

## Teaching Session on EDCs for MDs Answer Key

This teaching session examines the newly emerging concept of endocrine-disrupting chemicals (EDCs) and largely focuses on EDCs and other potentially toxic compounds that are either direct or indirect food additives that the AAP's Council on Environmental Health consider to pose health risks to children. Practical advice the pediatrician can offer is explored.

1. Introduction to Endocrine Disrupting Chemicals (EDCs) Endocrine Society and IPEN  
<https://www.endocrine.org/-/media/endsociety/files/advocacy-and-outreach/important-documents/introduction-to-endocrine-disrupting-chemicals.pdf?la=en>
2. Food Additives and Child Health (Policy Statement)  
<https://pediatrics.aappublications.org/content/pediatrics/142/2/e20181408>
3. Food Additives and Child Health (Technical Report)  
<https://pediatrics.aappublications.org/content/142/2/e20181410>
4. Food Additives: What Parents Should Know.  
<https://www.healthychildren.org/english/healthy-living/nutrition/pages/food-additives.aspx>
5. Questions & Answers: Arsenic in Rice and Rice Products  
<https://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm319948.htm>

1. Discuss the concept of endocrine-disrupting chemicals (EDCs) (use ref 1)
  - a. What is the Endocrine Society's definition of an EDC? (page 1 of ref 1).  
 "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action."
  - b. How many chemicals are thought to be EDCs? (page 1 ref 1)  
 While there are hundreds of thousands of manufactured chemicals – very few of these have been directly tested for EDC activity. However about 1,000 different manufactured chemicals are thought to be EDCs.
  - c. Name several categories of products and specific examples of chemicals that are EDCs from each category (pg 10 ref 1).

**TABLE 2. SOME KNOWN EDCS AND THEIR USES**

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterials	Triclosan
Textiles, clothing	Perfluorochemicals

Abbreviations: BPA: bisphenol A; 2,4-D: 2,4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls

- d. Is classical chemical risk assessment well suited for assessing risk from EDCs? (pg 2, 3, 23 ref 1)

No. Classical chemical toxicity risk assessment assumes that there is a single toxic effect (for example direct liver damage), that the dose-effect curve is linear and monotonic, generally involves testing in adult animals, tests one compound at a time, and frequently uses either death or cancer as the only outcome measured. In contrast EDCs act at very low doses (parts per billion or trillion), often have the greatest effect during narrow windows of exposure (fetal, infant etc), like hormones and medications EDCs often have non-monotonic dose response (example higher doses result in receptor down-regulation with loss of effect), frequently work in an additive or even synergistic fashion with other EDCs (i.e. need to study mixtures that reflect real life) and often affect neurodevelopmental outcomes (ADHD, loss of IQ, ASD) that are harder to study in animal models.

2. Children's health may be affected through ingestion of chemicals with endocrine-disrupting effects that are deliberately used in food production or packaging.

- a. What are indirect vs. direct food additives and give examples of each.

Direct food additives are chemicals such as dyes, flavorings and preservatives that are directly added to foods. Examples are nitrates and nitrites that are used as preservatives in meats like bacon, ham, hot dogs, bologna etc. Nitrates and nitrites are potential EDCs because they block the uptake of iodine by the sodium/iodine symporter (NIS) in the thyroid gland. They have also been classified as "probable human carcinogens" because they are converted into carcinogenic N-nitroso compounds (NOCs).

Indirect food additives are chemicals that are used in food processing and packaging that food comes into contact with and which may leach into food products. These include bisphenols, phthalates, perfluoralkyl chemicals (PFCs) and perchlorate. These compounds have a broad array of potential health effects.

- b. Discuss the number of chemicals that are allowable in food and food packaging materials.

Under the 1958 Food Additives Amendment to the 1938 Federal Food Drug and Cosmetic Act more than 10,000 chemicals are allowed to be added to food either directly or indirectly. Many of these chemicals were grandfathered in before the 1958 law.

- c. What is "GRAS" designation and how many chemicals are used under this designation?

GRAS stands for "generally recognized as safe" and is a designation that allows GRAS compounds to be used without US Food and Drug Administration approval or notification. About 1,000 chemicals with GRAS status are in use in the US.

- d. What are some issues that the AAP identify as weaknesses with using GRAS designation to regulate food additives?

- i. GRAS was intended to be used for limited cases but now is the main route by which most food additives enter the market.
- ii. The GAO concludes this mechanism prevents FDA from ensuring safety of existing and new food additives
- iii. Voluntary evaluation of GRAS status has high potential for conflict of interest as it is done by the company, their consultants or a panel of experts hired by their consultants. No evaluations have been prepared by third parties.
- iv. FDA does not have authority to obtain data on or reassess safety of chemicals already on the market (styrene and eugenol methyl ether are flavorings approved for use in foods but which have now been classified as "anticipated to be human carcinogens").
- v. Testing used to determine GRAS status historically has been inadequate, incomplete and often doesn't even include feeding studies, does not consider windows of developmental susceptibility, does not consider additive or synergistic effects of 2 or more compounds.

3. At a 2 year WCC a family asks your advice about purchasing plastic products that are labelled as “BPA Free”.
- a. What is BPA?  
Bisphenol A is a particular type of “bisphenol” and is a chemical that is used in the manufacture of polycarbonate plastics (clear rigid plastics) and epoxy that lines metal can such as soup, vegetables, beans etc. Not all can liners contain BPA but it is impossible for consumers to know which do and do not. BPA leaches into food from containers with most of exposure coming from ingestion. Thermal cash register receipts are the major dermal source of exposure and BPA can be inhaled/ingested in contaminated dust. BPA also enters surface water from discarded plastics. About 5.4 million metric tons of BPA are made annually for plastics production.
  - b. What is the evidence that BPA is an EDC that poses health risks to humans?  
BPA was shown to be an estrogen mimic in 1930’s and was originally developed as a medication to be used as an estrogen supplement (but diethylstilbestrol was chosen instead!). BPA interferes with estrogen signaling in several ways:
    - i. Directly bind and stimulate estrogen receptors (ER) – albeit weakly
    - ii. Low levels BPA alters density of ER in tissue such as brain thus altering tissue sensitivity to natural estrogens of DNA and hence can lead to developmental consequences
    - iii. BPA alters methylation with resultant epigenetic changes in gene expression that are linked to changes in neuroendocrine pathways affecting reproductive health, energy balance (obesity), behavior and increased risk of uterine and prostate cancers (animal models).
    - iv. Epidemiological studies link BPA exposure to:
      1. Reduced oocyte quality
      2. PCOS associated with elevated androgens
  - c. What are BPA-free plastic products made with, and is this safer than BPA?  
“BPA free” plastic products are made with a very similar compound bisphenol S (BPS). Early evidence suggest that BPS may be more estrogenic than BPA and hence may be an example of a “regrettable substitution” in which a more toxic compound replaces a toxic compound.
  - d. What practical advice can you offer this family if they wish to reduce risks?
    - i. Use glass, ceramic or stainless steel containers to store food.
    - ii. Never microwave plastics (accelerates leaching)
    - iii. Do not wash plastics in dishwasher – harsh soaps and high temperature accelerate leaching.
    - iv. Avoid canned foods if possible and choose foods packaged in glass jars or frozen to avoid leaching from can liner
    - v. Do not store cans in high temp or for longer periods (accelerates leaching)
    - vi. Avoid plastic with recycling code 7 (unless labelled as “biobased” or “greenware”)
    - vii. Use glass or stainless-steel water bottles – not “BPA Free” plastic b/c of doubts about BPS.
    - viii. Keep home clean, well vacuumed and wash hands – reduce exposure from contaminated dust
    - ix. Avoid handling cash register receipts (an occupational hazard for retail workers)
4. The mother of a 4 month old child you are seeing for WCC is interested in starting to feed her child infant cereal. The grandmother insists that mom should use rice cereal exclusively because that is what the grandmother was told to do by her pediatrician, but the mom has heard that there is arsenic in rice. Mom wonders if it is OK to feed her baby rice cereal and also wonders if arsenic in rice is a concern for the whole family. What advice would you give her (Ref 5)?
- a. What are the two forms of arsenic, where do they come from and how do they get into foods.  
Organic (bound to carbon) and inorganic. These are present in water and soils and are absorbed by some food crops as they grow. Inorganic arsenic is associated with adverse health risks.
  - b. What are health concerns with arsenic exposure?  
Long term exposure is associated with higher risk for skin bladder and lung cancer as well as

higher risk of cardiovascular disease. FDA found that exposure in infants and pregnant women can negatively impact the child's cognitive development.

c. Why is rice a concern?

- i. Rice is a crop that tends to accumulate arsenic more readily than other plants (and rice is a staple in diet around the world).
- ii. 53% of infant rice cereals sampled in the US by the FDA were found to have levels of inorganic arsenic > 100 parts per billion (ppb), exceeding the level set by the EU for rice and rice products for infants and children. Non-rice infant foods were all well below 100 ppb inorganic arsenic.
- iii. Infants fed rice cereal at least once daily may exceed the daily arsenic exposure limit of 0.17 µg/kg body weight per day based on drinking water standards

d. Do you recommend avoiding certain rice products?

Consider avoiding products that contain brown rice syrup (BRS). This sweetener is often used in place of high fructose corn syrup – often in high end products (it is the second ingredient in my Kashi Dark Mocha Almond Chewy Granola Bars!) and introduce high concentrations of inorganic arsenic into the diet. Especially avoid “organic” toddler formula with BRS as this was found to have > 6 x the upper limit of arsenic allowable in drinking water.

e. Mom asks if cooking rice like pasta (excessive water) is effective at reducing arsenic content.

Rinsing rice before cooking has little effect but cooking in excessive water (6:1 to 10:1) and pouring off water reduces arsenic content by 45-60%.

f. What does the FDA and AAP recommend concerning feeding rice cereal to infants?

Iron fortified infant cereals are an important source of iron for toddlers. Iron fortified rice cereal should not be the sole cereal source for infants and should not be the first source. Other sources are oat, barley and multigrain.

5. You were recently asked by a family in the newborn nursery if it is OK for them to use scented baby lotions, powders and soaps on their newborn infant. Based on your knowledge of endocrine disruptors you suggest that the family avoid these products as well as avoid air fresheners, scented candles, scented trash bags and fresh smelling detergents. Your attending wants to know what the basis for this advice is! (pg 45 ref 1, and ref 2,3)

a. What broad class of compounds with endocrine-disrupting effects are frequently used in scented products?

Phthalates are a broad family of compounds used in more than 200 different processes and products. They are frequently added to lotions, soaps, shampoos, detergents, air fresheners and “plug-ins” etc to provide scent.

b. Where else can they be found?

They are also used widely as plasticizers in pliable plastic products such as cling wrap, tubing, blood bags etc, vinyl, added as inert ingredients to medications.

c. What are the two classes of these compounds?

There are two broad categories or classes of phthalates: low and high molecular weight.

d. What are the routes of exposure for these two classes of compounds?

Dermal absorption is the main route for exposure from low molecular weight phthalates (and inhalation) while oral/ingestion is the main route for high molecular weight phthalates. Given their high surface area to body weight ratio infants are particularly susceptible to high levels of dermal absorption.

e. Name several health outcomes thought to be associated with exposure to this class of EDC.

Several forms of phthalates are known to be anti-androgenic and to affect male fetal genital development. They are directly toxic to the testis, inhibiting testosterone production with resultant increased risk of hypospadias and cryptorchidism at birth. They also are associated with reduced sperm quantity and quality in men. They may also promote development of obesity through interaction with peroxisome proliferator-activated receptors and increase inflammatory burden through increased oxidative stress.

- f. How can you know what products contain this EDC?  
There is no labelling requirement so unfortunately you cannot know if products contain phthalates or not. Johnson and Johnson has removed scent from their baby products because of high dermal absorption and some other products claim to be phthalate free.
  - g. What can you do to minimize exposure?
    - i. Avoid scented products
    - ii. purchase products scented with natural essential oils (but watch out for lavender as it is an estrogenic EDC that can affect boys),
    - iii. store food in glass, ceramic, stainless steel instead of cling wrap.
    - iv. Never microwave food in cling wrap
6. Discuss some simple low cost, low tech, approaches to minimizing EDC exposures (ref 4 and others).
- a. In addition to strategies mentioned above avoid processed meats that are preserved with nitrates/nitrites (thyroid disruption),
  - b. use iodized salt to help counterbalance the effects of EDCs that target the sodium/iodine symporter– this may be particularly important during pregnancy when fetus depends on maternal thyroid hormone
  - c. Keep home well cleaned/vacuumed as many EDCs become part of dust which children can be exposed to by hand-oral route
7. **\*\*\*Wild Card\*\*\*** Choose an environmental toxic not covered in these articles that is of interest to you to report back to the group on (like a pesticide, lead etc.)