risk of ER+ breast cancer. Perform estrogen metabolites in breast cancer prevention.

increasing interest in the role of various estrogen metabolites that have been hypothesized to affect the risk of

OHE1 ratio, may be associated with a reduced risk of



Endocr Relat Cancer. 2016 Jun;23(6):R249-66. doi: 10.1530/ERC-16-0118. Epub 2016 May 18.

In touch with your feminine side: how oestrogen metabolism impacts prostate cancer.

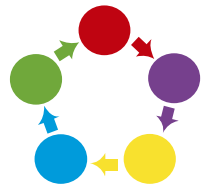
Rahman HP[1], Hofland J[2], Foster PA[3].

⊕ Author information

Abstract

Prostate cancer is the primary cancer in males, with increasing global incidence rates making this malignancy a significant healthcare burden. Androgens not only promote normal prostate maturity but also influence the development and progression of prostate cancer. Intriguingly, evidence now suggests endogenous and exogenous oestrogens, in the form of phytoestrogens, may be equally as relevant as androgens in prostate cancer growth. The prostate gland has the molecular mechanisms, catalysed by steroid sulphatase (STS), to unconjugate and utilise circulating oestrogens. Furthermore, prostate tissue also expresses enzymes essential for local oestrogen metabolism, including aromatase (CYP19A1) and 3β- and 17β-hydroxysteroid dehydrogenases. Increased expression of these enzymes in malignant prostate tissue compared with normal prostate indicates that oestrogen synthesis is favoured in malignancy and thus may influence tumour progression. In contrast to

"An imbalance of circulating oestrogens and androgens may be responsible for changes to the development and progression of prostate cancer. In addition to endogenous oestrogen availability, exposure to exogenous oestrogens in the form of phytoestrogens may also have a profound effect."



Medicine (Baltimore). 2016 Jul;95(27):e4066. doi: 10.1097/MD.0000000000004066.

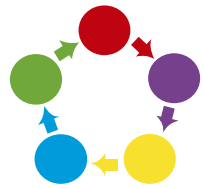
Genetic variants of the CYP1B1 gene as predictors of biochemical recurrence after radical prostatectomy in localized prostate cancer patients.

Gu CY[1], Qin XJ, Qu YY, Zhu Y, Wan FN, Zhang GM, Sun LJ, Zhu Y, Ye DW.

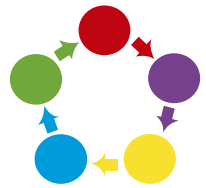
⊕ Author information

Abstract

Clinically localized prostate cancer is curative. Nevertheless many patients suffered from biochemical recurrence (BCR) after radical prostatectomy (RP). Mounting evidence suggest that estrogen and xenobiotic carcinogens play an essential role in progression of prostate cancervia oxidative estrogen metabolism. CYP1B1 is an enzyme involved in the hydroxylation of estrogens, a reaction of key relevance in estrogen metabolism. Given the role of CYP1B1 in the oxidative metabolism of endogenous/exogenous estrogen and compounds, CYP1B1 polymorphisms have the potential to modify its expression and subsequently lead to progression. We hypothesize that genetic variants of the CYP1B1 gene may influence clinical outcome in clinically localized prostate cancer patients. In this cohort study, we genotyped 9 tagging single nucleotide polymorphisms (SNPs) from the CYP1B1 gene in 312 patients treated with RP. For replication, these SNPs were genotyped in an independent cohort of 426 patients. The expression level of CYP1B1 in the adjacent normal prostate tissues was quantified by reverse transcription and real-time polymerase chain reaction. Kaplan-Meier analysis and Cox proportional hazard models were utilized to identify SNPs that correlated with BCR. CYP1B1 rs1056836 was significantly associated with BCR (hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.40-0.89, P = 0.002) and relative CYP1B1 mRNA expression. Our findings suggest inherited genetic variation in the CYP1B1 gene may contribute to variable clinical outcomes for patients with clinically localized prostate cancer.

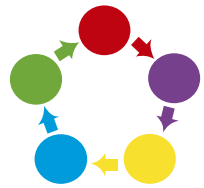


LABORATORY EVALUATION



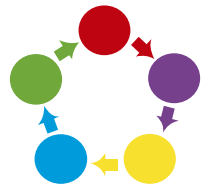
ESTROGEN METABOLITES

2-Hydroxyestrone (24hr urine)	6.46	0.26-13.68 mcg/24 hr
2-Methoxyestrone (24hr urine)	0.60	0.34-9.03 mcg/24 hr
16α-Hydroxyestrone (24hr urine)	6.63	0.25-7.89 mcg/24 hr
4-Hydroxyestrone (24hr urine)	2.92	0.33-1.98 mcg/24 hr
4-Methoxyestrone (24hr urine)	<0.38	0.20-1.60 mcg/24 hr
2-Hydroxyestrone/16α-Hydroxyestrone Ratio (24hr urine)	0.97	0.94-1.56
2-Methoxyestrone/2-Hydroxyestrone Ratio (24hr urine)	0.09	0.11-4.00
4-Methoxyestrone/4-Hydroxyestrone Ratio (24hr urine)	<0.13	0.18-3.60



PHASE I

Cytochrome P-450		
Result	Gene	
●	CYP1A1 *	www.genovations.com/gdgen01
●	CYP1B1 *	www.genovations.com/gdgen02
✔	CYP2A6	www.genovations.com/gdgen10
●	CYP2C9 *	www.genovations.com/gdgen05
●	CYP2C19 *	www.genovations.com/gdgen06
✔	CYP2D6	www.genovations.com/gdgen03
✔	CYP2E1	www.genovations.com/gdgen04
✔	CYP3A4 *	www.genovations.com/gdgen07



Phase II

Methylation

Result	Gene	SNP Location	Internet Information	Affects
+-	COMT	V158M		Liver/Gut

Acetylation (N-acetyl transferase)

SLOW METABOLIZER POLYMORPHISM

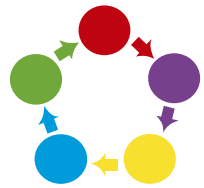
Result	Gene	SNP Location	Internet Information	Affects
- -	NAT1	R64W		All Cells
- -	NAT1	R187Q	www.genovations.com/gdr187q	Liver/Gut
- -	NAT2	I114T	www.genovations.com/gdi114t	Liver/Gut
+-	NAT2	R197Q	www.genovations.com/gdr197q	Liver/Gut
- -	NAT2	G286E	www.genovations.com/gdg286e	Liver/Gut
- -	NAT2	R64Q	www.genovations.com/gdr64q	Liver/Gut

FAST METABOLIZER POLYMORPHISM

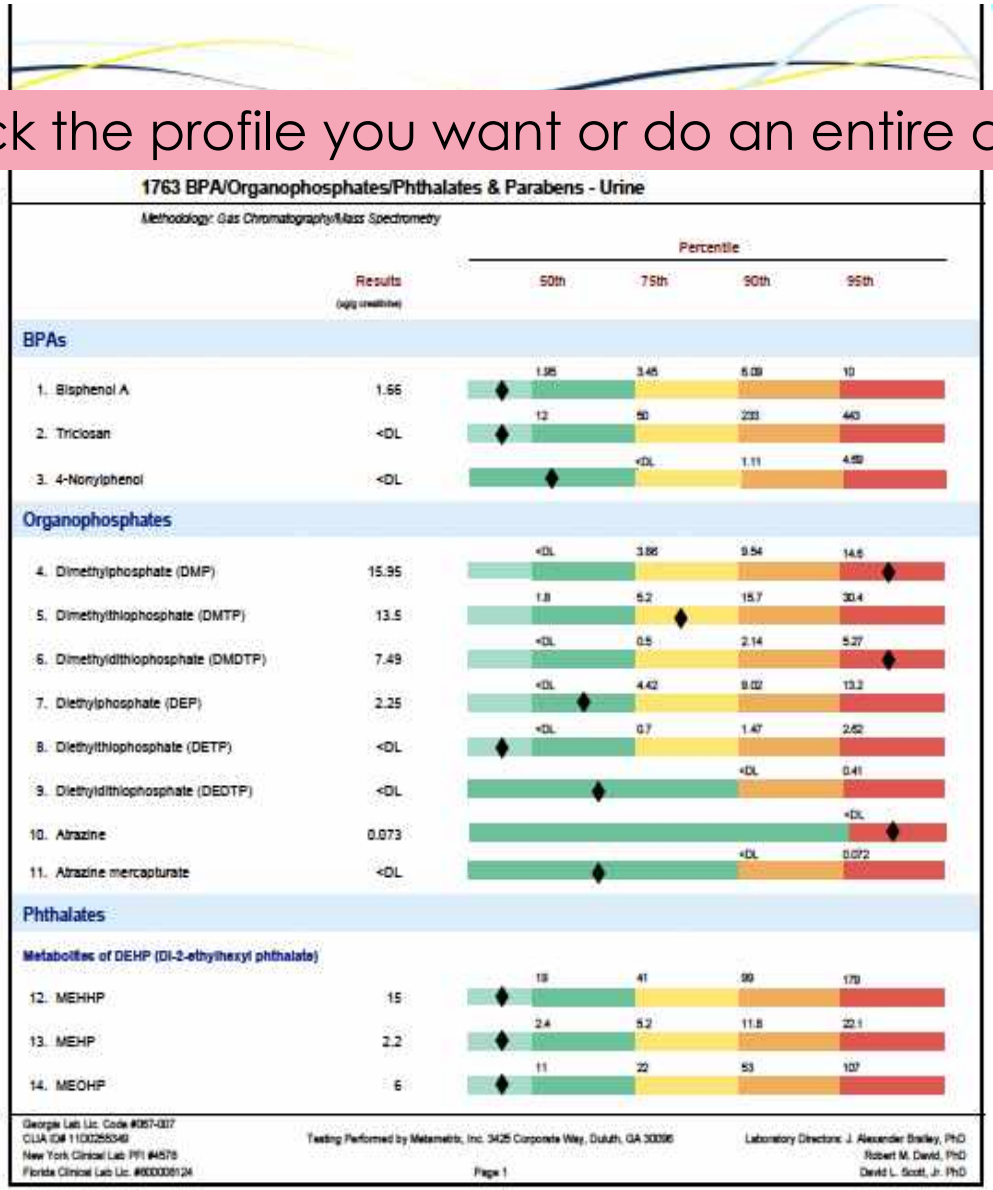
- -	NAT2	K268R	www.genovations.com/gdk268r	Liver/Gut

Glutathione Conjugation (Glutathione s-transferase)

Result	Gene	Location	Internet Information	Affects
ABSENT	GSTM1	1p13.3		Liver/Kidney
- -	GSTP1	I105V	[illegible]	Brain/Skin
- -	GSTP1	A114V	www.genovations.com/gda114v	Brain/Skin



Pick the profile you want or do an entire array:



1763 BPA/Organophosphates/Phthalates & Parabens - Urine

Methodology: Gas Chromatography/Mass Spectrometry

	Results (ug/g creatinine)	Percentile 50th	75th	90th	95th
BPAs					
1. Bisphenol A	1.66	1.95	3.45	6.09	10
2. Triclosan	<DL	12	50	233	443
3. 4-Nonylphenol	<DL	<DL	1.11	4.69	
Organophosphates					
4. Dimethylphosphate (DMP)	15.95	<DL	3.86	9.54	14.6
5. Dimethylthiophosphate (DMTP)	13.5	1.8	5.2	15.7	30.4
6. Dimethyldithiophosphate (DMDTP)	7.49	<DL	0.5	2.14	5.27
7. Diethylphosphate (DEP)	2.25	<DL	4.42	9.02	13.2
8. Diethylthiophosphate (DETP)	<DL	<DL	0.7	1.47	2.62
9. Diethyldithiophosphate (DEDTP)	<DL			<DL	0.41
10. Atrazine	0.073				<DL
11. Atrazine mercapturate	<DL			<DL	0.072
Phthalates					
Metabolites of DEHP (DI-2-ethylhexyl phthalate)					
12. MEHHP	15	19	41	99	179
13. MEHP	2.2	2.4	5.2	11.8	22.1
14. MEOHP	6	11	22	53	107

Georgia Lab Lic. Code #067-007
CLIA ID# 11D0265349
New York Clinical Lab PFI #4578
Florida Clinical Lab Lic. #800008124

Testing Performed by Metametrix, Inc. 3425 Corporate Way, Duluth, GA 30096

Page 1

Laboratory Directors: J. Alexander Bralley, PhD
Robert M. David, PhD
David L. Scott, Jr. PhD

0762 Volatile Solvents - Whole Blood

Methodology: Gas Chromatography/Mass Spectrometry

	Results (ng/mL)	Percentile 50th	75th	90th	95th
1. Benzene	<DL	<DL	0.06	0.17	0.26
2. Ethylbenzene	<DL	<DL	0.05	0.08	0.11
3. Styrene	<DL	<DL	0.05	0.09	0.12
4. Toluene	<DL	0.13	<DL	0.43	0.68
5. m,p-Xylene	<DL	<DL	0.2	0.28	0.34
6. o-Xylene	<DL	<DL	0.51	0.72	0.9

Percentile values are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009.

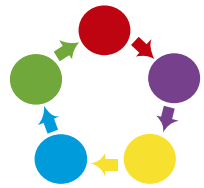
7. Hexane	211	183	209	254	278
8. 2-Methylpentane	45	52	63	75	88
9. 3-Methylpentane	93	100	116	142	164
10. Iso-octane	5.7	7.6	8.6	9.8	10.2

No national reference ranges are established for hexane, 2- and 3- methylpentane and iso-octane. Percentile ranges are based on patient samples analyzed at Metametrix.

<DL = less than detection limit

These levels provide a reference range to determine whether an individual has been exposed to higher levels of toxicants than found in the general population.

For interpretive information, visit www.metametrix.com/vs and select the Interpretive Guide from the downloads tab.



0763 Organophosphates Profile - Urine

Methodology: Gas Chromatography/Mass Spectrometry

	Results ug/g creatinine	Percentile 50th	75th	90th	95th
1. Dimethylthiophosphate (DMTP)	10	1.8	5.2	15.7	30.4
2. Dimethyldithiophosphate (DMDTP)	5.26	<DL	0.5	2.14	5.27
3. Diethylthiophosphate (DETP)	<DL	<DL	0.7	1.47	2.82
4. Diethyldithiophosphate (DEDTP)	<DL			<DL	0.41
5. Atrazine	0.32				<DL
6. Atrazine mercapturate	0.143			<DL	0.072

Creatinine = 66 mg/dL

Percentile values for organophosphates are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009. No national reference ranges are established for atrazine or atrazine mercapturate; percentile ranges are based on patient samples analyzed at Genova Diagnostics.

These levels provide a reference range to determine whether an individual has been exposed to higher levels of toxicants than found in the general population.

<DL = less than detection limit

For interpretive information, visit www.metametrix.com/gp and select the Interpretive Guide from the downloads tab.

POTENTIALLY TOXIC METALS

METALS	RESULT µg/g creat	REFERENCE RANGE	WITHIN REFERENCE RANGE	ELEVATED	VERY ELEVATED
Aluminum	3.8	< 25			
Antimony	< dl	< 0.3			
Arsenic	19	< 108			
Barium	2	< 7			
Beryllium	< dl	< 0.5			
Bismuth	< dl	< 10			
Cadmium	0.4	< 0.8			
Cesium	4.3	< 9			
Gadolinium	< dl	< 0.3			
Lead	0.4	< 2			
Mercury	0.8	< 3			
Nickel	4.7	< 10			
Palladium	< dl	< 0.3			
Platinum	< dl	< 1			
Tellurium	0.2	< 0.3			
Thallium	0.2	< 0.5			
Thorium	< dl	< 0.03			
Tin	0.2	< 9			
Titanium	N/A	< 15			
Tungsten	< dl	< 0.4			
Uranium	< dl	< 0.03			

URINE CREATININE

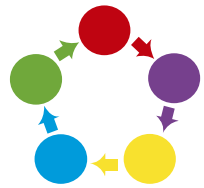
	RESULT mg/dL	REFERENCE RANGE	2SD LOW	1SD LOW	MEAN	1SD HIGH	2SD HIGH
Creatinine	65.4	45- 225					

SPECIMEN DATA

Comments:
Date Collected:
Date Received: 12/9/2010
Date Completed: 12/12/2010
Method: ICP-MS

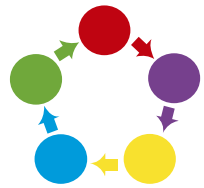
pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent: DMSA

Collection Period: timed: 6 hours
Volume: 1600 ml
Provocation:



SUGGESTED INITIAL LABORATORY WORK-UP

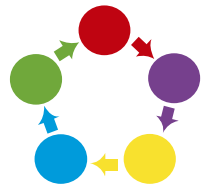
- Adiponectin
- Proinsulin
- HgbA1c
- Fasting Insulin, and 30 min insulin after 75g glucose load, 1 hour and 2hr insulin level
- Fasting glucose, 1 hour and 2 hr glucose after 75g load
- NMR Lipoprotein Profile
- Comprehensive Metabolic Panel
- GGTP
- Uric Acid
- Methane breath test
- Comprehensive stool test



ADDITIONAL LABS

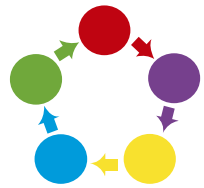
- 25-OH Vitamin D
- Homocysteine
- Lipoprotein (a)
- CRP-HS
- Apolipoprotein B and Apoliproprotein A1
- Gliadin Antibody
- Celiac Panel
- Celiac Genetic panel (HLA-DQ2 and DQ8)
- Nutrient Analysis
- LpPLA2
- PAI-1
- Inflammatory Cytokines: IL-6, IL-8, TNF-alpha
- Resistin?

Luo Z, Zhang Y, Li F, He J, Ding H, Yan L, Cheng H. *Resistin induces insulin resistance by both AMPK-dependent and AMPK-independent mechanisms in HepG2 cells.* Endocrine. 2009 May 8.



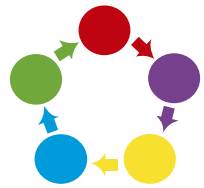
COMPREHENSIVE STOOL ANALYSIS

- Diversity
- Microbiology
  - Pathogenic bacteria
  - Fungi
  - Parasites
  - Good bacteria
    - Lactobacillus
    - Bifidobacterium
- SCFA's
  - Proprionate
  - Butyrate
  - Acetate
- Pancreatic Function

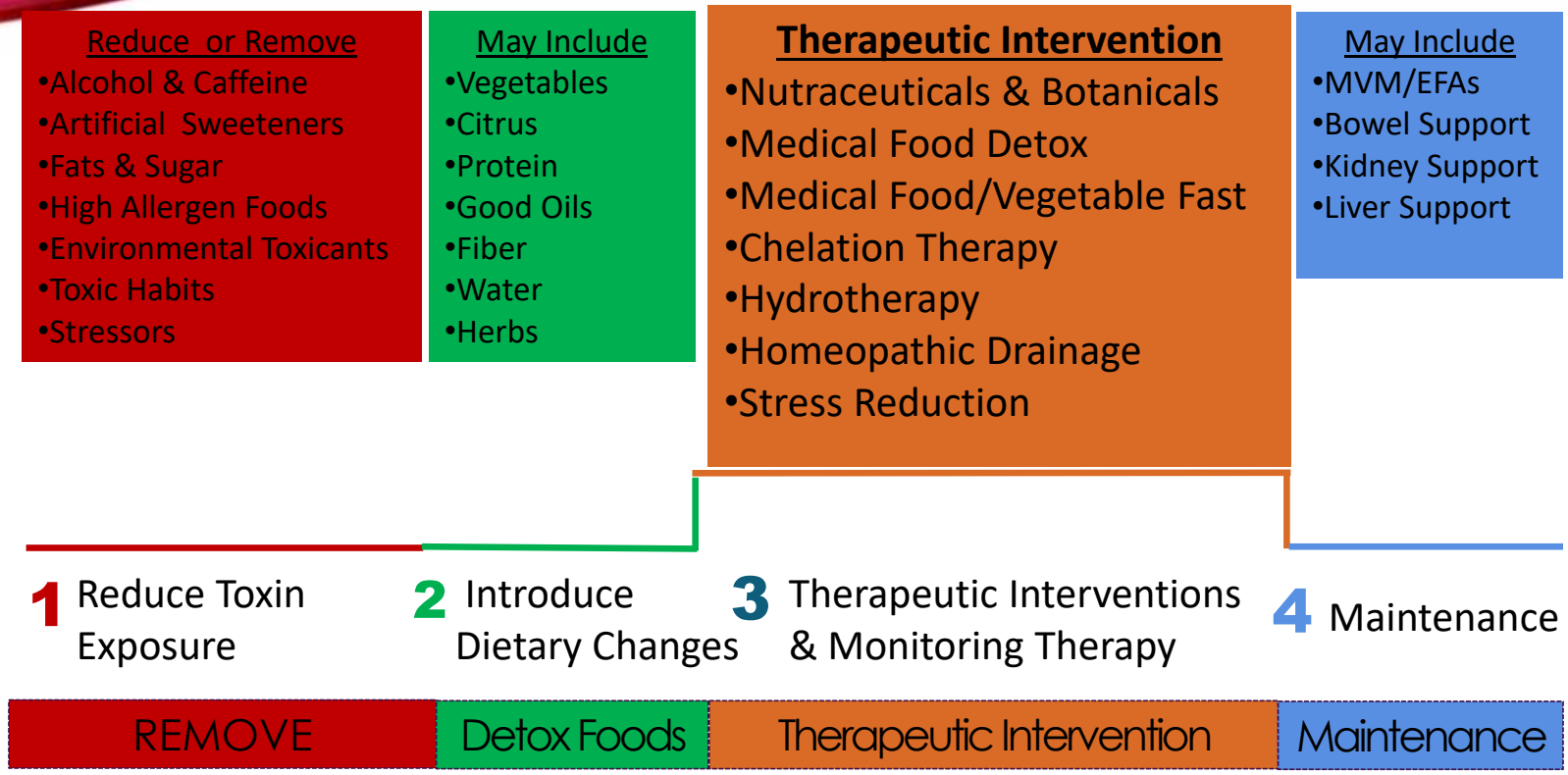


HOW DO WE DECREASE OUR RISK?

- Proper Risk Assessment
  - Connect the dots
- Decrease exposure
- Promote detoxification
- Enhance Elimination
- Awareness

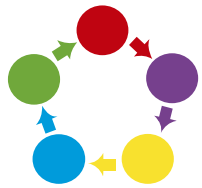


SEQUENCING A DETOX PROGRAM



My Approach

- Nutritional Support with wholesome food (fresh, whole, unprocessed, organic, colorful (12 servings vegetables/fruit), high fiber (35g soluble), with nuts, seeds, fermented.
- Digestion
- Elimination Diet and 5R Program
  - personalize
- Decrease Insulin Stimulation
- Address the underlying cause/causes: Detoxification
- Lifestyle Modification
- Exercise/Movement
- Sleep
- Stress
- Modify/address gut microbiota
- Targeted Supplementation
  - Food is the foundation
- Mind-body-spirit connection
- Support



Am J Clin Nutr. 2011 Sep;94(3):900-5. doi: 10.3945/ajcn.111.015578. Epub 2011 Jul 20.

Dietary fiber intake and risk of breast cancer: a meta-analysis of prospective cohort studies.

Dong JY[1], He K, Wang P, Qin LQ.

Author information

[1]Department of Nutrition and Food Hygiene, School of Radiation Medicine and Public Health, Soochow University, Suzhou, China. dongjy@mail3.sysu.edu.cn

Abstract

BACKGROUND: Observational and preclinical studies suggest that dietary fiber intake may reduce the risk of breast cancer, but the results are inconclusive.

OBJECTIVE: We aimed to examine the association between dietary fiber intake and risk of breast cancer by conducting a meta-analysis of prospective cohort studies.

DESIGN: Relevant studies were identified by a PubMed database search through January 2011. Reference lists from retrieved article
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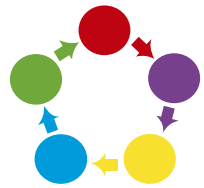
CONCLUSION: This meta-analysis provides evidence of a significant inverse dose-response association between dietary fiber intake and breast cancer risk.

A meta-analysis of 10 prospective studies showing a significant inverse association between dietary fiber and risk of BC, with no differences by geographical region or menopausal status.



Breast Cancer Res Treat. 2011 May;127(1):23-31. doi: 10.1007/s10549-011-1467-5. Epub 2011 Mar 27.

Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies.

Dong JY[1], Zhang L, He K, Qin LQ.

Author information

Abstract

Epidemiologic findings are inconsistent regarding risk for breast cancer related to dairy consumption. We performed a meta-analysis of prospective cohort studies to examine the association between diary product consumption and risk of breast cancer. A PubMed database search through January 2011 was performed for relevant studies. We included prospective cohort studies that reported relative risks with 95% confidence intervals for the association of dairy consumption and breast cancer risk. A random effects model was used to calculate the summary risk estimates. We identified 18 prospective cohort studies eligible for analysis, involving 24,187 cases and 1,063,471 participants. The summary relative risk of breast cancer for the highest intake of total dairy food compared with the lowest was 0.85 (95% confidence interval: 0.76-0.95), with evidence of heterogeneity (P = 0.01, I (2) = 54.5%). For milk consumption, the summary relative risk was 0.91 (95% confidence interval: 0.80-1.02), and substantial heterogeneity was observed (P = 0.003, I (2) = 59.7%). Subgroup analyses based on limited numbers

"…findings of the present meta-analysis indicate that increased consumption of total dairy food, but not milk, may be associated with a reduced risk of breast cancer."

Am J Clin Nutr. 2013 Feb;97(2):344-53. doi: 10.3945/ajcn.112.034025. Epub 2012 Dec 26.

Dietary fiber intake and risk of hormonal receptor-defined breast cancer in the European Prospective Investigation into Cancer and Nutrition study.

Ferrari P[1], Rinaldi S, Jenab M, Lukanova A, Olsen A, Tjønneland A, Overvad K, Clavel-Chapelon F, Fagherazzi G, Touillaud M, Kaaks R, von Rüsten A, Boeing H, Trichopoulou A, Lagiou P, Benetou V, Grioni S, Panico S, Masala G, Tumino R, Polidoro S, Bakker MF, van Gils CH, Ros MM, Bueno-de-Mesquita HB, Krum-Hansen S, Engeset D, Skeie G, Pilar A, Sánchez MJ, Buckland G, Ardanaz E, Chirlaque D, Rodriguez L, Travis R, Key T, Khaw KT, Wareham NJ, Sund M, Lenner P, Slimani N, Norat T, Aune D, Riboli E, Romieu I.

⊕ Author information

Abstract

BACKGROUND: Limited scientific evidence has characterized the association between dietary fiber intake and risk of breast cancer (BC) by menopausal status and hormone receptor expression in tumors.

OBJECTIVE: We investigated the relation between total dietary fiber and its main food sources (vegetables, fruit, cereals, and legumes) and BC risk by using data from the European Prospective Investigation into Cancer and Nutrition (EPIC).

DESIGN: A total of 11,576 invasive BC cases in 334,849 EPIC women mostly aged 35-70 y at baseline were identified over a median follow-up of 11.5 y. Dietary fiber was estimated from country-specific dietary questionnaires. Multivariable Cox proportional hazards regression models were used to quantify the association between dietary variables and BC risk with energy adjustment by

"Diets rich in dietary fiber and, particularly, fiber from vegetables may be associated with a small reduction in risk of BC, independently of menopausal status."

Int J Cancer. 1998 Mar 16;75(6):825-30.

Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms.

Ambrosone CB[1], Freudenheim JL, Sinha R, Graham S, Marshall JR, Vena JE, Laughlin R, Nemoto T, Shields PG.

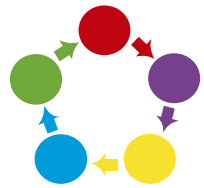
Author information

Abstract

Although inconsistencies exist, some studies have shown that meat consumption is associated with breast cancer risk. Several heterocyclic amines (HAs), formed in the cooking of meats, are mammary carcinogens in laboratory models. HAs are activated by polymorphic N-acetyltransferase (NAT2) and rapid NAT2 activity may increase risk associated with HAs. We investigated whether ingestion of meat, chicken and fish, as well as particular concentrated sources of HAs, was associated with breast cancer risk, and if NAT2 genotype modified risk. Caucasian women with incident breast cancer (n = 740) and community controls (n = 810) were interviewed and administered a food frequency questionnaire. A subset of these women (n = 793) provided a blood sample. Polymerase chain reaction and restriction fragment length polymorphism analyses were used to determine NAT2 genotype. Consumption of red meats, as well as an index of concentrated sources of HAs, was not associated with increased breast cancer risk, nor did risk vary by NAT2 genotype. In post-menopausal women, higher fish consumption was inversely associated with risk (odds ratio = 0.7; 95% confidence interval, 0.4-1.0); among pre-menopausal women, there was the suggestion of inverse associations between risk and pork and chicken intake. Our results suggest that consumption [illegible] risk. However, due to the str[illegible]urement error in evaluation of [illegible]

...higher fish consumption was **inversely** associated with risk.

PMID: 9506525 [PubMed - indexed for MEDLINE]



Public Health Nutr. 2011 Dec;14(12A):2323-32. doi: 10.1017/S1368980011002588.

Olive oil, an essential component of the Mediterranean diet, and breast cancer.

Escrich E[1], Moral R, Solanas M.

Author information

Abstract

OBJECTIVE: The Mediterranean diet has been related to a lower risk of some chronic diseases, including cancer. We aim to gain insight into the effects of the main source of fat of this diet on breast cancer, the most common type of malignancy in women.

DESIGN: Data from sixteen experimental series analysing the effects of dietary lipids on mammary carcinogenesis in an animal model, in the context of the international literature on the Mediterranean diet, olive oil and breast cancer risk.

SETTING: Experimental and human data on the effects of olive oil and Mediterranean diet on breast cancer.

SUBJECTS: An animal model of induced breast cancer and other human and experimental studies in the literature.

RESULTS: Diets rich in extra virgin olive oil (EVOO) exert a negative modulatory effect on experimental breast cancer to a weak promoting effect, much lower than that obtained with a high-corn oil diet. EVOO confers to the mammary adenocarcinomas a clinical behaviour and morphological features compatible with low tumour aggressiveness. This

Consumption of EVOO in moderate quantities and throughout the lifetime appears to be a healthy choice and may favourably influence breast cancer risk.

Eur J Cancer Prev. 2014 Apr 9. [Epub ahead of print]

Dietary extra-virgin olive oil and corn oil differentially modulate the mRNA expression of xenobiotic-metabolizing enzymes in the liver and in the mammary gland in a rat chemically induced breast cancer model.

Manzanares MA[1], Solanas M, Moral R, Escrich R, Vela E, Costa I, Escrich E.

Author information

Abstract

High extra-virgin olive oil (EVOO) and corn oil diets differentially modulate experimental mammary carcinogenesis. We have investigated their influence on the initiation stage through the modulation of the expression of xenobiotic-metabolizing enzymes (XMEs) in the liver and the mammary gland. Female Sprague-Dawley rats were fed a low-fat (LF), high corn oil (HCO), or high EVOO (HOO) diet from weaning and gavaged with 7,12-dimethylbenz(a)anthracene (DMBA). The HCO diet increased the mRNA levels of the phase I enzymes CYP1A1, CYP1A2 and, to a lesser extent, CYP1B1, in the liver. The Aryl hydrocarbon receptor (AhR) seemed to be involved in this upregulated CYP1 expression. However, a slight trend toward an increase in the mRNA levels of the phase II enzymes GSTP1 and NQO1 was observed with the HOO diet. At least in the case of GSTP1, this effect was linked to an increased Nrf2 transactivation activity. This different regulation of the XMEs expression led, in the case

"The HOO diet was associated with a slower phase I metabolism accompanied by a faster phase II detoxification, thus reducing the output of the active compounds to the target tissues".

Breast Cancer Res Treat. 2010 Jan;119(2):463-74. doi: 10.1007/s10549-009-0407-0. Epub 2009 May 8.

Genetic polymorphisms in phase I and phase II enzymes and breast cancer risk associated with menopausal hormone therapy in postmenopausal women.

MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk[1].

⊕ Collaborators (30)

⊕ Author information

Erratum in

Breast Cancer Res Treat. 2010 Jan;119(2):475.

Abstract

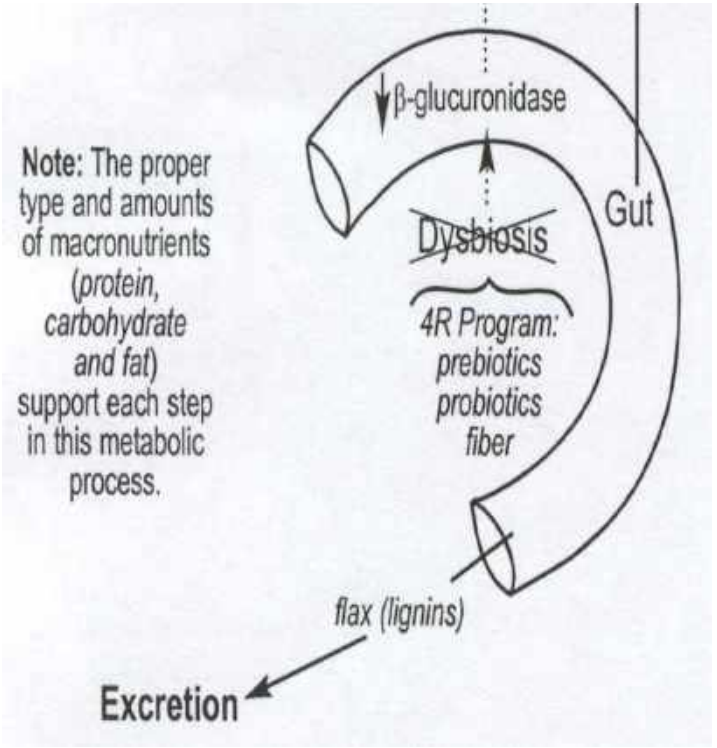
Recent findings indicate a greater risk of postmenopausal breast cancer with estrogen-progestagen therapy than estrogen monotherapy, and more so for current than past use. Few studies have examined individual genetic susceptibility to the effects of menopausal hormone therapy. We used two population-based case-control studies with 3,155 postmenopausal breast cancer patients and 5,496 controls to evaluate modification of breast cancer risk associated with duration of hormone use by genes involved in hormone metabolism and detoxification. Twenty-eight polymorphisms in eight genes of phase I (CYP1A1, CYP1A2, CYP1B1, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP3A7) and nine genes of phase II enzymes (COMT, GSTM1, GSTM3, GSTP1, GSTT1, SULT1A1, UGT1A1, UGT1A6, UGT2B7) were genotyped. The risk associated with duration of use of combined estrogen-progestagen therapy was significantly modified by genetic polymorphisms located in CYP1B1, GSTP1, and GSTT1. In homozygote

"Postmenopausal breast cancer risk associated with hormone therapy may be modified by genetically determined variations in phase I and II enzymes involved in steroid hormone metabolism".

ENCOURAGE HEALTHY INTESTINAL **EXCRETION**

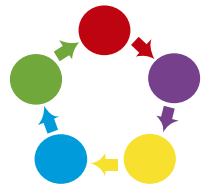
Improve Gut Ecology
Supply factors shown to assist in estrogen and fat soluble metabolic waste and toxin excretion

- Lipotropic factors choline, B_6, FA, B_{12} to promote bile synthesis and efficiently bundle toxins and estrogen metabolites for removal from the body via the gut
- Phytoestrogens Lignans (flax) – increase SHBG to bind circulating estrogens
- Probiotics *L. acidophilus* (NCFM), *Bifidobacteria lactis* BI-07 – beta glucuronidase deactivation
- Fiber 55% insoluble fiber, 45% soluble fiber, Lignins (fiber) – transit time



Nutrients for Healthy Bile Flow

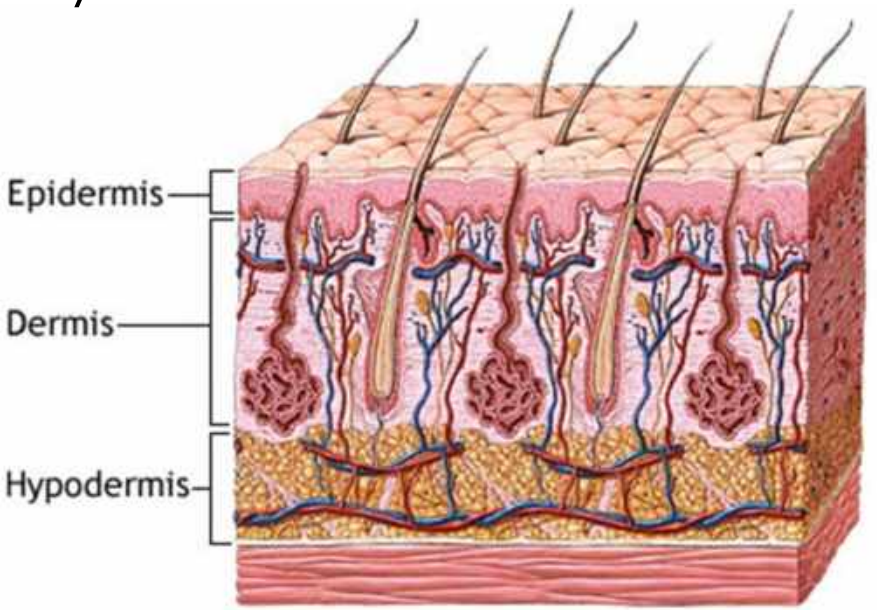
- **Select nutrients and herbs to assist with healthy bile flow and gallbladder function as well as fat metabolism:**
  - Vitamin C, B6, folic acid, B12, Mg, choline, inositol, taurine, methionine, betaine HCl
  - Artichoke leaf extract
  - Chen Pi (*Citrus reticulata*) containing chlorogenic acid, hyperoside, caffeic acid and rutin



Sweating and Hydrotherapy

Elimination via Skin

- Acts as a second kidney and eliminates water, salts and urea
- Function is improved if skin is clean of dead skin cells
  - Dry skin brushing—brush toward the heart
  - Loofah sponge when bathing
  - Soap tends to block pores
- Sweat therapy
  - Replenish the 1 pint of fluid per hour lost to protect kidneys from dehydration



cells

MDPI

Review

The Microbiome–Estrogen Connection and Breast Cancer Risk

Sheetal Parida and Dipali Sharma *

Department of Oncology, Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA; sparida1@jhu.edu

* Correspondence: dsharma7@jhmi.edu

Received: 25 October 2019; Accepted: 6 December 2019; Published: 15 December 2019

check for updates

Abstract: The microbiome is undoubtedly the second genome of the human body and has diverse roles in health and disease. However, translational progress is limited due to the vastness of the microbiome, which accounts for over 3.3 million genes, whose functions are still unclear. Numerous studies in the past decade have demonstrated how microbiome impacts various organ-specific cancers by altering the energy balance of the body, increasing adiposity, synthesizing genotoxins and small signaling molecules, and priming and regulating immune response and metabolism of indigestible dietary components, xenobiotics, and pharmaceuticals. In relation to breast cancer, one of the most prominent roles of the human microbiome is the regulation of steroid hormone metabolism since endogenous estrogens are the most important risk factor in breast cancer development especially in postmenopausal women. Intestinal microbes encode enzymes capable of deconjugating conjugated estrogen metabolites marked for excretion, pushing them back into the enterohepatic circulation in a biologically active form. In addition, the intestinal microbes also break down otherwise indigestible

"The present account discusses the potential role of gastrointestinal microbiome in breast cancer development by mediating metabolism of steroid hormones and synthesis of biologically active estrogen mimics."

the majority of commensals are not conventionally culturable, and partly due to the vastness of the microbiome accounting for over 3.3 million genes [2] whose functions are not fully understood. In addition, microbes reside as consortia in different body sites, and most of the known physiological functions of microbial dysbiosis are community-effects rather than effects of individual microbes. On the bright side, we are now equipped with deep sequencing techniques like shotgun sequencing and multiple tools to perform gene and functional annotations enabling better understanding of the genome–metagenome puzzle. The findings of the human microbiome project continue to unearth the

AAPS J. 2014 Jul;16(4):705-13. doi: 10.1208/s12248-014-9610-y. Epub 2014 May 13.

Pharmacokinetics and pharmacodynamics of phenethyl isothiocyanate: implications in breast cancer prevention.

Morris ME[1], Dave RA.

Author information

Abstract

Phenethyl isothiocyanate (PEITC)-a naturally occurring isothiocyanate in cruciferous vegetables-has been extensively studied as a chemopreventive agent in several preclinical species and in humans. Pharmacokinetic features of unchanged PEITC are (I) linear and first-order absorption, (II) high protein binding and capacity-limited tissue distribution, and (III) reversible metabolism and capacity-limited hepatic elimination. Membrane transport of PEITC is mediated by BCRP, multidrug resistance-associated protein (MRP) 1, and MRP2 transporters belonging to the ATP-binding-cassette (ABC) family. PEITC is metabolized by glutathione S-transferase (GST) in the liver, with the glutathione conjugate of PEITC undergoing further

"The pharmacodynamics of PEITC in breast cancer include cancer cell apoptosis by up-regulation of apoptotic genes, cell cycle arrest at G2/M phase by generation of reactive oxygen species and depletion of intracellular glutathione, down-regulation of the estrogen receptor, decrease in sensitivity to estrogen, and inhibition of tumor metastasis".

Biochem Pharmacol. 2018 Sep;155:252-263. doi: 10.1016/j.bcp.2018.07.006. Epub 2018 Jul 20.

Resveratrol represses estrogen-induced mammary carcinogenesis through NRF2-UGT1A8-estrogen metabolic axis activation.

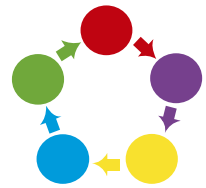
Zhou X[1], Zhao Y[1], Wang J[1], Wang X[1], Chen C[1], Yin D[1], Zhao F[1], Yin J[1], Guo M[2], Zhang L[3], Du L[1], Zhang B[4], Yin X[5].

⊕ Author information

Abstract

Estrogen plays a pivotal role in the pathological development of breast cancer. Resveratrol has chemo-preventive effects against breast cancer, whereas, the mechanism of antitumor activities of resveratrol remains unanswered. In this study, we showed that estrogen homeostasis profile was disturbed in both breast cancer patients and in experimental breast cancer model rats, with carcinogenic

"Here we found that the mammary nuclear factor erythroid 2-related factor 2 (NRF2) - UGT1A8 signaling was down-regulated in breast cancer rats, whereas treatment with resveratrol could upregulate the expression of NRF2 and UGT1A8, accelerate metabolic elimination of catechol estrogens, inhibit estrogen-induced DNA damage and suppress the pathological development of breast cancer."



Toxicol Lett. 2018 Jul;291:77-85. doi: 10.1016/j.toxlet.2018.04.008. Epub 2018 Apr 11.

Fingolimod interrupts the cross talk between estrogen metabolism and sphingolipid metabolism within prostate cancer cells.

Allam RM[1], Al-Abd AM[2], Khedr A[3], Sharaf OA[4], Nofal SM[5], Khalifa AE[6], Mosli HA[7], Abdel-Naim AB[8].

Author information

Abstract

Sphingolipids are critical regulators of tumor microenvironments and play an important role in estrogen-dependent cancers. Estrogen and estrogen metabolites were found to be involved in prostate cancer. Fingolimod (FTY720) is a sphingokinase-1 (SphK1) inhibitor with anticancer properties against various tumor cell types. Herein, we investigated the interference of FTY720 with the cross talk between sphingolipid metabolism and estrogen metabolism within prostate cancer cells. FTY720 showed cytotoxic antiproliferative effects against androgen-dependent and -independent prostate cancer cells with IC_{50} ranging from 3.0±0.3 to 6.8±1.7μM. Exposure of prostate cancer cells to FTY720 resulted in a dramatic decrease in the concentration of estradiol, estrone, 4-hydroxyestradiol and 16α-hydroxyestrone compared to control cells. However, FTY720 significantly increased the concentration of 2-methoxyestrone and 2-methoxyestradiol within prostate cancer cells. This was mirrored by significant downregulating of the expression of estrogen and catechol estrogen-synthesizing enzymes (CYP19, CYP1A1 and CYP1B1) within prostate cancer cells. On the other hand, FTY720 significantly upregulated

"We found that fingolimod (FTY720) could modulate the estrogenic micromilieu and interrupt its cross talk with sphingolipid metabolism."

Int J Cancer. 2018 Aug 1;143(3):580-590. doi: 10.1002/ijc.31387. Epub 2018 Apr 6.

Open/close author inform

A dietary pattern based on estrogen metabolism is associated with breast cancer risk in a prospective cohort of postmenopausal women.

Guinter MA[1,2], McLain AC[2], Merchant AT[2], Sandler DP[3], Steck SE[2,4].

⊕ Author information

Abstract

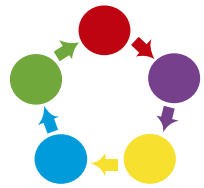
Increased exposure to estrogen is a risk factor for postmenopausal breast cancer, and dietary factors can influence estrogen metabolism. However, studies of diet and breast cancer have been inconclusive. We developed a dietary pattern associated with levels of unconjugated estradiol and the ratio of 2- and 16-hydroxylated estrogen metabolites in a subsample of Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO) participants (n = 653) using reduced rank regression, and examined its association with postmenopausal breast cancer prospectively in the larger PLCO cohort (n = 27,488). The estrogen-related dietary pattern (ERDP) was comprised of foods with positively-weighted intakes (non-whole/refined grains, tomatoes, cruciferous vegetables, cheese, fish/shellfish high in ω-3 fatty acids, franks/luncheon meats) and negatively-weighted intakes (nuts/seeds, other vegetables, fish/shellfish low in ω-3 fatty acids, yogurt, coffee). A 1-unit increase in the ERDP score was associated with an increase in total (HR: 1.09, 95% CI: 1.01-1.18), invasive (HR: 1.13; 95% CI: 1.04-1.24) and estrogen receptor (ER)-positive (HR: 1.13, 95% CI: 1.02-1.24) breast cancer risk after adjustment for confounders. Associations were observed for the fourth quartile of ERDP compared with the first quartile for overall breast cancer (HR: 1.14; 95% CI: 0.98-1.32), invasive cases (HR: 1.20, 95% CI: 1.02-1.42) and ER-positive cases (HR: 1.19; 95% CI: 0.99-1.41). The increased risk associated with increasing ERDP score was more apparent in strata of some effect modifiers (postmenopausal

"Results suggest a dietary pattern based on estrogen metabolism is positively associated with postmenopausal breast cancer risk, possibly through an estrogenic influence."

EXERCISE

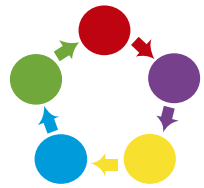
- Tailor to individual patient
- Swimming to help circulation
- Gentle movement
- Support lymph circulation
- Bathing in magnesium rich sea salt

Int J Dermatol. 2005 Feb;44(2):151-7



NUTRACEUTICALS

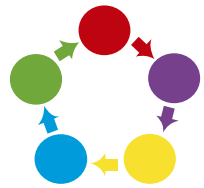
- Micronutrient Support
- Medical Foods
- Botanicals
- Support all conjugation reactions of phase 2



METHYLATION SUPPORT

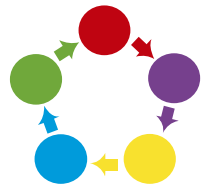
COMT uses SAMe as its methyl donor; therefore, maintaining SAMe availability will encourage COMT activity

- Methionine-esp important if low homocysteine
- Magnesium
- B2, B6, B12
- Folic acid (also as folinic acid, 5-formyl THF, or 5-methyl THF)
- TMG (betaine)



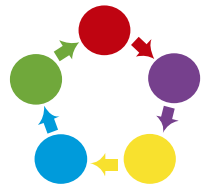
DIETARY SUPPLEMENTS TO OPTIMIZE REDUCED GLUTATHIONE LEVELS

- Reduced glutathione 1-3 g/day
- N-acetyl cysteine 600-3,000 mg/day
- Lipoic acid 200-1,000 mg/day
- Whey protein concentrates 2-3 servings/day
- Magnesium 400 + mg
- Vitamin C: 500+mg
- Vitamin E: 400 IU
- Silymarin 400-1,200 mg/day
- Pantothenic acid 500-1,000 mg/day
- SAMe 400-800 mg/day

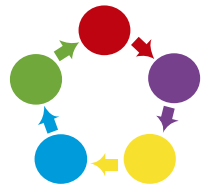


DIETARY SUPPLEMENTS TO OPTIMIZE REDUCED GLUTATHIONE LEVELS CONTINUED…

- Glycine,
- Glutamine
- B vitamins (B2, B6, B12, 5MTHF)
- Turmeric extract, bilberry, melatonin, theanine, strawberry/black raspberry extracts
- Anti-oxidants (to discourage formation of quinone compounds)

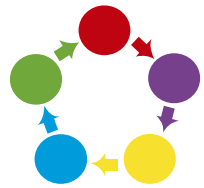


MY APPROACH TO INSULIN RESISTANCE TREATMENT

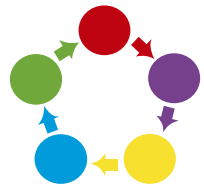


DIETARY MANAGEMENT FOR THE PATIENT WITH INSULIN RESISTANCE

- Decrease insulin stimulation.
  - Dietary modifications which decrease insulin release:
    - Fiber
    - 'Good' (vs. 'bad') fat
    - 'Good' (vs. 'bad') carbohydrates; Low glycemic load, remove NAS
    - Protein at every meal
    - Elimination of most inflammatory food:
    - Wheat, dairy, soy, corn, nightshades….
- Modify Gut Microbiota
  - Food first
  - Fermented Foods
  - Probiotics/prebiotics
- Increase cellular responsiveness to insulin.
  - Agents that modify insulin responsiveness at the cellular level:
    - Spices
    - Herbs
    - Chromium
    - Vitamin D
    - Magnesium
    - Omega-3



INSULIN RESISTANCE AND GUT MICROBIOTA



Int. J. Mol. Sci. **2014**, *15*, 11678-11699; doi:10.3390/ijms150711678

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Review

Mediterranean Diet and Health: Food Effects on Gut Microbiota and Disease Control

Federica Del Chierico [1,†], Pamela Vernocchi [1,2,†], Bruno Dallapiccola [3] and Lorenza Putignani [4,*]

[1] Unit of Metagenomics, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, Rome 400165, Italy; E-Mails: federica.delchierico@opbg.net (F.D.C.); pamela.vernocchi@opbg.net (P.V.)
[2] Interdepartmental Centre for Industrial Research-CIRI-AGRIFOOD, Alma Mater Studiorum, University of Bologna, Piazza Goidanich, Cesena-FC 47521, Italy
[3] Scientific Directorate, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio
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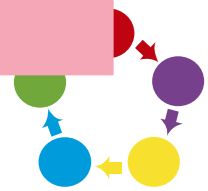
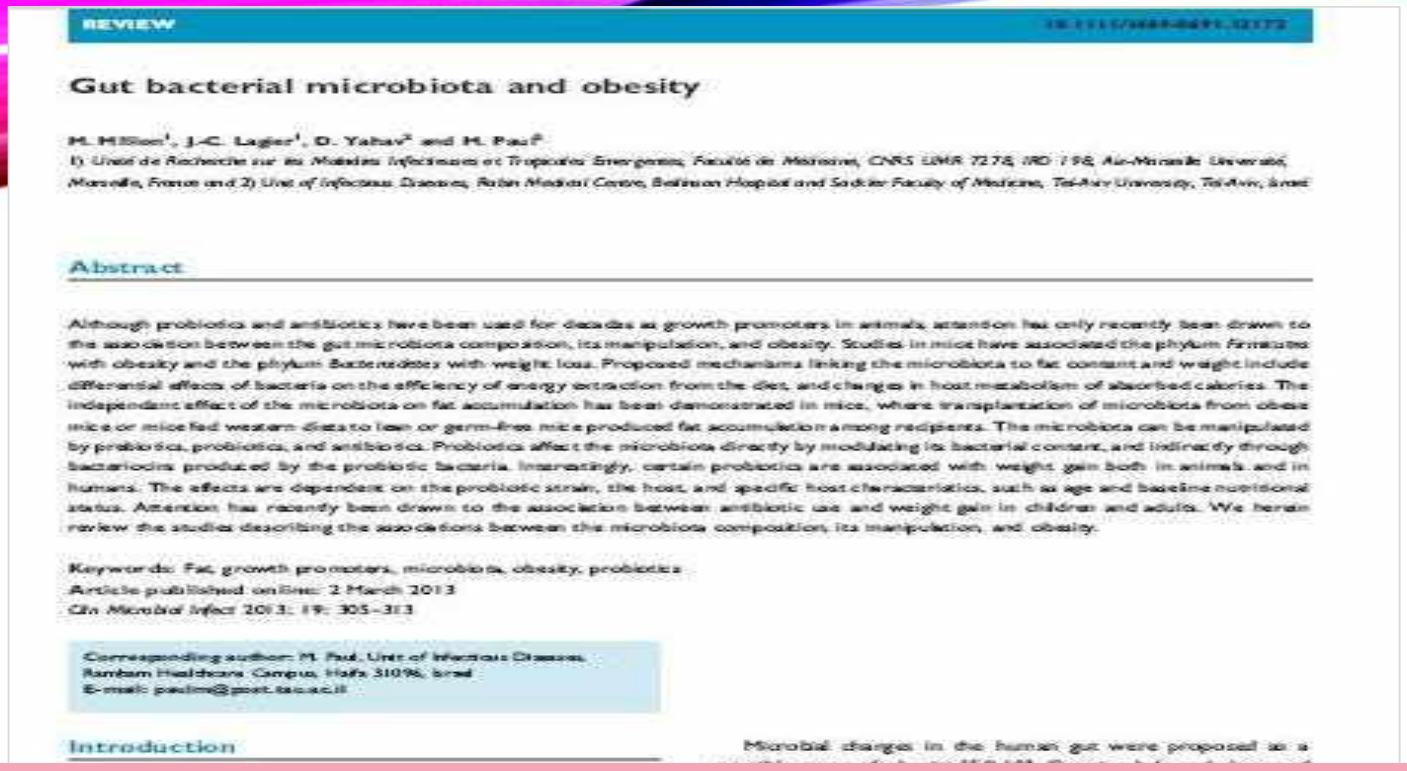
new tools, acting as a systems biology-based proof of evidence to evaluate MD effects on gut microbiota homeostasis. Data integration of food metabotypes and gut microbiota

Three main variants or "enterotypes" in adults represented by:

1. *Bacteroides*
2. *Prevotella*
3. *Ruminococcus*

The authors performed a controlled-feeding trial based on a small subject cohort (10 subjects), which was randomized, subjected to high-fat/low-fiber or low-fat/high-fiber diets and sampled over 10 days. **The results showed that microbiome profiles clearly changed within 24 h of the diet, while the "enterotype" identity remained stable**, indicating that long-term diet is strongly related with specific "enterotypes."





REVIEW

Gut bacterial microbiota and obesity

M. Million[1], J.-C. Lagier[1], D. Yahav[2] and M. Paul[2]
1) Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Faculté de Médecine, CNRS UMR 7278, IRD 198, Aix-Marseille Université, Marseille, France and 2) Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Abstract

Although probiotics and antibiotics have been used for decades as growth promoters in animals, attention has only recently been drawn to the association between the gut microbiota composition, its manipulation, and obesity. Studies in mice have associated the phylum *Firmicutes* with obesity and the phylum *Bacteroidetes* with weight loss. Proposed mechanisms linking the microbiota to fat content and weight include differential effects of bacteria on the efficiency of energy extraction from the diet, and changes in host metabolism of absorbed calories. The independent effect of the microbiota on fat accumulation has been demonstrated in mice, where transplantation of microbiota from obese mice or mice fed western diets to lean or germ-free mice produced fat accumulation among recipients. The microbiota can be manipulated by prebiotics, probiotics, and antibiotics. Probiotics affect the microbiota directly by modulating its bacterial content, and indirectly through bacteriocins produced by the probiotic bacteria. Interestingly, certain probiotics are associated with weight gain both in animals and in humans. The effects are dependent on the probiotic strain, the host, and specific host characteristics, such as age and baseline nutritional status. Attention has recently been drawn to the association between antibiotic use and weight gain in children and adults. We herein review the studies describing the associations between the microbiota composition, its manipulation, and obesity.

Keywords: Fat, growth promoters, microbiota, obesity, probiotics
Article published online: 2 March 2013
Clin Microbiol Infect 2013; 19: 305–313

Corresponding author: M. Paul, Unit of Infectious Diseases, Rambam Healthcare Campus, Haifa 31096, Israel
E-mail: paulm@post.tau.ac.il

Introduction

Microbial changes in the human gut were proposed as a

The microbiota can be manipulated by prebiotics, probiotics, and antibiotics. Probiotics affect the microbiota directly by modulating its bacterial content, and indirectly through bacteriocins produced by the probiotic bacteria.

Surprisingly, we discovered that oral L. reuteri therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and age-associated weight gain in mice regardless of their baseline diet

OPEN ACCESS Freely available online

PLOS ONE

Microbial Reprogramming Inhibits Western Diet-Associated Obesity

Theofilos Poutahidis[1,2☯], Markus Kleinewietfeld[3,4☯], Christopher Smillie[5], Tatiana Levkovich[1], Alison Perrotta[5], Siddheshvar Bhela[5], Bernard J. Varian[1], Yassin M. Ibrahim[1], Jessica R. Lakritz[1], Sean M. Kearney[1,6], Antonis Chatzigiagkos[2], David A. Hafler[3,4*], Eric J. Alm[4,5,6*], Susan E. Erdman[1*]

1 Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America, 2 Laboratory of Pathology, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece, 3 Departments of Neurology and Immunobiology, Yale School of Medicine, New Haven, Connecticut, United States of America, 4 Broad Institute, Massachusetts Institute of Technology and Harvard University, Cambridge, Massachusetts, United States of America, 5 Civil and Environmental Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America, 6 Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States of America

Abstract

A recent epidemiological study showed that eating 'fast food' items such as potato chips increased likelihood of obesity, whereas eating yogurt prevented age-associated weight gain in humans. It was demonstrated previously in animal models of obesity that the immune system plays a critical role in this process. Here we examined human subjects and mouse models consuming Westernized 'fast food' diet, and found $CD4^+$ T helper (Th)17-biased immunity and changes in microbial communities and abdominal fat with obesity after eating the Western chow. In striking contrast, eating probiotic yogurt together with Western chow inhibited age-associated weight gain. We went on to test whether a bacteria found in yogurt may serve to lessen fat pathology by using purified *Lactobacillus reuteri* ATCC 6475 in drinking water. Surprisingly, we discovered that oral *L. reuteri* therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and age-associated weight gain in mice regardless of their baseline diet. These beneficial microbe effects were transferable into naïve recipient animals by purified $CD4^+$ T cells alone. Specifically, bacterial effects depended upon active immune tolerance by induction of $Foxp3^+$ regulatory T cells (Treg) and interleukin (Il)-10, without significantly changing the gut microbial ecology or reducing *ad libitum* caloric intake. Our finding that microbial targeting restored $CD4^+$ T cell balance and yielded significantly leaner animals regardless of their dietary 'fast food' indiscretions suggests population-based approaches for weight management and enhancing public health in industrialized societies.

Citation: Poutahidis T, Kleinewietfeld M, Smillie C, Levkovich T, Perrotta A, et al. (2013) Microbial Reprogramming Inhibits Western Diet-Associated Obesity. PLoS ONE 8(7): e68596. doi:10.1371/journal.pone.0068596

Editor: Laurel L. Lenz, National Jewish Health and University of Colorado School of Medicine, United States of America

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Competing Interests: The authors have declared that no competing interests exist.

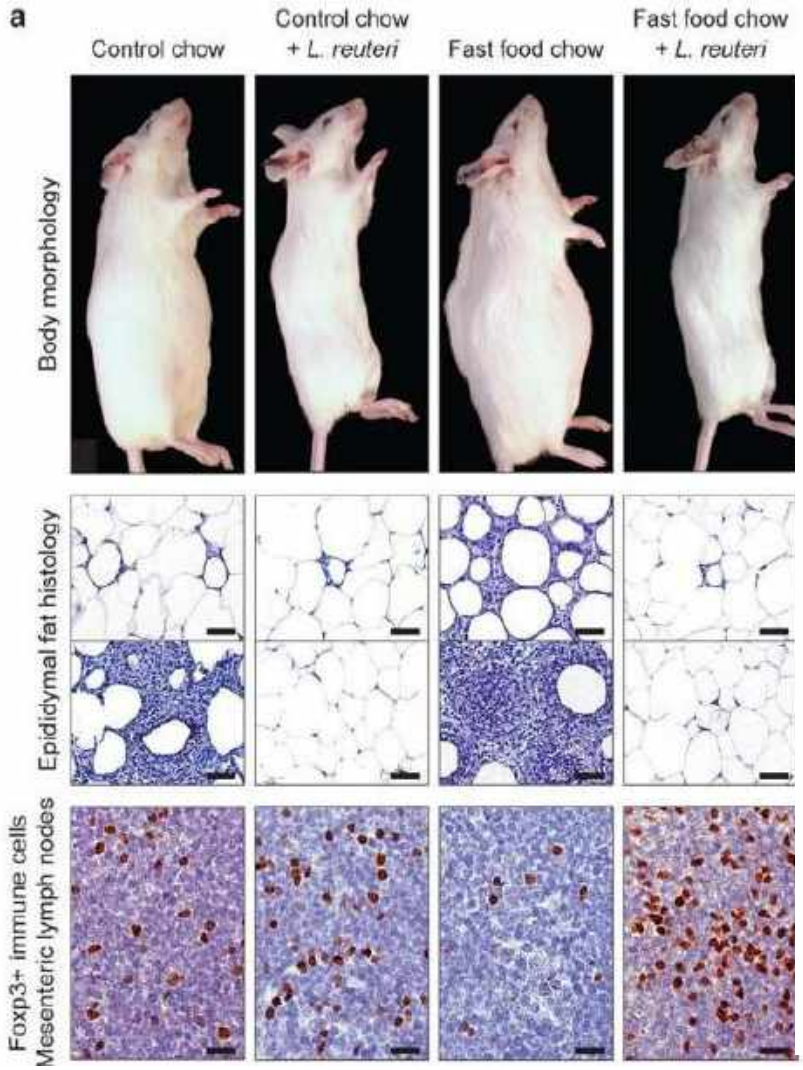
* E-mail: ejalm@mit.edu (EJA); david.hafler@yale.edu (DAH); serdman@mit.edu (SEE)

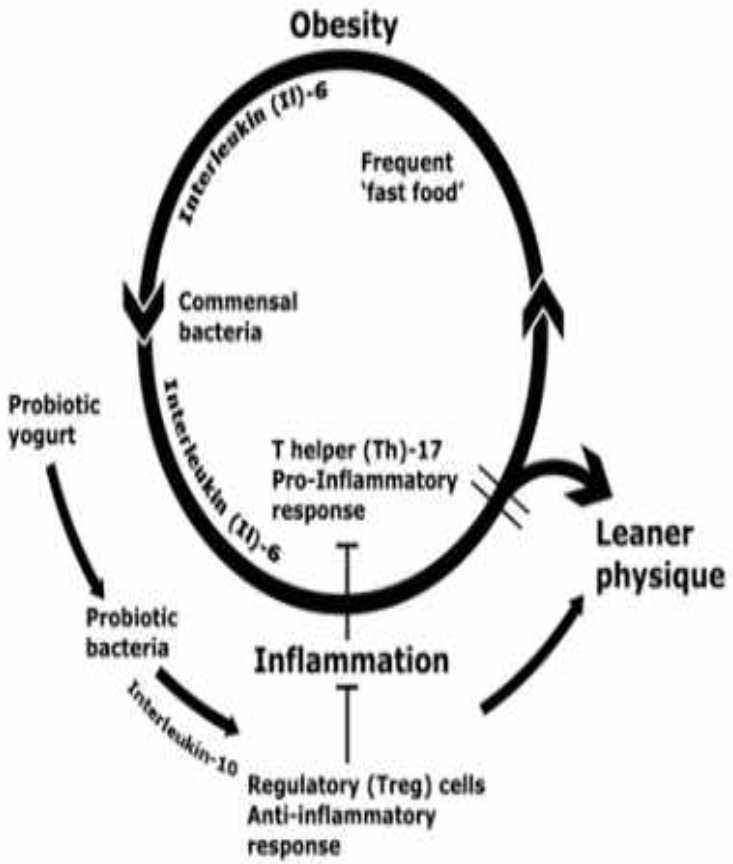
☯ These authors contributed equally to this work.

Introduction

The risk of developing obesity rises with a Westernized lifestyle. In industrialized and developing countries obesity contributes to increased mortality by predisposing to serious pathological conditions such as type 2 diabetes, cardiovascular disease, fatty liver, arthritis, asthma, and neoplasia [1–2]. Clinical and experimental data suggest that the white adipose tissue of obese organisms is in a low-grade, persistent state of chronic inflammation that exerts adverse systemic effects [2–3]. The most prominent inflammatory cell type of the obesity-associated inflammation is the adipose tissue macrophage. Macrophages are recruited and surround dead adipocytes, thus creating the so-called crown-like structures (CLS). These cells along with hypertrophic adipocytes are thought to be the key cells initiating the unique subclinical pro-inflammatory signaling cascade encountered in obesity [2,4–5]. Macrophages, B and T lymphocytes, and up-regulated pro-inflammatory cytokines including TNF-α, IL-1, IL-6, IL-17, and monocyte chemoattractant protein-1 (MCP-1) have been reported to contribute to obesity-associated pathologies. In parallel, regulatory T cells down-regulate host inflammatory responses [2–3,6–10].

It is well documented that "fast food" with high fat and salt content at relatively low cost is a major cause of the obesity epidemic in Western societies. Recent epidemiological research shows while dietary 'fast food' contributes to obesity, eating yogurt surprisingly prevents age-associated weight gain, though the mechanism is unknown. It has been thought that slenderizing outcomes of yogurt are due to a probiotic bacteria-mediated mechanism [1]. Dietary probiotic consumption alters gut microbiota and may be an effective strategy not only for weight loss but also for preventing weight regain after loss [11–14]. Furthermore, alterations in the composition of gut microbiota may affect not only gut health but also distant tissues and overall health and longevity via immune-mediated mechanisms [15–20].





Theofilos Poutahidis et al. Microbial Reprogramming Inhibits Western Diet-Associated Obesity. PLoS ONE 8(7): e68596. doi:10.1371/journal.pone.0068596.

Korean J Fam Med. 2013;34:80-89 http://dx.doi.org/10.4082/kjfm.2013.34.2.80

Effect of *Lactobacillus gasseri* BNR17 on Overweight and Obese Adults: A Randomized, Double-Blind Clinical Trial

Original Article

Seung-Pil Jung*, Keun-Mi Lee, Ji-Hee Kang[1], Sung-Il Yun[1], Han-Oh Park[1], Yong Moon[2], Jong-Yeon Kim[3]

Department of Family Medicine, Obesity Clinic, Yeungnam University College of Medicine, Daegu; [1]R&D Center of Bioneer Corporation, Daejeon; [2]Department of Health Administration, Namseoul University, Cheonan; [3]Department of Physiology, Center of Metabolism and Obesity, Yeungnam University College of Medicine, Daegu, Korea

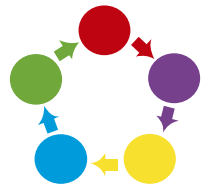
Background: *Lactobacillus gasseri* BNR17 is a type of probiotic strain isolated from human breast milk. A study was reported regarding the fact that BNR17 was an inhibitor of obesity and diabetic activities in the human body through previous animal experiments. This study was furthered to investigate the effect of BNR17, a probiotic strain isolated from human breast milk, on obese and overweight adults.

Methods: Sixty-two obese volunteers aged 19 to 60 with body mass index ≥ 23 kg/m^2 and fasting blood sugar ≥ 100 mg/dL participated in a placebo controlled, randomized, and double-blind trial. For 12 weeks, 57 participants were given either placebo or BNR17 and were tested by measuring body fat, body weight, various biochemical parameters, vital signs, and computed tomography at the start of the study and at weeks 4, 8, and 12. The subjects assumed usual daily activities without having to make behavioral or dietary modifications during the course of the study.

Results: At the 12th week, a slight reduction in body weight was noted in the BNR17 group, but there were no significant weight changes between groups. Decrease of waist and hip circumferences in the BNR17 group was more pronounced than those in the placebo group. The two groups had no special or severe adverse reactions.

Conclusion: Despite there being no change in behavior or diet, administration of only the supplement of BNR17 reduced weight and waist and hip circumference. However, there were no significant differences between the two groups. These findings warrant a subsequent longer-term prospective clinical investigation with a large population.

Keywords: Probiotics; Obesity; Metabolic Disorders; Human Breast Milk



The primary findings of the present study are that L. Casei ingestion markedly prevents rats from the onset and development of glycemia in both fasting and postprandial 2 h blood glucose levels, as well as OGTT levels.

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Correspondence and requests for materials should be addressed to H.P.Z. (hepingdd@vip.sina.com)

* Current address: The Key Laboratory of Dairy Biotechnology and Engineering, Education Ministry of P. R. China, Inner Mongolia Agricultural University, 306 Zhaowuda Road, Hohhot, China, 010018.

Lactobacillus casei reduces susceptibility to type 2 diabetes via microbiota-mediated body chloride ion influx

Yong Zhang, Xiao Guo, Jianlin Guo, Qiuwen He, He Li, Yuqin Song & Heping Zhang*

Key Laboratory of Dairy Biotechnology and Engineering, Education Ministry of P. R. China, Department of Food Science and Engineering, Inner Mongolia Agricultural University, Hohhot 010018, P. R. China.

Gut microbiota mediated low-grade inflammation is involved in the onset of type 2 diabetes (T2DM). In this study, we used a high fat sucrose (HFS) diet-induced pre-insulin resistance and a low dose-STZ HFS rat models to study the effect and mechanism of *Lactobacillus casei* Zhang in protecting against T2DM onset. Hyperglycemia was favorably suppressed by *L. casei* Zhang treatment. Moreover, the hyperglycemia was connected with type 1 immune response, high plasma bile acids and urine chloride ion loss. This chloride ion loss was significantly prevented by *L. casei* via upregulating of chloride ion-dependent genes (*ClC1-7*, *GlyRα1*, *SLC26A3*, *SLC26A6*, *GABAAα1*, *Bestrophin-3* and *CFTR*). A shift in the caecal microflora, particularly the reduction of bile acid 7α-dehydroxylating bacteria, and fecal bile acid profiles also occurred. These change coincided with organ chloride influx. Thus, we postulate that the prevention of T2DM onset by *L. casei* Zhang may be via a microbiota-based bile acid-chloride exchange mechanism.

Obesity-associated T2DM has drawn much scientific attention, as evident by the rapidly increasing number of published investigations. Data showed that the world population is facing a surge in T2DM as well as individuals with prediabetes due to rapid change in lifestyle[1]. Thus, both strategies for both the prevention and treatment of diabetes are needed, especially in the dietary aspect.

Diet is directly associated with intestinal microbiota. There is a growing interest in understanding the changes of gut microbiota in the context of diabetes. In recent years, metagenomics has opened a new era of microbial ecology that has allowed deeper understanding of microbiome associated hyperglycemia[2,3]. On the other hand, it is proposed that high-fat diet induces a low-grade inflammation through modifying microflora and thus increases lipopolysaccharides (LPS) and in turn triggers the development of metabolic diseases[4]. More interestingly, commensal microbiota and related bile acids profile could be rapidly reshaped by dietary alteration[5], but how the pathogenesis of T2DM relates with the interaction between bile acids and chloride ion is rarely studied. This aspect is of particular interest because both bile acids and choride ions can act as regulating signaling molecules for metabolic homeostasis[6,7].

Several studies have also shown that probiotic products could regulate the blood glucose level in diabetic human[8,9]. Moreover, *L. casei* Shirota has been reported to reduce blood glucose level through reducing lipopolysaccharide-binding protein[10]. One research showed that *B. animalis* 420 could prevent mice from obesity-induced T2DM through an improvement of bacterial translocation and overall inflammatory status[11]. Recently, the gut microbe, *Akkermansia muciniphila*, exhibited an insulin resistance-reducing effect and may have potential application in T2DM[12].

Our previous research showed that *L. casei* Zhang could improve impaired glucose tolerance in rats due to altered microbiota composition which led to an upregulation of osteocalcin level[13]. The aims of the present study were to investigate whether probiotic *L. casei* Zhang supplementation could prevent the symptoms of rat model of T2DM and identify its mechanisms.

Methods

Animals and housing. The protocol was approved by the Animal Care and Use Committee at Inner Mongolia Agricultural University in Hohhot, China. All the methods were carried out in accordance with the approved guidelines. Male sprague-dawley (SD) rats, initial weight

Mediators Inflamm. 2014;2014:348959. doi: 10.1155/2014/348959. Epub 2014 Mar 26.

Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial.

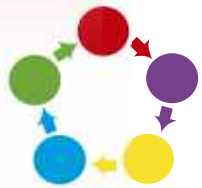
Rajkumar H[1], Mahmood N[1], Kumar M[1], Varikuti SR[1], Challa HR[1], My

Author information

Abstract

To evaluate the effects of probiotic (VSL#3) and omega-3 fatty ac
and inflammation, we conducted a clinical trial in 60 overweight (BM
years. After initial screening the subjects were randomized into fou
groups received, respectively, placebo, omega-3 fatty acid, probic
probiotic, for 6 weeks. Blood and fecal samples were collected at
probiotic (VSL#3) supplemented group had significant reduction in
and VLDL and had increased HDL ($P < 0.05$) value. VSL#3 improved insulin sensitivity ($P < 0.01$), decreased hsCRP, and favorably affected the composition of gut microbiota. Omega-3 had significant effect on insulin sensitivity and hsCRP but had no effect on gut microbiota. Addition of omega-3 fatty acid with VSL#3 had more pronounced effect on HDL, insulin sensitivity and hsCRP. Subjects with low HDL, insulin resistance, and high hsCRP had significantly lower total lactobacilli and bifidobacteria count and higher E. coli and bacteroides count.

Addition of omega-3 fatty acid with VSL#3 had more pronounced effect on HDL, insulin sensitivity and hsCRP.



Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Pilot study

Beneficial effects of *Lactobacillus plantarum* on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome

Fabíola Málaga Barreto M.Sc.[a], Andréa Name Colado Simão Ph.D.[b], Helena Kaminami Morimoto Ph.D.[b], Marcell Alysson Batisti Lozovoy Ph.D.[b], Isaias Dichi M.D., Ph.D.[c,*], Lúcia Helena da Silva Miglioranza Ph.D.[a]

[a] Department of Food Science and Technology, University of Londrina, Londrina, Paraná, Brazil
[b] Department of Pathology, Clinical Analysis and Toxicology, University of Londrina, Londrina, Paraná, Brazil
[c] Department of Internal Medicine, University of Londrina, Londrina, Paraná, Brazil

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Homocysteine
Cytokines

ABSTRACT

Objective: Metabolic syndrome (MetS) in postmenopausal women is an important risk factor for cardiovascular morbidity, especially stroke and coronary heart disease and mortality. Preventing and treating MetS would be useful in preventing disability and promoting normal aging. Previous human studies have found some beneficial effects of *Lactobacillus* species on some isolated parameters of MetS. Nevertheless, we are not aware, to date, of any study which has verified the influence of probiotics in patients with MetS. Therefore, the aim of the present study was to evaluate the influence of fermented milk with *L. plantarum* in the classical parameters related to MetS, as well as in other parameters related to cardiovascular risk in postmenopausal women.
Methods: Twenty-four individuals were paired by age, ethnicity, and body mass index in two groups: Non-fermented milk (NFM – 12) 80 mL/d and fermented milk (FM – 12) 80 mL/d. Anthropometric and blood pressure measurements, biochemical, inflammatory, and immunologic

Fermented milk with L. Plantarum showed more favorable results in women with Met Syn.

Introduction

Metabolic syndrome (MetS) is a pathologic condition that includes insulin resistance, arterial hypertension, obesity, and dyslipidemia, which accelerate atherosclerosis, and promote a higher risk for cardiovascular disease (CVD) [1]. MetS also has been considered a chronic low-grade inflammatory syndrome [2]. The prevalence of MetS rises with increasing age, which is mainly attributed to the significant increase in overweight and obesity [3].

Previous human studies have found some beneficial effects of *Lactobacillus* species in reducing adiposity in overweight

FMB was responsible for recruiting the patients, the original concept of the study, interpretation of the results, and writing the manuscript. MABL and HM were responsible for the laboratorial analysis. ANCS and ID were responsible for interpretation of the results and the writing of the manuscript. LHSM were responsible for the original concept of the study, the study design, interpretation of the results and the writing of the manuscript. All authors read and approved the final manuscript.

* Corresponding author. Tel.: +55 43 3371 2332; fax: +55 43 3371 2328.
E-mail address: DichiI@sercomtel.com.br (I. Dichi).

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MICROBIAL ECOLOGY in Health and Disease

COMMENTARY

ENGHR SUPPLEMENT

Manipulating the gut microbiota to maintain health and treat disease

Karen P. Scott[1], Jean-Michel Antoine[2], Tore Midtvedt[3] and Saskia van Hemert[4]*

[1]Rowett Institute of Nutrition and Health, University of Aberdeen, Aberdeen, UK; [2]Danone Research, Cedex, France; [3]Department of Microbiology, Tumor and Cell Biology (MTC) Karolinska Institute, Stockholm, Sweden; [4]Winclove Probiotics, Amsterdam, The Netherlands

Background: The intestinal microbiota composition varies between healthy and diseased individuals for numerous diseases. Although any cause or effect relationship between the alterations in the gut microbiota and disease is not always clear, targeting the intestinal microbiota might offer new possibilities for prevention and/or treatment of disease.

Objective: Here we review some examples of manipulating the intestinal microbiota by prebiotics, probiotics, and fecal microbial transplants.

Results: Prebiotics are best known for their ability to increase the number of bifidobacteria. However, specific prebiotics could potentially also stimulate other species they can also stimulate other species associated with health, like *Akkermansia muciniphila*, *Ruminococcus bromii*, the Roseburia/*Enterococcus rectale* group, and *Faecalibacterium prausnitzii*. Probiotics have beneficial health effects for different diseases and digestive symptoms. These effects can be due to the direct effect of the probiotic bacterium or its products itself, as well as effects of the probiotic on the resident microbiota. Probiotics can influence the microbiota composition as well as the activity of the resident microbiota. Fecal microbial transplants are a drastic intervention in the gut microbiota, aiming for total replacement of one microbiota by another. With numerous successful studies related to antibiotic-associated diarrhea and *Clostridium difficile* infection, the potential of fecal microbial transplants to treat other diseases like inflammatory bowel disease, irritable bowel syndrome, and metabolic and cardiovascular disorders is under investigation.

Conclusions: Improved knowledge on the specific role of gut microbiota in prevention and treatment of disease will help more targeted manipulation of the intestinal microbiota. Further studies are necessary to see the (long term) effects for health of these interventions.

Keywords: *Clostridium difficile*, *fecal microbial transplants*, *inflammatory bowel disease*, *irritable bowel syndrome*, *obesity*, *prebiotics*, *probiotics*

*Correspondence to: Saskia van Hemert, Winclove Probiotics, Hulstweg 11, 1032LB Amsterdam, The Netherlands, Email: saskiavanhemert@winclove.nl

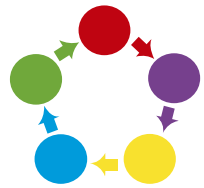
This paper is part of the *Proceedings from the 2013 ENGHR Conference in Valencia, Spain*. More papers from this supplement can be found at http://www.microbecolhealthdis.net

Microbes existed on Earth long before humans; therefore, it is logical that humans have learned to live with them, in fact co-evolved with them. All animals can be looked upon as dualistic 'super-organisms', i.e. their selves and their microbiota. Establishment and maintenance of an intestinal microbiota is of utmost importance for health in all mammals.

In the last 2–3 decades, an increasing number of metagenomic analyses have provided us with information about differences in gut microbiota composition between healthy and diseased individuals. Generally, high microbial diversity is thought to be associated with a healthy gut microbiota, while loss of diversity seems to correlate with disease. Nowadays over 25 diseases or syndromes have been linked to an altered intestinal microbiome (1). These diseases range from gastrointestinal diseases like inflammatory bowel diseases (IBDs), irritable bowel syndrome, and colorectal cancer to metabolic diseases and potentially even to diseases like Alzheimer's disease, autistic spectrum disorders, chronic fatigue syndrome, Parkinson's disease, and autoimmune diseases like rheumatoid arthritis and multiple sclerosis. The most studied disease conditions in relation to intestinal microbiota are obesity, metabolic syndrome, and type II diabetes on

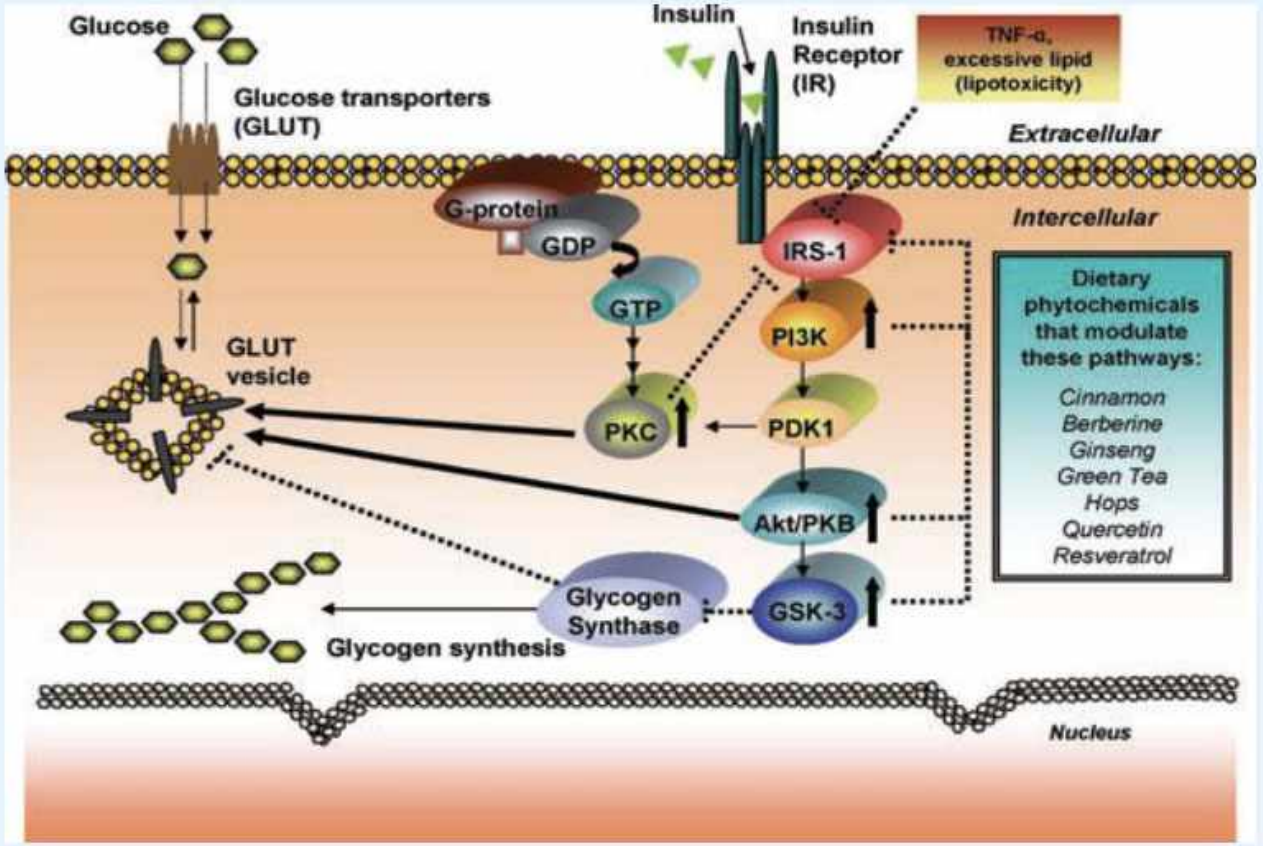
Citation: Microbial Ecology in Health & Disease 2015, 26: 29877 - http://dx.doi.org/10.3402/mehd.v26.29877

Prebiotics act to enhance the growth and/or activity of bacteria that are resident in the colon, acting as growth substrates to selectively boost numbers and/or activities of particular bacteria.



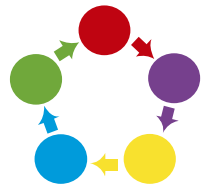
Dietary Recommendations for Insulin Resistance Beyond Macronutrients

Minich and Bland, Nutrition Reviews 2008 66(8):429-444.



NUTRIENTS KNOWN TO MODIFY INSULIN RESPONSIVENESS AT THE CELLULAR LEVEL

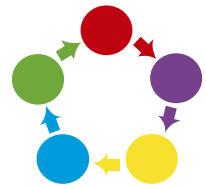
- Chromium
- Alpha-lipoic acid
- CoQ10
- Vitamin D
- Magnesium
- Vitamin C, vitamin E and other antioxidants
- Omega 3 fatty acids
- Curcumin
- Vanadium
- Serum kinase receptor modulators (SKRM's)



- 600 to 1800 mg/day of alpha lipoic acid (ALA) can improve insulin sensitivity in patients with type 2 diabetes.
- 600-1200 mg/day of ALA may improve microcirculation and diabetic polyneuropathy.

Jacob S, et al. Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo- controlled pilot trial. Free Radic Biol Med, 1999. 27(3-4): p. 309-14.

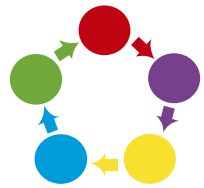
Haak E, et al. Effects of alpha-lipoic acid on microcirculation in patients with peripheral diabetic neuropathy. Exp Clin Endocrinol Diabetes, 2000. 108(3): p. 168-74.



- 120 mg/day of Coenzyme Q10 improves glycemic control and blood pressure in NIDDM
- 200mg of CoQ10 daily improved HgA1C and blood pressure in NIDDM patients.

Singh RB, et al. Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. J Hum Hypertens, 1999. 13(3): p. 203-8.

Hodgson JM, et al. Coenzyme Q(10) improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. Eur J Clin Nutr, 2002. 56(11): p. 1137-42.



Cholecalciferol improves glycemic control in type 2 diabetic patients: a 6-month prospective interventional study

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Aml Mohamed Nada[1]
Dalia A Shaheen[2]

[1]Faculty of Medicine, Department of Internal Medicine, [2]Faculty of Medicine, Department of Medical Biochemistry, Mansoura University, Mansoura, Egypt

Background and purpose: To investigate the effects of vitamin D supplementation on glucose homeostasis and lipid profile in type 2 diabetic patients who have vitamin D deficiency.

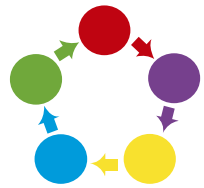
Patients an
glycemic ag
crinology cli
mass index (
of serum vit
lipid profile
was calculat
14 females) were started on cholecalciferol replacement–45,000 units once weekly for 8 weeks and then 22,500 units once weekly for 16 weeks. Calcium carbonate tablets 500 mg once daily were also prescribed for the initial 2 months of treatment. Measured variables were reassessed after 6 months of replacement therapy. During the trial, subjects were instructed not to change their diabetes drugs or lifestyle.

"Cholecalciferol helps improve blood glucose control and cholesterol profile in vitamin D3-deficient type 2 diabetic patients".

- Epidemiological studies show that high daily Mg intake is predictive of a lower incidence of NIDDM.
- Poor intracellular Mg concentration are found in NIDDM and in hypertensive patients.
- Daily Mg administration in NIDDM patients and in insulin resistant patients restores intracellular Mg concentration and contributes to improves insulin sensitivity and glucose uptake.

1. Barbagallo M, et al. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. Mol Aspects Med, 2003. **24**(1-3): p. 39-52

2. Guerrero-Romero F, et al: *Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. Diabetes Metab 2004;30:253–258*



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PLOS ONE

High Dietary Magnesium Intake Is Associated with Low Insulin Resistance in the Newfoundland Population

Farrell Cahill[1☯], Mariam Shahidi[1☯], Jennifer Shea[1], Danny Wadden[1], Wayne Gulliver[1], Edward Randell[2], Sudesh Vasdev[1], Guang Sun[1*]

1 Division of Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Canada, 2 Discipline of Laboratory Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Canada

Abstract

Background: Magnesium plays a role in glucose and insulin homeostasis and evidence suggests that magnesium intake is associated with insulin resistance (IR). However, data is inconsistent and most studies have not adequately controlled for critical confounding factors.

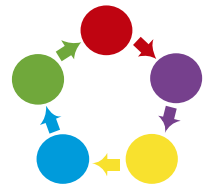
Objective: The study investigated the association between magnesium intake and IR in normal-weight (NW), overweight (OW) and obese (OB) along with pre- and post- menopausal women.

Design: A total of 2295 subjects (590 men and 1705 women) were recruited from the CODING study. Dietary magnesium intake was computed from the Willett Food Frequency Questionnaire (FFQ). Adiposity (NW, OW and OB) was classified by body fat percentage (%BF) measured by Dual-energy X-ray absorptiometry according to the Bray criteria. Multiple regression analyses were used to test adiposity-specific associations of dietary magnesium intake on insulin resistance adjusting for caloric intake, physical activity, medication use and menopausal status.

Results: Subjects with the highest intakes of dietary magnesium had the lowest levels of circulating insulin, HOMA-IR, and

"The results of this study indicate that **higher dietary magnesium intake is strongly associated with the attenuation of insulin resistance** and is more beneficial for overweight and obese individuals in the general population and pre-menopausal women. Moreover, **the inverse correlation between insulin resistance and dietary magnesium** intake is stronger when adjusting for %BF than BMI."

☯ These authors contributed equally to this work.



ENDOCRINE DISRUPTORS AND DETOXIFICATION STRATEGIES

Filomena Trindade, MD, MPH, AAARM, ABFM, ABOIM, IFMCP

Email: info@drtrindade.com

www.drtrindade.com