

Endocrine disruptors

Their role in conception and long term health

By Dr. Jodie Peacock ND

Dr.jpeacock@gmail.com

Speaker disclosures

Practicing
Naturopathic
doctor

Founder of
the Canadian
Fertility Show

Author of
Preconceived

Chief medical
officer for
NFH

Co-Founder of
Exceptional
ND

OAND Board
of directors

What does the future hold?

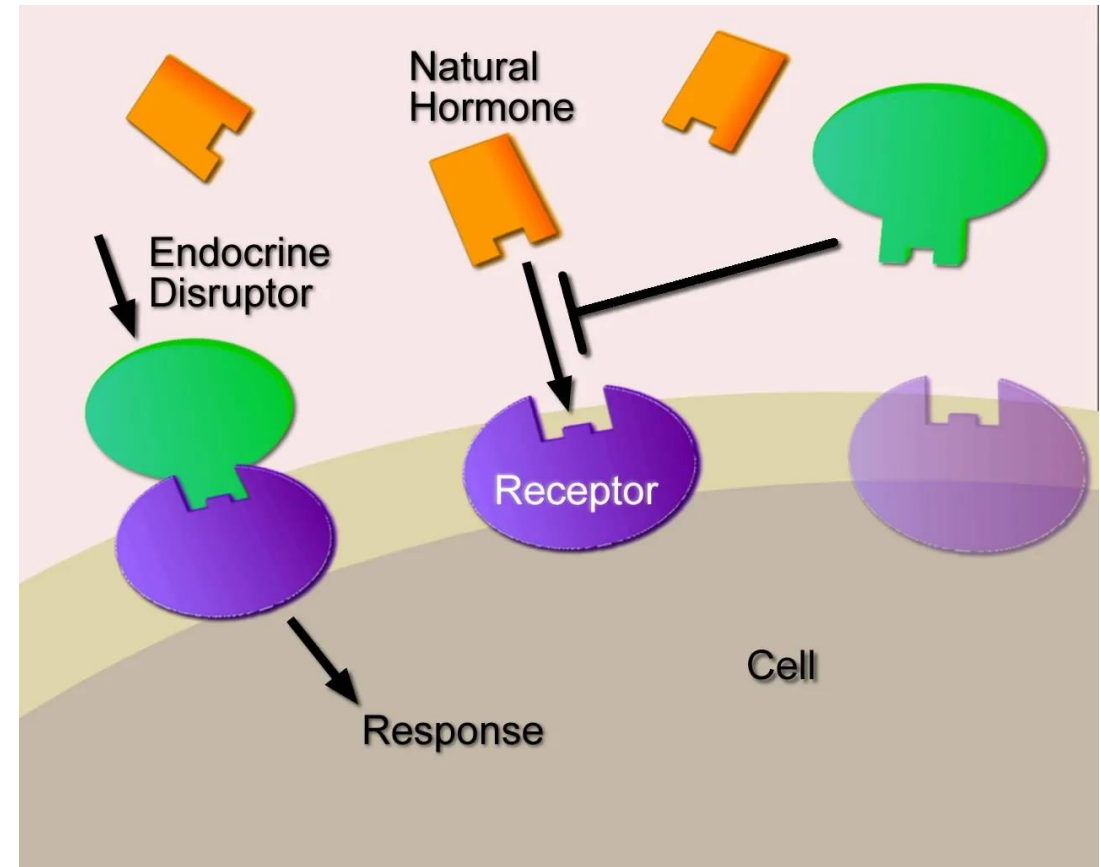
- ▶ “The current generation of children being born are the first in human history that aren’t expected to have a longer life expectancy than their parents.”
- ▶ Naturopathic doctors are the best positioned health care providers to change this stat
- ▶ Long term health of our next generation all starts during the preconception time

Learning Objectives

- ▶ Understand where patients have highest exposures to endocrine disruptors (EDs)
- ▶ Be able to educate patients about the role of EDs in chronic disease such as diabetes, heart disease and cancers
- ▶ Be able to discuss with patient's best practices to minimize exposures particularly during preconception/conception but also lifelong
- ▶ Feel confident discussing with patients how to optimize detoxification pathways and excretion of ED's

What is an endocrine disruptor?

- ▶ European Union has one on the best definition
- ▶ An ED is an “exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function”



Endocrine disruptors

- ▶ Association between exposure to EDs and health
 - ▶ Infertility
 - ▶ Poor sperm/oocyte quality
 - ▶ Developmental disorders
 - ▶ Endometriosis
 - ▶ Breast/ testicular and other types of cancer
 - ▶ Immune dysfunction
 - ▶ Nervous system concerns
 - ▶ ADHD
 - ▶ Cardiovascular disease
 - ▶ Parkinson's and Alzheimer's
 - ▶ Obesity and metabolic disorders

Toxins- Non-persistent Endocrine disrupting compounds

- ▶ Bisphenol A (BPA)
- ▶ Triclosan (TCL)
- ▶ Parabens
- ▶ Phthalates



Toxins- Persistent Endocrine disrupting compounds



- ▶ Perfluorinated compounds (PFCs)
- ▶ Polychlorinated biphenyls (PCBs)
- ▶ Organochlorine pesticides (DDE and DDT)
- ▶ Lead/Mercury

Bisphenol A Exposure

- ▶ Used to make many common consumer products
 - ▶ Polycarbonate plastic bottles
 - ▶ Epoxy resins for lining food and beverage cans
 - ▶ Water pipes
 - ▶ Some Dental sealants and composites
 - ▶ Thermal paper
- ▶ Exposure can occur via ingestion, inhalation and dermal absorption



- ▶ BPA has been detected in human follicular fluid, urine, serum, saliva, breast milk, umbilical cord blood and amniotic fluid
- ▶ Can act on both alpha and beta estrogen receptors and interfere with folliculogenesis
- ▶ Impact endometrial receptivity during implantation

Bisphenol A-
female

BPA continued

Discarded human oocytes -BPA altered oocyte meiotic maturation, spindle morphology and chromosome alignment

During IVF one study found increasing BPA exposure correlated with an average decrease in antral follicle count (AFC)

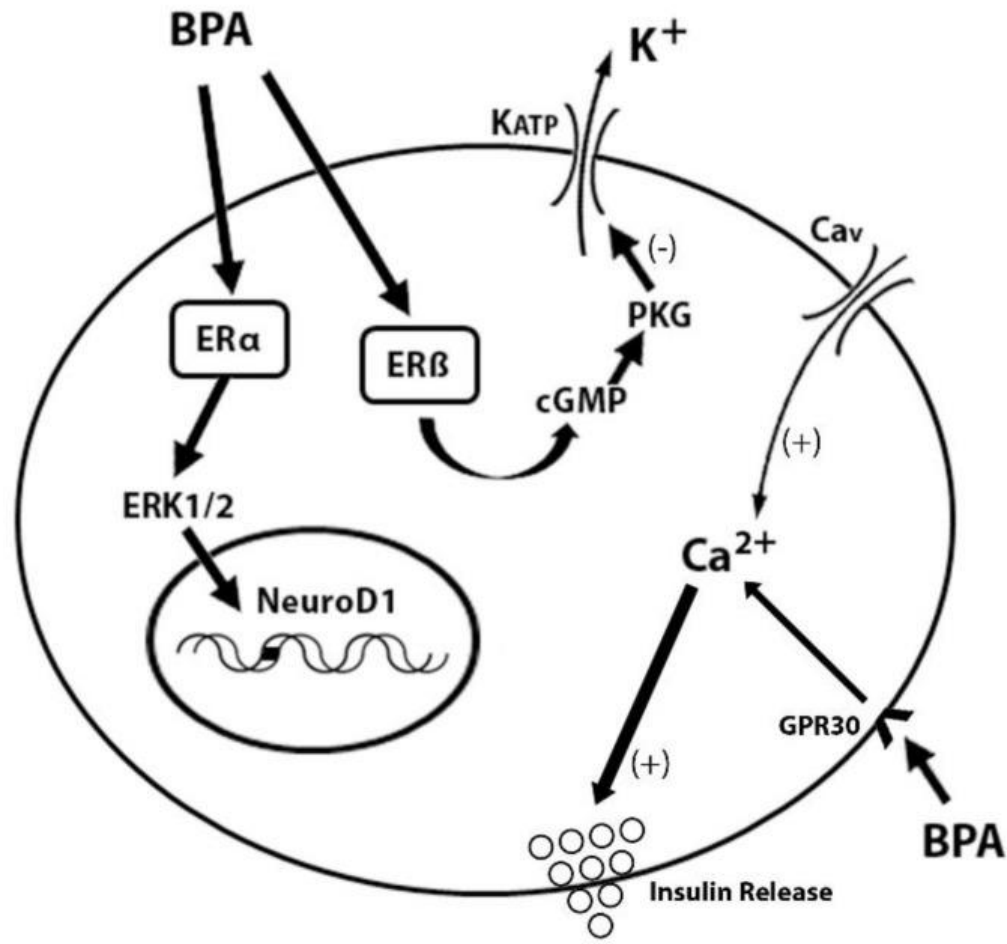


Bisphenol A- male

- ▶ Urinary BPA levels and male infertility
- ▶ Highest BPA levels were negatively associated with semen quality and antioxidant levels

BPA in Type 2 diabetes and obesity

- ▶ Multiple epidemiological studies see a link between BPA levels in urine and obesity and diabetes in both adults and children
- ▶ BPA regulates the concentration of pancreatic insulin through a mechanism that involves the activation of ER- α
- ▶ Environmental BPA produces the same response as endogenous estrogen in pancreatic cells
- ▶ ER- α is the main receptor involved in regulating insulin content for BPA and estrogen



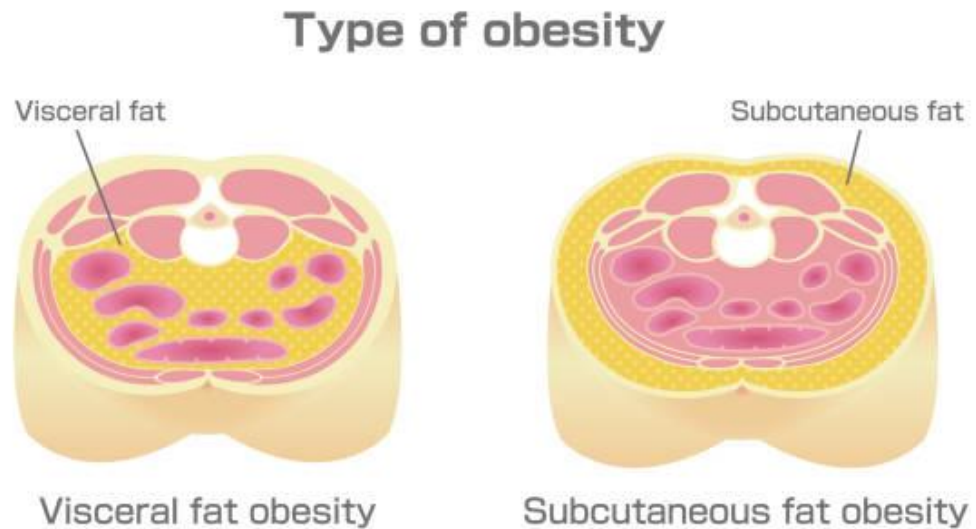
BPA in Type 2 diabetes and obesity

- ▶ Exposure during pregnancy in women causes:
 - ▶ glucose intolerance
 - ▶ high levels of insulin
 - ▶ Triglycerides
 - ▶ leptin in plasma compared to the control group,
- ▶ Indicate that exposure to BPA during pregnancy promotes glucose intolerance
- ▶ The long-term consequences that were observed were weight gain for at least four months, increased perigonadal fat, decreased insulin sensitivity, and elevated plasma insulin levels compared to the control group
- ▶ Elevation of leptin levels remained for several months

BPA in Type 2 diabetes and obesity

- ▶ Exposure to BPA decreases adipocyte sensitivity to insulin due to decreased expression of glucose transporter 1 (GLUT1) and phosphorylation of the insulin receptor
- ▶ BPA can induce disorders in the metabolism of glucose and increases the risk of type 2 diabetes
- ▶ Study in 3390 adults age >40
- ▶ Levels of BPA in urine are positively associated with obesity, increased abdominal fat, and insulin resistance in Chinese adults and the elderly.
- ▶ Study of 48 children age 7-8
- ▶ Exposure to BPA in pre-adolescents can disrupt endocrine metabolism due to its ability to act as a natural estrogen.
- ▶ Group exposed to BPA, the levels of base estradiol and androstenedione were significantly higher than in the control group.
- ▶ A year later, the girls who had been exposed to BPA showed elevated levels of these hormones as well as insulin resistance.

BPA in Type 2 diabetes and obesity



- ▶ 76 Male patient mean age 53.5
- ▶ In subjects with higher levels of BPA in the blood,
- ▶ Higher levels of
 - ▶ inflammation markers
 - ▶ higher percentages of visceral fat
 - ▶ higher metabolic syndrome and insulin resistance prevalence

BPA and Parkinson's

- ▶ Cause of Parkinson's disease is known to be multifactorial -one of these factors is oxidative stress induced by exposure to environmental toxicants.
- ▶ Bisphenol A (BPA) at concentrations of 0.5 mM and 1 mM, the concentration of 1 mM corresponding to Lowest Observed Adverse Effect Level (LOAEL) for humans in adult *Drosophila melanogaster* (flies).
- ▶ BPA induced oxidative stress was established by increased levels of malondialdehyde, decreased activity superoxide dismutase and catalase, glutathione-S-transferase
- ▶ A reduction of acetylcholinesterase activity and a reduction of dopamine levels, which are related to the decreased locomotion activity as observed in negative geotaxis, open field and equilibrium behaviors in group exposed to 1 mM of BPA.
- ▶ Oxidative stress also impaired mitochondrial and cellular metabolic activity in the head causing an increase in the mortality of flies exposed to both BPA concentrations.
- ▶ BPA induced Parkinsonian-like changes in flies -possible that the oxidative stress is closely related to this effect

Avoid Exposure to BPA

- ▶ Minimize canned food
- ▶ Avoid hard plastic containers marked either PC or #7
- ▶ Never microwave in plastic
- ▶ Receipts of thermal paper
- ▶ Environmental working group is a great resource





Photos: Pieter Vanhaecke, gkdavie, Jenn Durfey, Joe Hsu, citychicountrymouse, SCA Svenska Cellulosa Aktiefolaget

Triclosan (TCL) exposure

- ▶ Absorbed orally via ingestion, by inhalation and through the dermis
- ▶ Detected in blood, urine, breast milk, adipose tissue and liver
- ▶ Estrogenic activity in vitro
- ▶ TCL concentration associated with decrease oocyte yield

Parabens

- ▶ Exposure to parabens via ingestion, inhalation and dermal absorption
- ▶ Excreted via urine, sweat, bile and faeces
- ▶ Estrogenic and can bind to both alpha and beta estrogen receptors
- ▶ Estrogenic activity increases with the length on the alkyl chain
- ▶ Butylparaben (BP) > propylparaben (PP) > methylparaben(MP)

Parabens

- ▶ Prenatal ethyl paraben (EtP) exposure may affect early childhood BMI
- ▶ Study aimed to evaluate associations between urinary phenols, parabens metabolites, and total and individual CVDs
- ▶ Cross-sectional study analyzed 7 urinary chemicals detected among the general population from the 2005-2016 National Health and Nutrition Examination Survey (NHANES, n=10,428)
- ▶ Compared with the lowest quartile, URBPA (OR: 1.52; 95% CI: 1.20-1.91; P=0.001) levels in the highest quartile were independently associated with increased total CVD
- ▶ High combined levels of phenols, and parabens are associated with an increased CVD risk, with URBPA contributing the highest risk

Phthalates - mechanism of reproductive toxicity

- ▶ Phthalate metabolites DEHP, MEHP and MEP (monoethyl phthalate) impact mean antral follicle count (AFC)
- ▶ Urinary levels of phthalate metabolites (DEHP) associated with:
 - ▶ lower yield of IVF oocytes
 - ▶ increased risk of implantation failure
 - ▶ lower clinical pregnancy rates

Phthalates - type 2 diabetes & CVD

- ▶ Study looked at 675 men with type 2 diabetes
- ▶ level of monoethyl phthalate and monoisobutyl phthalate were associated with CVD
- ▶ Monoisobutyl phthalate and monobenzyl phthalate were positively associated with carotid intima-media thickness and common carotid artery diameter
- ▶ phthalate exposure was positively associated with CVD in Chinese with type 2 diabetes.
- ▶ Type 2 diabetic men who smoke, have an uncontrolled lipid profile, and are not using statins might be more susceptible to CVD when exposed to phthalates.

Persistent endocrine disrupting chemicals

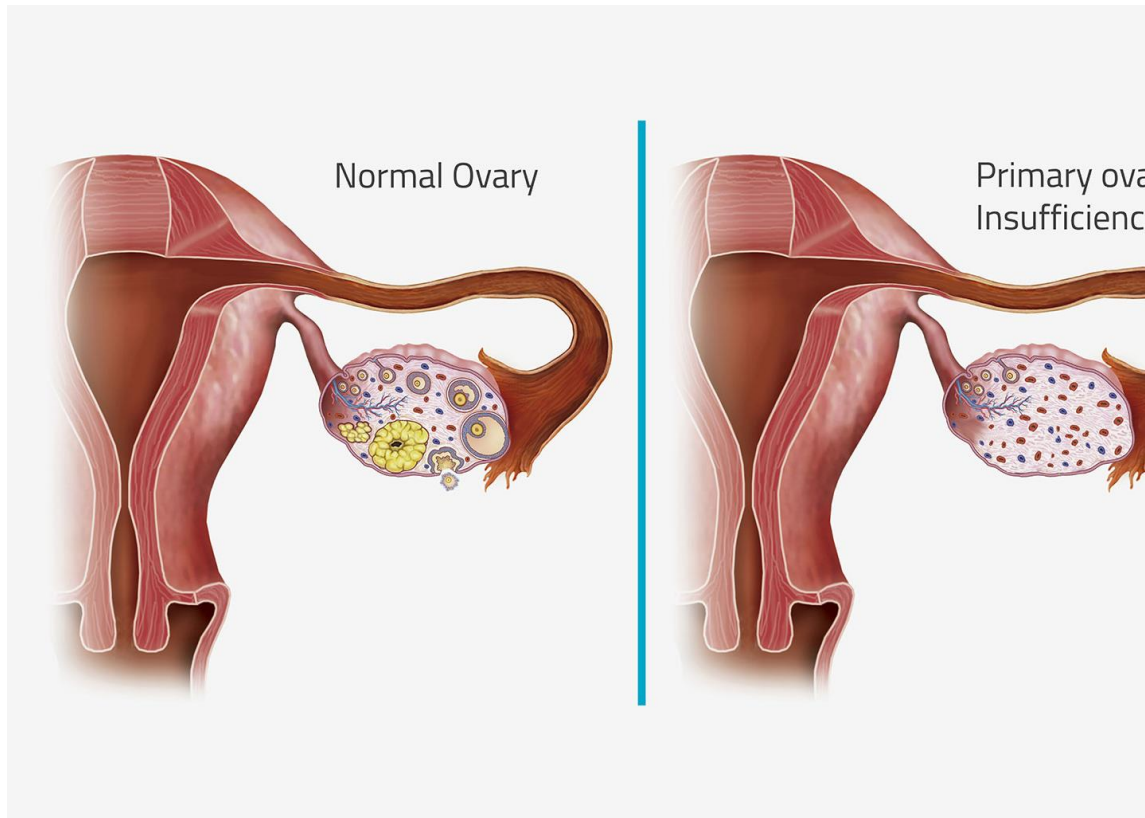
Organochlorine pesticides

- ▶ DDT- direct estrogenic potential
- ▶ DDE - antiandrogenic properties
- ▶ DDT/DDE also interact with the progesterone-response pathway
- ▶ PCBs exhibit estrogenic, antiestrogenic, androgenic or antiandrogenic properties

Persistent organic pollutants (POPs) and primary ovarian insufficiency (POI)

- ▶ Case-control study looked at association between serum levels of selected POPs and risk for POI in a Chinese female population
- ▶ 157 cases and 217 healthy controls
- ▶ Serum concentrations of polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs)
- ▶ Serum levels of reproductive hormones FSH, LH, anti-Mullerian hormone (AMH) and estradiol were measured.

Persistent organic pollutants (POPs) and primary ovarian insufficiency (POI)



- ▶ Higher concentrations of PCBs and DDT associated with elevated risk of POI.
- ▶ In patients with POI,
 - ▶ exposure to PCBs = higher levels of LH
 - ▶ exposure to POPs associated lower levels of AMH

Organophosphates and reproduction

Diazinon (DZN) (organophosphate) has cytotoxic and pathological effects on the reproductive system

Oxidative stress (OS) from ROS may be the main mechanism

Can be associated with;

- sperm DNA fragmentation
- reduced integrity of sperm cell membrane
- Apoptosis
- depletion of antioxidants
- poor sperm quality
- Male infertility
- (Harchegani AB, et al, 2018)

Organophosphates and reproduction

- ▶ 211 women enrolled in the Environment And Reproductive Health (EARTH) prospective cohort study (2005-2015) gave urine samples during IVF
- ▶ Measured 5 Urinary PFR metabolites
- ▶ Detection frequencies were high for BDCIPP (87%), DPHP (94%), and ip-PPP (80%), but low for tb-PPP (14%) and BCIPP (0%)
- ▶ Declines from lowest to highest quartile of PFR were observed for the proportion of cycles resulting in successful fertilization (10% decrease), implantation (31%), clinical pregnancy (41%), and live birth (38%)

- ▶ Carignan, C et al. 2017

Organophosphates gut microbiota

- ▶ Several studies show an association between POP-induced gut microbial dysbiosis and prevalence of disorders.
 - ▶ ingestion of polychlorinated biphenyls, polybrominated diphenyl ethers or organochlorine pesticides influenced bile acid metabolism via alteration of bile salt hydrolase activity of *Lactobacillus*, *Clostridium* or *Bacteroides* genus.
 - ▶ DDE can elevate Proteobacteria and Firmicutes/Bacteroidetes ratio influencing which increases short-chain fatty acid synthesis, ensuing obesity or a pre-diabetic state.

Organophosphates Type 1 diabetes

- ▶ Study looked at association between POPs and T1D in youth
- ▶ Explored the impacts of POPs on pancreatic β -cell function and viability in vitro
- ▶ treatment with p,p'-DDE or PCB-153, at concentrations ranging from 1×10^{-15} M to 5×10^{-6} M, impaired the ability of pancreatic β -cells to produce and secrete insulin in response to glucose
- ▶ Treatment with PCB-153 or p,p'-DDE for 2 days did not affect β -cell viability, longer treatment progressively killed the β -cells.
- ▶ results support a potential role of POPs in T1D etiology and demonstrate a high sensitivity of pancreatic β -cells to POPs

Endocrine disruptors and allergies

EDC such as benzophenone, p-octylphenol, and tributyltin chloride (TBT) promote Th2 polarization indirectly via the depletion of glutathione

This leads to modulation of IL-10 and IL-12 production may exacerbate allergies and potentially airway inflammation in asthma

We know endocrine
disruptors cause harm
so now what?

Start by reducing exposures

The background features a series of overlapping, semi-transparent green triangles and polygons of various shades, ranging from light lime green to dark forest green. These shapes are primarily located on the right side of the frame, creating a dynamic, layered effect against the white background.



Dirty Dozen

1. Strawberries
2. Spinach
3. Kale
4. Nectarines
5. Apples
6. Grapes
7. Peaches
8. Cherries
9. Pears
10. Tomatoes
11. Celery
12. Potatoes



Clean 15

1. Avocados
2. Sweet corn
3. Pineapples
4. Frozen sweet peas
5. Onions
6. Papayas
7. Eggplants
8. Asparagus
9. Kiwis
10. Cabbages
11. Cauliflower
12. Cantaloupes
13. Broccoli
14. Mushrooms
15. Honeydew melons

Monterey Bay Aquarium – list of least toxic fish

<https://www.seafoodwatch.org>

- 
- ▶ Barramundi (US & Vietnam farmed)
 - ▶ Bass (US hooks and lines, farmed)
 - ▶ Catfish (US)
 - ▶ Clams
 - ▶ Mussels
 - ▶ Mahi Mahi (US handlines)
 - ▶ Oysters (farmed & Canada)
 - ▶ Prawn (Canada & US)
 - ▶ Salmon (New Zealand)
 - ▶ Scallops (farmed)
 - ▶ Seaweed (farmed)
 - ▶ Squid (US)
 - ▶ Tilapia (Canada, Ecuador, Peru & US)

PERSONAL CARE PRODUCTS QUICK TIPS FOR CHOOSING SAFER PERSONAL CARE PRODUCTS! **GUIDE**

Home » Why Skin Deep

Why Skin Deep

Like 21 Tweet Share 414

Why Skin Deep?

The American government doesn't require health studies or pre-market testing of the chemicals in personal care products, even though just about everyone is exposed to them. Through Skin Deep, we put the power of information in consumers' hands. When you know what's in the products you bring into your home and how those chemicals may affect your health and the environment, you can make informed purchasing decisions — and help transform the

Essential Tips and Facts

See that long list of ingredients on the back of the bottle? Some probably aren't as safe as you'd hope.

- 1 Top tips for safer products
- 2 Frequently asked questions (FAQs)
- 3 Why Skin Deep®?
- 4 Myths on cosmetic safety
- 5 User's guide to Skin Deep®

Enhanced Fertility...pptx Canadian Fertility...pdf Canadian Fertility...pdf Canadian Fertility...pdf Canadian Fertility...pdf Show all X

Type here to search 10:50 PM 2019-09-22 ENG 6

Switching personal care products

Use Skindeep database website <https://www.ewg.org/skindeep/>

The background features a series of overlapping, semi-transparent green geometric shapes, primarily triangles and quadrilaterals, that create a dynamic, layered effect. The colors range from light, pale greens to deep, forest greens. The shapes are positioned on the right side of the frame, extending towards the center, while the left side remains mostly white.

Naturopathic interventions

Persistent organic pollutants (POPs)

- ▶ POPs make free radicals that trigger proinflammatory pathways
- ▶ For PCBs to turn on the inflammatory genes there has to be an increase in cellular oxidative stress
- ▶ Antioxidants can protect against endothelial cell damage caused by these POPs

- ▶ Ratios of omega-6 to omega-3 fatty acids can modulate PCB-induced inflammatory parameters in vascular endothelial cells
- ▶ Omega-3 fatty acids are extremely protective against pollutant-induced inflammation

Omega 3 fatty acids and PCBs


PCBs and EGCG

- ▶ Primary vascular endothelial cells were pretreated with EGCG, followed by exposure to the PCB 126
- ▶ Exposure to PCB 126
 - ▶ increased cytochrome P450 1A1 (Cyp1A1) mRNA and protein expression
 - ▶ Decreased superoxide production
- ▶ Both attenuated following pre-treatment with EGCG



Phthalate excretions

All patients had MEHP (mono (2-ethylhexyl) phthalate) in their blood, sweat, and urine samples



Some participants had DEHP (di (2-ethylhexyl) phthalate) in sweat but not in serum



MEHP concentration in sweat was on average double urine levels



BPA excretion

- ▶ BPA found in sweat, even in some individuals with no BPA detected in their serum or urine samples
- ▶ Induced sweating appears to be a potential method for elimination of BPA

BPA and CoQ10

Effects of CoQ10 against BPA-induced testicular toxicity in rats



4 groups- Results looked at

plasma glutathione
(GSH)

serum superoxide
dismutase activities,

testicular GSH activity
sperm viability (%)
decreased with BPA

Both improved with
COQ10

NAC (N-acetylcysteine)

- ▶ Study for women with PCOS and undergoing ICSI compared 600mg of NAC three times per day to 1500mg/day of metformin for 6 weeks leading up to egg retrieval
- ▶ NAC group has less immature or abnormal oocytes and a higher number of good quality embryos compared to placebo

NAC (N-acetylcysteine)



- NAC functions as an antioxidant by serving as a precursor of glutathione peroxidase. (Safarinejad et al, 2009)
- 2 studies, looked at NAC and sperm parameters at 600 mg/day for 26 weeks (Safarinejad et al, 2009) and 13 weeks (Ciftci et al, 2009)
- Both studies demonstrated an improvement in sperm motility, however only one study observed an increase in sperm concentration and morphology (Safarinejad et al, 2009)

NAC and BPA

- ▶ A mouse placebo-controlled study
- ▶ Gave BPA (50 $\mu\text{g}/\text{mL}$) during oocyte in vitro maturation (IVM)
 - ▶ inhibited nuclear maturation
 - ▶ decreased fertilization and blastocyst formation rates
 - ▶ Increased ROS levels
 - ▶ Decreased GSH content in oocytes



NAC and BPA continued

- ▶ Adding NAC
 - ▶ Weakened the BPA-induced suppression of nuclear maturation
 - ▶ Improved downregulation of the fertilization and blastocyst formation
 - ▶ Mitigated the increased ROS levels and decreased GSH content

Melatonin and BPA

- ▶ BPA in a mouse model
 - ▶ compromises the first polar body extrusion (78.0% vs 57.0%, $P < .05$) by disrupting normal spindle assembly and chromosome alignment
- ▶ The defect was ameliorated (76.7%, $P < .05$) by oral administration of melatonin
- ▶ Melatonin improved IVF success via improving oocyte quality by reducing ROS levels and inhibiting apoptosis

Melatonin



- ▶ Important to educate about natural ways to improve melatonin secretion
 - ▶ Minimize blue light from devices
 - ▶ Consistent bedtime/wake time
 - ▶ Completely dark sleep space

Probiotics and ED's

- ▶ Growing evidence has shown that intestinal bacterial alterations caused by BPA exposure play an important role in several local and systemic diseases
- ▶ Growth of *L. acidophilus* and *B. bifidum* was inhibited by Nonylpolyphenol (NP)
- ▶ NP may interfere with normal gastrointestinal microbiota.
- ▶ May alter immunomodulation in the intestinal mucosa and be correlated with an increase in the incidence of allergic diseases or other gastrointestinal disorders

Probiotics and ED's

- ▶ Microbes can protect the gastrointestinal system by counteracting the biological activity of genotoxic compounds-including ED's, and thus preventing the DNA damage
- ▶ Probiotics (mainly lactobacilli) can inhibit the related DNA damage in the gut and highlights the emerging perspectives to enlarge and further investigate the microbial bio-protective role at intestinal level

Case #1

Visit #1 Oct 2021

- ▶ 31 yoa male patient CC – Fertility – Trying to conceive for over 2 years
- ▶ Sperm analysis – July 2021
 - ▶ spermatozoa- $4 \times 10^6/\text{mL}$
 - ▶ Spermatozoa- progressive – 11%
 - ▶ Spermatozoa- nonprogressive – 8%
 - ▶ Spermatozoa – immotile – 81%
 - ▶ Spermatozoa- normal – 0%
 - ▶ High DNA fragmentation
- ▶ Had varicocele surgery in March 2021

Case #1

Visit #1 Oct 2021

- ▶ Works as an accountant
- ▶ Lifestyle- non-smoker, no recreational or prescription medications, alcohol- 4 drinks/week
- ▶ Uses “regular” cleaning products and personal care products
- ▶ Exercise – runs 2km twice a week, walks dog twice/day 0.5-1km
- ▶ Diet recall- B- cereal or granola with yogurt, coffee
 - ▶ L- Leftovers
 - ▶ D- tofu, chicken, fish or beef, rice and salad
- ▶ Digestion – 1-2 BM’s/day no concerns

Case #1

Treatment #1 Oct 2021

- ▶ Formulation to support sperm motility, morphology and count-containing – CoQ10, acetyl-L-Carnitine, NAC, zinc, B12, Folate, selenium, vitamin C, mixed tocopherols – 2 caps twice a day
- ▶ Curcumin 500mg- 1 cap twice a day
- ▶ Diet- 2 cups of vegetables at lunch and dinner – review dirty dozen and clean 15, eliminate gluten for 3 months
- ▶ Eliminate alcohol
- ▶ Visit EWG.org to review personal care products and cleaning products
- ▶ During work-day ensure you get up at least once a hour and walk around to reduce testicular temperature
- ▶ Exercise – something to induce sweating at least 3 times a week

Case #1

Visit #2 Dec 2021

- ▶ Diet – has had big focus on vegetables and is meeting targets
- ▶ Exercise – getting 2 days a week but also do home improvement activities as well, is getting up and moving around every hour during work-day
- ▶ Being compliant with supplementation
- ▶ Has switched to natural cleaning products and changed his personal care products
- ▶ With no alcohol and changes finds sleep and energy have improved overall feeling good

Case #1

Treatment #2 Dec 2021

- ▶ Continue all recommendations from October with bigger focus on exercise
- ▶ Maintain diet with higher vegetables and no gluten

Case #1

Jan 2022

Patient reached out to let me know they had a positive pregnancy test (happened before he could do a repeat sperm analysis)

Healthy baby girl arrived August 2022

Case #2

Patient – TK 44 yoa female - #1 visit Feb 2022

- ▶ CC – 2ndary infertility has been trying for 4 years, has 5-year-old daughter conceived naturally
- ▶ Cycle- is regular no concerns with PMS, period lasts 5 days
- ▶ Over past 3 years has had 6 failed IUI's and 4 failed IVF transfers
- ▶ Supplements – currently takes Prenatal and Vitamin D
- ▶ Digestion – good – 2 formed BM's per day, no concern with bloating or heartburn
- ▶ Stress – high because of concern with fertility and is a teacher so through pandemic has been challenging
- ▶ Also reported low libido

Case #2

Patient – TK 44 yoa female - #1 visit Feb 2022

- ▶ Labs – Ferritin – 48
 - ▶ B12 – 458
 - ▶ CBC- WNL
 - ▶ STI screen negative
 - ▶ Liver and Kidney function – WNL
 - ▶ Clinic monitoring – patient appears to ovulate each month around day 13

Case #2

Patient – TK 44 yoa female - #1 visit Feb 2022

- ▶ Not currently exercising (was regularly before first pregnancy)
- ▶ Diet – eats generally well- doesn't focus on organic eating
 - ▶ B- oatmeal or eggs
 - ▶ L- salad with protein
 - ▶ D- protein, rice or potato and vegetables or pasta
 - ▶ Eats out on occasion has some snacks of chips or cookies but no daily
- ▶ Personal care products and cleaning products are usual items you buy at the grocery store or shoppers

Case #2

Patient – TK 44 yoa female - #1 visit Feb 2022

- ▶ Treatment after visit 1
- ▶ Exercise – resume your at home workouts 4 days a week (ensure you are sweating)
- ▶ Discussed clean 15/ dirty dozen and the relevance for everyone in the family
- ▶ Start castor oil packs over the abdomen with heat for 30 minutes 3 days a week
- ▶ Added supplementation to support egg quality – NAC, CoQ10, Acetyl-L-carnitine, ALA, inositol, mixed tocopherols and vitamin C
- ▶ Recommended – Ashwagandha 500mg twice a day and Maca – 750mg twice a day, Fish oil 2g combo EPA/DHA per day

Case #2

#2 visit March 2022

- ▶ Patient reported an improvement in general sense of calm and some improvement in libido (still further room for improvement)
- ▶ Now having intercourse more regularly
- ▶ Is really enjoying exercising again and feels her energy and sleep quality have both improved
- ▶ No new concerns from previous visit

Case #2

#2 visit March 2022

- ▶ Treatment – continue previous recommendations
- ▶ Discussed looking at personal care products on skin deep database and working on ensuring any products going on the skin where rank at 1-3
- ▶ Discussed also starting to change over cleaning products at home

Case #2

#3 visit May 2022

- ▶ Patient reported stress increasing – found out will be teaching grade 8 the following school year (instead of grade 2)
- ▶ Finds is having conflict with school administrators
- ▶ Frustrated that isn't pregnant still and unsure what else to do
- ▶ Patients husband (who was also at visit) had calm her down a few times when she was crying

Case #2

#3 visit Treatment Recommendations May 2022

- ▶ Recommended patient to a psychotherapist (with specialty in fertility)
- ▶ Had discussion around other family planning options – donor eggs, embryo adoption, adoption etc
- ▶ Discussed starting to journal (this is something she had found helping in the past)
- ▶ Every day spend at least 15 minutes doing something fun that makes you laugh or smile
- ▶ Recommended adding Gaba – 300mg twice a day and L-Theanine – 500mg per day
- ▶ And continuing with pervious recommendations

Case #2

#4 visit Aug 2022

- ▶ Patient reported stress being lower with being off over the summer and feeling that school would be okay with the older age group- but still feeling a little anxious about it
- ▶ Had used the Gaba and Theanine in May/June but stopped for the summer
- ▶ Felt psychotherapy has been helpful and journalling was good
- ▶ Has been able to switch over all cleaning and personal care products and is feeling good about it
- ▶ Still exercising regularly and doing castor oil packs

Case #2

#4 visit Aug 2022

- ▶ Treatment – recommended resume the Gaba and Theanine for the first month of school and then we could reassess
- ▶ Diet – focus on increasing healthy fats – 5 servings per day
- ▶ Discussed trying intermittent fasting 16:8 5 days a week
- ▶ Add probiotic daily to support immune function going back to school/work and for supporting uterine microbiome

Case #2

#5 visit Oct 2022

- ▶ Patient reported having a positive pregnancy test last week and had seen doctor for confirmation blood work
- ▶ Has ultrasound scheduled for 6 week mark
- ▶ So far has been feeling good – a bit of fatigue but no other concerns

Case #2

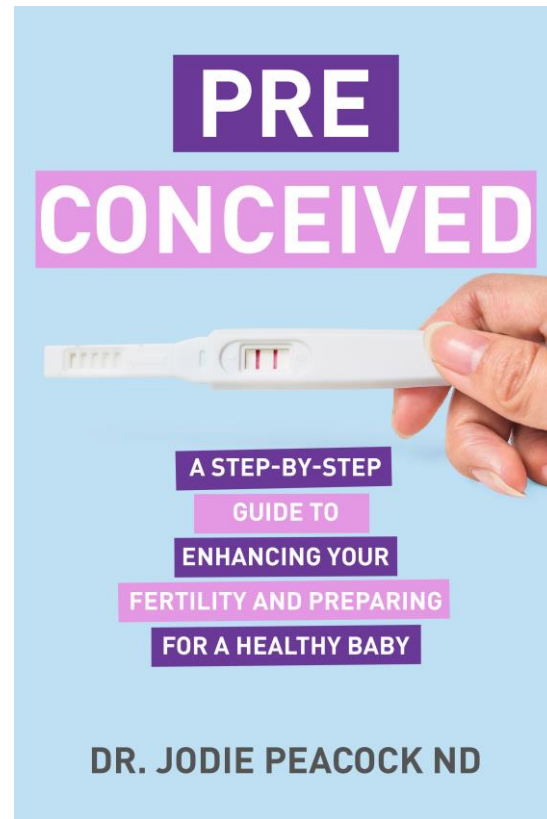
#5 Treatment Oct 2022

- ▶ Recommended patient continue her Prenatal, Probiotic and Fish oil
- ▶ Continue with changes that they have made around products in the house and with diet
- ▶ Patient delivered a healthy baby boy June 2023

Summary

- ▶ Endocrine disrupting chemicals have a negative impact on reproduction and long-term health
- ▶ Minimizing exposure does limit the negative impacts
- ▶ Optimizing detoxification routes of sweating, liver and kidney function will reduce negative effects
- ▶ Ensuring adequate antioxidant intake and supporting glutathione production is very protective
- ▶ Looking at gut microbiome will also support improved outcomes

Resource book available for patients



References

- ▶ Abdelrazik, H., et al., L-carnitine decreases DNA damage and improves the in vitro blastocyte development rate in mouse embryos. *Fertil Steril*. 2009. 91(2): 589-96
- ▶ Aboulmaouhib, S et al. Impact of alcohol and cigarette smoking consumption in male fertility potential: Looks at lipid peroxidation, enzymatic antioxidant activities and sperm DNA damage. *Andrologia* 2017 Nov 21. doi: 10.1111/and.12926. [Epub ahead of print]
- ▶ Ahmadi S, et al. Antioxidant supplements and semen parameters: An evidence based review. *Int J Reprod Biomed (Yazd)*. 2016;14(12):729-736.
- ▶ Ames, B.N., and J. Liu. "Delaying the mitochondrial decay of aging with acetylcarnitine." *Annals of the New York Academy of Sciences*. Vol. 1033 (2004): 108-116.
- ▶ Anetta Karwacka, Dorota Zamkowska, Michał Radwan & Joanna Jurewicz (2019) Exposure to modern, widespread environmental endocrine disrupting chemicals and their effect on the reproductive potential of women: an overview of current epidemiological evidence, *Human Fertility*, 22:1, 2-25, DOI: 10.1080/14647273.2017.1358828
- ▶ Artini, PG., et al., Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. *Gynecol Endocrinol*. 2013. 29(4): 375-9
- ▶ Arzuaga X, Ren N, Stromberg A, Black EP, Arsenescu V, Cassis LA, et al. Induction of gene pattern changes associated with dysfunctional lipid metabolism induced by dietary fat and exposure to a persistent organic pollutant. *Toxicol Lett*. 2009;189(2):96-101
- ▶ Balercia G., et al. Coenzyme Q 10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. *Fertil Steril* 2009; 91: 1785-1792.
- ▶ [Bennett M](#). Vitamin B12 deficiency, infertility and recurrent fetal loss. *J Reprod Med*. 2001 Mar;46(3):209-12.
- ▶ Barim-Oz, O., et al., The influence of dietary antioxidant on ovarian eggs and levels of vitamin E, C, A, astaxanthin, β - carotene and oxidative stress in tissues of *Astacus leptodactylus* (Eschscholtz) during reproduction. *Cell Mol Biol (Noisy-le-grand)*. 2016. 62(14): 1-10.
- ▶ Brede, C., Fjeldal, P., Skjevrak, I., & Herikstad, H. (2003). Increased migration levels of bisphenol A from polycarbonate baby bottles after dishwashing, boiling and brushing. *Food Additives & Contaminants*, 20, 684-689. doi: 10.1080/0265203031000119061
- ▶ Benkhalifa M, Ferreira YJ, Chahii H, Louanjli N, Miron P, Merviel P, et al. Mitochondria: Participation to infertility as source of energy and cause of senescence. *The International Journal of Biochemistry & Cell Biology*. 2014;55:60-4.

References

- ▶ Byford, J.R., Shaw, L.E., Drew, M.G., Pope, G.S., Sauer, M.J., & Darbre, P.D. (2002). Oestrogenic activity of parabens in MCF7 human breast cancer cells. *Journal of Steroid Biochemistry and Molecular Biology*, 80, 49-60. doi: 10.1016/S0960-0760(01)00174-1.
- ▶ Carignan, C et al. Urinary Concentrations of Organophosphate Flame Retardant Metabolites and Pregnancy Outcomes among Women Undergoing *in Vitro* Fertilization. *Environ Health Perspect*. 2017 Aug; 125(8): 087018.
- ▶ Chiu T, Rogers M, Law E, Briton-Jones C, Cheung L, Haines C. Follicular fluid and serum concentrations of myo-inositol in patients undergoing IVF: relationship with oocyte quality. *Human Reproduction*. 2002;17(6):1591-1596
- ▶ Ciftci, H., et al. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. *Urology* 2009; 74, 73-76.
- ▶ Cooke, P.S., Buchanan, D.L., Young, P., Setiawan, T., Brody, J., Korach, K.S., ... Cunha, G.R. (1997). Stromal estrogen receptors mediate mitogenic effects of estradiol on uterine epithelium. *Proceedings of the National Academy of Sciences of the United States of America*, 94, 6535-6540. Retrieved from: <http://www.pnas.org/content/94/12/6535>.
- ▶ Craig, Z.R., Singh, J., Gupta, R.K., & Flaws, J.A. (2014). Co-treatment of mouse antral follicles with 17 β -estradiol interferes with mono-2-ethylhexyl phthalate (MEHP)-induced atresia and altered apoptosis gene expression. *Reproductive Toxicology*, 45, 45-51. doi: 10.1016/j.reprotox.2014.01.002.
- ▶ Di Nisio A and C Foresta. Water and soil pollution as determinant of water and food quality/contamination and its impact on male fertility. *Reprod Biol Endocrinol*. 2019 Jan 6;17(1):4.
- ▶ Dodge LE, Williams PL, Williams MA, Missmer SA, Toth TL, Calafat AM, Hauser R. 2015. Paternal urinary concentrations of parabens and other phenols in relation to reproductive outcomes among couples from a fertility clinic. *Environ Health Perspect* 123:665-671; <http://dx.doi.org/10.1289/ehp.1408605>
- ▶ Dodge, L. E., Williams, P. L., Williams, M. A., Missmer, S. A., Toth, T. L., Calafat, A. M., ... Hauser, R. (2015b). Paternal urinary concentrations of parabens and other phenols in relation to reproductive outcomes among couples from a fertility clinic. *Environmental Health Perspectives*, 123, 665-671. doi: 10.1289/ehp.1408605.
- ▶ ESHRE Guideline: management of women with premature ovarian insufficiency. *Human Reproduction*. 2016;31(5):926-37.
- ▶ Facchine F., et,al., Results from the International Consensus Conference on Myo-inositol and d-chiro-inositol in Obstetrics and Gynecology: the link between metabolic syndrome and PCOS. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2015;195:72-76.
- ▶ Fenkci, SM., et al., Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome. *Hum Reprod*. 2008. 23(7): 1602-6

References

- ▶ Galand, P., Mairesse, N., Degraef, C., & Rooryck, J. (1987). o,p- DDT(1,1,1-trichloro-2(p-chlorophenyl) 2-(o-chlorophenyl) ethane is a purely estrogenic agonist in the rat uterus in vivo and in vitro. *Biochemical Pharmacology*, 36, 397-400. doi: 10.1016/0006-2952(87)90302-9.
- ▶ Genazzani, AD., et al., Modulatory effects of alpha-lipoic acid (ALA) administration on insulin sensitivity in obese PCOS patients. *J Endocrinol Invest*. 2017. doi: 10.1007/s40618-017-0782-z.
- ▶ Genuis, Stephen et al. Human Elimination of Phthalate Compounds: Blood, Urine, and Sweat (BUS) Study *ScientificWorldJournal*. 2012; 2012: 615068. Published online 2012 Oct 31. doi: [10.1100/2012/615068](https://doi.org/10.1100/2012/615068)
- ▶ Golden, R., Gandy, J., & Vollmer, G. (2005). A review of the endocrine activity of parabens and implications for potential risks to human health. *Critical Reviews in Toxicology*, 35, 435-458. doi: 10.1080/10408440490920104.
- ▶ [Güles Ö et al.](#) Protective effect of coenzyme Q10 against bisphenol-A-induced toxicity in the rat testes. *Toxicol Ind Health*. 2019 Jul;35(7):466-481. doi: 10.1177/0748233719862475
- ▶ Gulcin, I., et al., Antioxidant and antiradical activities of L-carnitine. *Life Sci*. 2006. 78(8): 803-11
- ▶ [Gundersen TD](#), et al. Association Between Use of Marijuana and Male Reproductive Hormones and Semen Quality: A Study Among 1,215 Healthy Young Men. *Am J Epidemiol*. 2015 Sep 15;182(6):473-81
- ▶ Gupta, R.K., Singh, J.M., Leslie, T.C., Meachum, S., Flaws, J.A., & Yao, H.H.-C. (2010). Di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate inhibit growth and reduce estradiol levels of antral follicles in vitro. *Toxicology and Applied Pharmacology*, 242, 224-230. doi: 10.1016/j.taap.2009.10.011.
- ▶ Ha MH, Lee DH, Jacobs DR. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999-2002. *Environ Health Perspect*. 2007;115(8):1204-1209.
- ▶ [Han SG et al.](#) EGCG protects endothelial cells against PCB 126-induced inflammation through inhibition of AhR and induction of Nrf2-regulated genes. *Toxicol Appl Pharmacol*. 2012 Jun 1;261(2):181-8. doi: 10.1016/j.taap.2012.03.024. Epub 2012 Apr 6.
- ▶ Harchegani AB, et al. Mechanisms of diazinon effects on impaired spermatogenesis and male infertility. *Toxicol Ind Health*. 2018 Sep;34(9):653-664.
- ▶ Hauser, R., Gaskins, A.J., Souter, I., Smith, K.W., Dodge, L.E., Ehrlich, S., ... Williams, P.L. (2016) Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: Results from the EARTH study. *Environmental Health Perspectives*, 124, 831-839. doi: 10.1289/ehp.1509760.

References

- ▶ Hectors TLM, Vanparys C, van der Ven K, Martens GA, Jorens PG, Van Gaal LF, et al. Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function. *Diabetologia*. 2011;54(6):1273-1290.
- ▶ Hennig B, Reiterer G, Majkova Z, Oesterling E, Meerarani P, Toborek M. Modification of environmental toxicity by nutrients: implications in atherosclerosis. *Cardiovasc Toxicol*. 2005;5(2):153-160.
- ▶ Hrdina, P. D., Singhal, R. S., & Ling, G. M. (1975). DDT and related chlorinated hydro-carbon insecticides: Pharmacological basis of their toxicity in mammals. *Advances in Pharmacology and Chemotherapy*, 12, 31-88. Retrieved from: <http://www.sciencedirect.com/science/article/pii/S1054358908602197>
- ▶ Ismail, AM., et al., Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014. 180: 148-52
- ▶ Jonsson, H., Keil, J., Gaddy, R., Loadholt, C., Hennigar, G., & Walker, E. (1975). Prolonged ingestion of commercial DDT and PCB; effects on progesterone levels and reproduction in the mature female rat. *Archives of Environmental Contamination and Toxicology*, 3, 479-490. doi:10.1007/ BF02220818.
- ▶ Kathirvel, E., et al. "Acetyl-L-carnitine and lipoic acid improve mitochondrial abnormalities and serum levels of liver enzymes in a mouse model of nonalcoholic fatty liver disease." *Nutrition Research*. Vol. 33, No. 11 (2013): 932-941.
- ▶ Keskes-Ammar L., et al. Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. *Arch Androl* 2003; 49: 83-94.
- ▶ Lafuente R., et al. Coenzyme Q10 and male infertility: a meta-analysis. *J Assis Reprod Gen* 2013; 30: 1147-1156.
- ▶ Lange, A., Carignan, C.C., Minguez-Alarcon, L., Williams, P., Calafat, A.M., Toth, T.L., & Hauser, R. (2015). Triclosan exposure and treatment outcomes in women undergoing in vitro fertilization. *Fertility and Sterility*, 104, e86. doi: 10.1016/j.fertnstert.2015.07.264.
- ▶ Layne J, Majkova Z, Smart EJ, Toborek M, Hennig B. Caveolae: a regulatory platform for nutritional modulation of inflammatory diseases. *J Nutr Biochem*. 2011;22(9):807-811
- ▶ [Li Q¹](#), [Zhao Z²](#) Influence of N-acetyl-L-cysteine against bisphenol a on the maturation of mouse oocytes and embryo development: in vitro study. *BMC Pharmacol Toxicol*. 2019 Jul 22;20(1):43. doi: 10.1186/s40360-019-0323-9.
- ▶ [Machtinger R](#) et al. Bisphenol-A and human oocyte maturation in vitro. *Hum Reprod*. 2013 Oct;28(10):2735-45.

References

- ▶ Majkova Z, Toborek M, Hennig B. The role of caveolae in endothelial cell dysfunction with a focus on nutrition and environmental toxicants. *J Cell Mol Med.* 2010;14(10):2359-2370.
- ▶ Meldrum DR, Casper F, Diez-Juan A, Simon C, Domar AD, Frydman R. Aging and the environment affect gamete and embryo potential: can we intervene? *Fertility and Sterility.* 2016;105(3):548-59.
- ▶ Menchini-Fabris GF., et al. Free L-carnitine in human semen: its variability in different andrologic pathologies. *Fertil Steril* 1984;42:263-267.
- ▶ Michels K.A. et al. Folate, homocysteine and the ovarian cycle among healthy regularly menstruating women. *Hum Reprod.* 2017 Aug 1;32(8):1743-1750.
- ▶ Moncada ML., et al. Effect of acetylcarnitine treatment in oligoasthenospermic patients. *Acta Eur Fertil* 1992; 23, 221-224.
- ▶ Mongioi L. The role of carnitine in male infertility. *Andrology.* 2016 Sep;4(5):800-7.
- ▶ Musachio EAS, Araujo SM, Bortolotto VC, de Freitas Couto S, Dahleh MMM, Poetini MR, Jardim EF, Meichtry LB, Ramborger BP, Roehrs R, Petri Guerra G, Prigol M. Bisphenol A exposure is involved in the development of Parkinson like disease in *Drosophila melanogaster*. *Food Chem Toxicol.* 2020 Mar;137:111128. doi: 10.1016/j.fct.2020.111128. Epub 2020 Jan 14. PMID: 31952986.
- ▶ Murphy LE, et al. Folate and vitamin B12 in idiopathic male infertility. *Asian J Androl.* 2011 Nov;13(6):856-61.
- ▶ Nemati, M et al. Comparison of metformin and N-acetyl cysteine, as an adjuvant to clomiphene citrate, in clomiphene-resistant women with polycystic ovary syndrome. *J Gynecol Obstet Hum Reprod.* 2017 Sep;46(7):579-585
- ▶ Omran G. et al. Potential hazards of bisphenol A exposure to semen quality and sperm DNA integrity among infertile men. *Reprod Toxicol.* 2018 Oct;81:188-195
- ▶ Pacchiarotti, A., et al., Effect of myo-inositol and melatonin versus myo-inositol, in a randomized controlled trial, for improving in vitro fertilization of patients with polycystic ovarian syndrome. *Gynecol Endocrinol.* 2016. 32(1): 69-73
- ▶ Pal L, Jindal S, WiS BR, Santoro N. Less is more... Increased gonadotropin use for ovarian stimulation adversely influences clinical pregnancy and live birth following IVF. *Fertility Sterility* 2008; 89:1694-701.
- ▶ Pan W, et al. **Selected persistent organic pollutants associated with the risk of primary ovarian insufficiency in women.** . *Environ Int.* 2019 Aug;129:51-58. doi: 10.1016/j.envint.2019.05.023. Epub 2019 May 17.
- ▶ *Res.* 2017 Apr;62(3). doi: 10.1111/jpi.12396. Epub 2017 Mar 1

References

- ▶ Pérez-Bermejo M, Mas-Pérez I, Murillo-Llorente MT. The Role of the Bisphenol A in Diabetes and Obesity. *Biomedicines*. 2021 Jun 10;9(6):666. doi: 10.3390/biomedicines9060666. PMID: 34200822; PMCID: PMC8230545.
- ▶ Popli S, Badgular PC, Agarwal T, Bhushan B, Mishra V. Persistent organic pollutants in foods, their interplay with gut microbiota and resultant toxicity. *Sci Total Environ*. 2022 Aug 1;832:155084. doi: 10.1016/j.scitotenv.2022.155084. Epub 2022 Apr 6. PMID: 35395291.
- ▶ Phillips KP, Tanphaichitr N. *J Toxicol Environ Health B Crit Rev*, Part B 2008; 11: 188-220
- ▶ Rahmani, E., et al., The effect of coenzyme Q10 supplementation on gene expression related to insulin, lipid and inflammation in patients with polycystic ovary syndrome. *Gynecol Endocrinol*. 2017. 26: 1-6
- ▶ Rago, R., et al., Effect of myo-inositol and alpha-lipoic acid on oocyte quality in polycystic ovary syndrome non-obese women undergoing in vitro fertilization: a pilot study. *J Biol Regul Homeost Agents*. 2015. 29(4): 913-23
- ▶ Ramadass P. et al. **Dietary flavonoids modulate PCB-induced oxidative stress, CYP1A1 induction, and AhR-DNA binding activity in vascular endothelial cells.** *Toxicol Sci*. 2003 Nov;76(1):212-9. Epub 2003 Sep 11.
- ▶ Refaey, A., et al., Combined coenzyme Q10 and clomiphene citrate for ovulation in clomiphene-citrate-resistant polycystic ovary syndrome. *Reprod Biomed Online*. 2014. 29(1): 119-24
- ▶ Reimann B, Vrijens K, Roels HA, Wang C, Cosemans C, Van Overmeire I, Nawrot TS, Plusquin M. In utero exposure to parabens and early childhood BMI z-scores - Associations between placental ethyl paraben, longitudinal BMI trajectories and cord blood metabolic biomarkers. *Environ Int*. 2021 Dec;157:106845. doi: 10.1016/j.envint.2021.106845. Epub 2021 Aug 30. PMID: 34474324; PMCID: PMC8484768.
- ▶ Rodricks, J.V., Swenberg, J.A., Borzelleca, J.F., Maronpot, R.R., & Shipp, A.M. (2010). Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. *Critical Reviews in Toxicology*, 40, 422-484. doi: 10.3109/10408441003667514.
- ▶ Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of alcohol consumption on in vitro fertilization. *Obstet Gynecol*. 2011;117:136-42.
- ▶ Ruder, EH., et al., Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility. *Fertil Steril*. 2014. 101(3): 759-66
- ▶ Safarinejad, M.R., and Safarinejad, S. Efficacy of selenium and/ or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. *J. Urol*. 2009; 181, 741-751.
- ▶ Safarinejad MR., et al. Effects of the reduced form of coenzyme Q 10 (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study. *J Urol* 2012; 188: 526-531.
- ▶ Sandborgh-Englund G, Adolfsson-Erici M, Odham G, and Ekstrand J. 2006 Pharmacokinetics of triclosan following oral ingestion in humans. *J Toxicol Environ Health A* 69: 1861-1873.

References

- ▶ Seko L, Moroni R, Leitao V, Teixeira D, Nastri C, Martins W. Melatonin supplementation during controlled ovarian stimulation for women undergoing assisted reproductive technology: systematic review and meta-analysis of randomized controlled trials. *Fertility and Sterility*. 2014;101(1): 154-161.e4.
- ▶ Shang, XJ. et al. Effect and safety of L-carnitine in the treatment of idiopathic oligoasthenozoospermia: a systemic review. *Zhonghua Nan Ke Xue*. 2015 Jan;21(1):65-73.
- ▶ Sinclair S. Male infertility: nutritional and environmental considerations. *Altern Med Rev*. 2000 Feb;5(1):28-38.
- ▶ Smith, K.W., Souter, I., Dimitriadis, I., Ehrlich, S., Williams, P. L., Paige, W. L., ... Hauser, R. (2013). Urinary paraben concentrations and ovarian aging among women from a fertility center. *Environmental Health Perspectives*, 121, 1299-1305. doi: 10.1289/ehp.1205350.
- ▶ Souter, I., Smith, K.W., Dimitriadis, I., Ehrlich, S., Williams, P.L., Calafat, A.M., & Hauser, R. (2013a). The association of 24 A. KARWACKA ET AL. bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. *Reproductive Toxicology*, 42, 224-231. doi: 10.1016/j.reprotox.2013.09.008.
- ▶ Takasaki A, Tamura H, Miwa I, Taketani T, Shimamura K, Sugino N (April 2010). "Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium". *Fertil. Steril.* 93 (6): 1851-8.
- ▶ Tartibian B., Maleki B. H. (2012). Correlation between seminal oxidative stress biomarkers and antioxidants with sperm DNA damage in elite athletes and recreationally active men. *Clinical Journal of Sport Medicine*, 22, 132-139
- ▶ Thomas, P., & Dong, J. (2006). Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. *The Journal of Steroid Biochemistry and Molecular Biology*, 102, 175-179. doi: 10.1016/j.jsbmb.2006.09.017.
- ▶ Tolstrup JS, Kjaer S, Holst C, Sharif H, Munk C, Osler M, et al. Alcohol use as predictor for infertility in a representative population of Danish women. *Acta Obs Gynecol Scand*.2003;82:744-9.
- ▶ Wang L, Reiterer G, Toborek M, Hennig B. Changing ratios of omega-6 to omega-3 fatty acids can differentially modulate polychlorinated biphenyl toxicity in endothelial cells. *Chem Biol Interact*. 2008;172(1):27-38
- ▶ Wise L, Rothman K, Mikkelsen E, Sørensen H, Riis A, Hatch E. A prospective cohort study of physical activity and time to pregnancy. *Fertility and Sterility*. 2012;97(5):1136-1142.e4.
- ▶ Wong, W.Y., et al. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. *Fertil. Steril.* 2002, 77, 491-498.
- ▶ Zhang M et al. Melatonin protects oocyte quality from Bisphenol A-induced deterioration in the mouse. *J Pineal Res*. 2017 Apr;62(3). doi: 10.1111/jpi.12396. Epub 2017 Mar 1.