Early-life exposure to EDCs and children's health: inadvertent sources of exposure

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Endocrine disruption

What have we learned?

- Exposure to EDCs is ubiquitous and inadvertent.
- Exposure to multiple residues at low doses.
- Biological plausibility.
- Cocktail effects.
- Critical periods of life for EDC exposure: pregnancy, infancy, childhood, adolescence.
- The precautionary principle has not yet been translated into a systematic approach to EDCs and still focuses on a case by case approach.

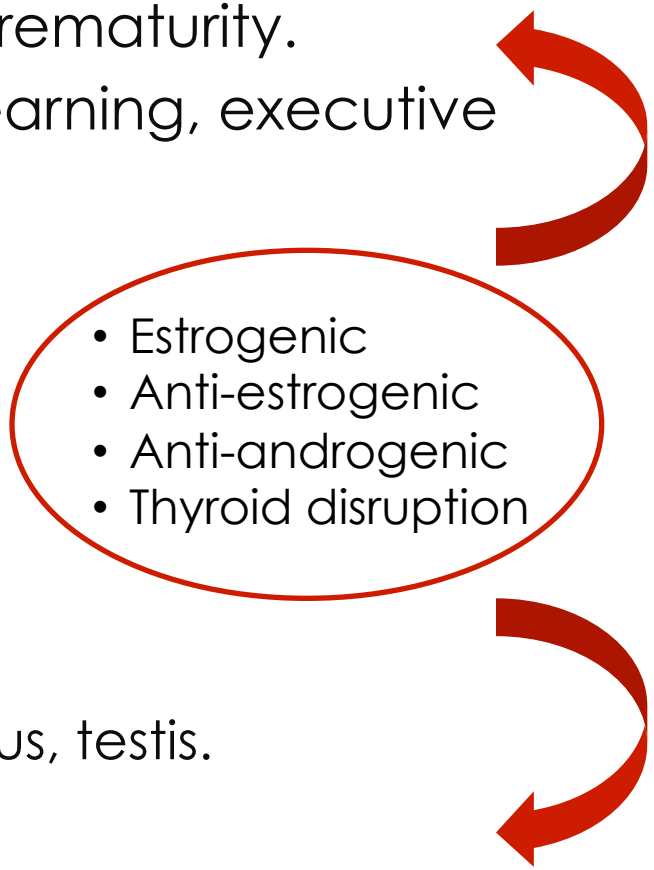
EDC: exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

Census of EDCs

Pesticides	Agriculture, domestic use, urban settings
PCBs	Industry, electrical transformers
Bisphenols (A, S, F)	Polycarbonate, epoxy resins
PFOS, PFOA	Non-stick coating, grease-resistant packaging
Phthalates	Plastics, antioxidants
Parabens	Cosmetics and creams
Triclosan	Antimicrobial compound
Benzophenones	UV filters
PBDEs, PBBs	Flame retardants
OP flame retardants	Flame retardants
Dioxins and furans	Combustion by-products
Alkylphenols	Industrial surfactants, detergents
Camphor, cinnamate	UV filters
Tributyltin	Biocide
Heavy metals: Cd, Hg	Smoking, food, industry

Effects of early-life exposure to EDCs

- Urogenital malformations: cryptorchidism, hypospadias
- Adverse pregnancy outcomes: LBW, prematurity.
- Cognitive and behavioral problems: learning, executive function, ADHD, autism,…
- Altered hormone levels
- Precocious puberty (girls)
- Cancer: leukemia, brain tumors
- Respiratory, allergic disorders (asthma)
- Metabolic disorders: obesity.
- Later in life….
  - Hormone-dependent cancer: breast, uterus, testis.
  - Poor sperm quality, infertility
  - Endometriosis, ovarian dysfunction
  - Diabetes (type 2), metabolic syndrome
  - CV and immune disorders
  - Hypothyroidism, hypovitaminosis D



Determination of bisphenol A and bisphenol S concentrations and assessment of estrogen- and anti-androgen-like activities in thermal paper receipts from Brazil, France, and Spain

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Inadvertent sources of exposure to EDCs: BPA and parabens

Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities

Carmen Freire[a,b,c], José-Manuel Molina-Molina[a,b,c], Luz M. Iribarne-Durán[a,d], Inmaculada Jiménez-Díaz[a], Fernando Vela-Soria[a], Vicente Mustieles[a,c,d], Juan Pedro Arrebola[a,e], Mariana F. Fernández[a,b,c,d], Francisco Artacho-Cordón[a,d,*], Nicolás Olea[a,b,c,d,f]

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Healthcare: NICUs

Exposure to EDCs in NICU infants

NICU infants are in intimate contact with many medical appliances and products made of **polycarbonate and/or PVC plastics**, in which residual non-polymerized BPA can remain after the polymerization process and may leach from the product.

Inadvertent exposure to EDCs (BPA, PBs, phthalates) *via* dermal, ingestion, inhalation, intravenous , and parenteral routes.

- ✓ Literature on exposure of NICU neonates to BPA/PBs:
  - **Calafat et al. (2009)** → higher urinary BPA and methyl-PB levels in NICU neonates with high (*vs.* low) intensity of use of medical device.
  - **Duty et al. (2013)** → higher urinary BPA levels in NICU neonates than in those from the general population.
- ✓ Daily BPA exposure of NICU infants has been estimated at **3000 ng/kg** bw (exposure for adult dialysis patients ~57 ng/kg bw)

Urgent research is needed on the composition and release of BPA and other EDCs from medical devices!! (Scenihr, 2015)

Presence of Bisphenol A and Parabens in a Neonatal Intensive Care Unit: An Exploratory Study of Potential Sources of Exposure

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- ✓ Assessment of BPA and parabens content in a wide array of medical products/devices.
- ✓ Assessment of (anti-)androgenic and (anti-)estrogenic activities.

NICU, Virgen de las Nieves University Hospital, Granada, Spain.

Justification

Bisphenol A (BPA):

- ✓ Used in the manufacturing of epoxy resins and polycarbonate plastics and as an additive in many other plastics, e.g. PVC .
- ✓ Estrogenic and anti-androgenic activity.
- ✓ Evidence of adverse health effects associated with early-life exposure:
  - Obesity
  - Asthma
  - Behavioral problems
  - Altered puberty timing
  - Changes in blood pressure
  - Altered serum hormones

Parabens (methy-, ethyl-, propyl-, butyl-paraben):

- ✓ Included in PCPs and pharmaceuticals as antimicrobial preservatives and as an additive in plastics for food packaging.
- ✓ Weak estrogenic activity.
- ✓ Evidence of adverse health effects associated with early-life exposure:
  - Adverse pregnancy outcomes
  - Reduced neonatal thyroid hormones
  - Altered puberty timing
  - Behavioral problems
  - Respiratory and allergic disorders

Methods

Analysis of **52 items** habitually used in the NICU:

- 25 plastic medical devices
- 18 textiles
- 9 semisolid/liquid products (ointments and nutritional supplements)

Main route of exposure:

- **Oral**: 8
- **Dermal**: 26
- **Intravenous and parenteral**: 14
- **Inhalation**: 4

✓ **BPA and PBs** analysis:

- Extraction: different methodologies according to the nature of the material.
- Liquid chromatography (UHPLC-MS/MS)

✓ **Hormone-like activity** assessment:

- E-Screen bioassay (E_2eq/g) – E_2 equivalents per gram.
- PALM luciferase assay (Proceq/g) – Procymidone equivalents per gram.

✓ When high BPA/PB content or estrogenic/anti-androgenic activity was detected in plastic components, the concentration of released BPA and PBs was studied under soft extraction conditions.

Items 1-19	Main route of exposure
Feeding syringe I	Oral
Feeding syringe II	Oral
Gastro-duodenal feeding tube	Oral
Extension tube for feeding syringe	Oral
Feeding sampling straw	Oral
Small dummy	Oral
Large dummy	Oral
Human milk fortifier	Oral
Pulse oximeter adhesive sensor I	Dermal
Pulse oximeter adhesive sensor II	Dermal
ECG electrode	Dermal
Light therapy protection glasses	Dermal
Occlusive skin wrap	Dermal
Sterile gloves	Dermal
Latex gloves	Dermal
Patterned transparent film dressing	Dermal
White hypoallergenic paper tape	Dermal
Textile tape	Dermal
Surgical tape	Dermal

Items 20-37	Main route of exposure
Self-adhesive dressing pad	Dermal
Wound dressing transparent with paper frame	Dermal
Transparent adhesive film dressing	Dermal
Hydrocolloid transparent dressing	Dermal
White cohesive bandage	Dermal
Infant flow LP headgear	Dermal
Sterile non-woven swabs	Dermal
Non-sterile non-woven swabs	Dermal
Absorbent bed underpad	Dermal
XS-sized diaper	Dermal
S-sized diaper	Dermal
Chlorhexidine	Dermal
Hand sanitizer	Dermal
Talcum and zinc oxide cream	Dermal
Proteolytic enzyme cream	Dermal
Winged IV catheter (transparent section)	IV/parenteral
Winged IV catheter	IV/parenteral
Single lumen umbilical vein catheter	IV/parenteral

Items 38-52	Main route of exposure
Double lumen umbilical vein catheter	IV/parenteral
Extension set for the IV infusion system	IV/parenteral
Extension set for the IV infusion system (light resistant)	IV/parenteral
Three-way stopcock	IV/parenteral
Disinfecting cap for needle-free connectors	IV/parenteral
Hypodermic injection needle	IV/parenteral
Syringe	IV/parenteral
Caffeine perfusion 20 mg/ml	IV/parenteral
Water for injection solvent for parenteral use	IV/parenteral
0,9% Sodium chloride solution for IV flush (syringe)	IV/parenteral
0,9% Sodium chloride solution for IV (ampoule)	IV/parenteral
Endotracheal tube	Respiratory
Closed suction system	Respiratory
Nasal cannula	Respiratory
Nasal prong	Respiratory

Results

- ✓ **3 out of 5** items contained **BPA**
- ✓ **4 out of 5** items contained **parabens**
- ✓ **27%** of items were **estrogenic**
- ✓ **10%** of items were **anti-androgenic**

All items with estrogenic activity contained detectable BPA

BPA content

>7000 ng/g

100 ng/g

- Three-way stopcock (clear section)
- Patterned transparent film dressing
- Gastro-duodenal feeding tube
- Sterile gloves
- Single-lumen umbilical catheter
- Intravenous infusion extension set

Hormone-like activity

- Small dummy nipple
- Three-way stopcock
- Patterned transparent film dressing

Parabens content

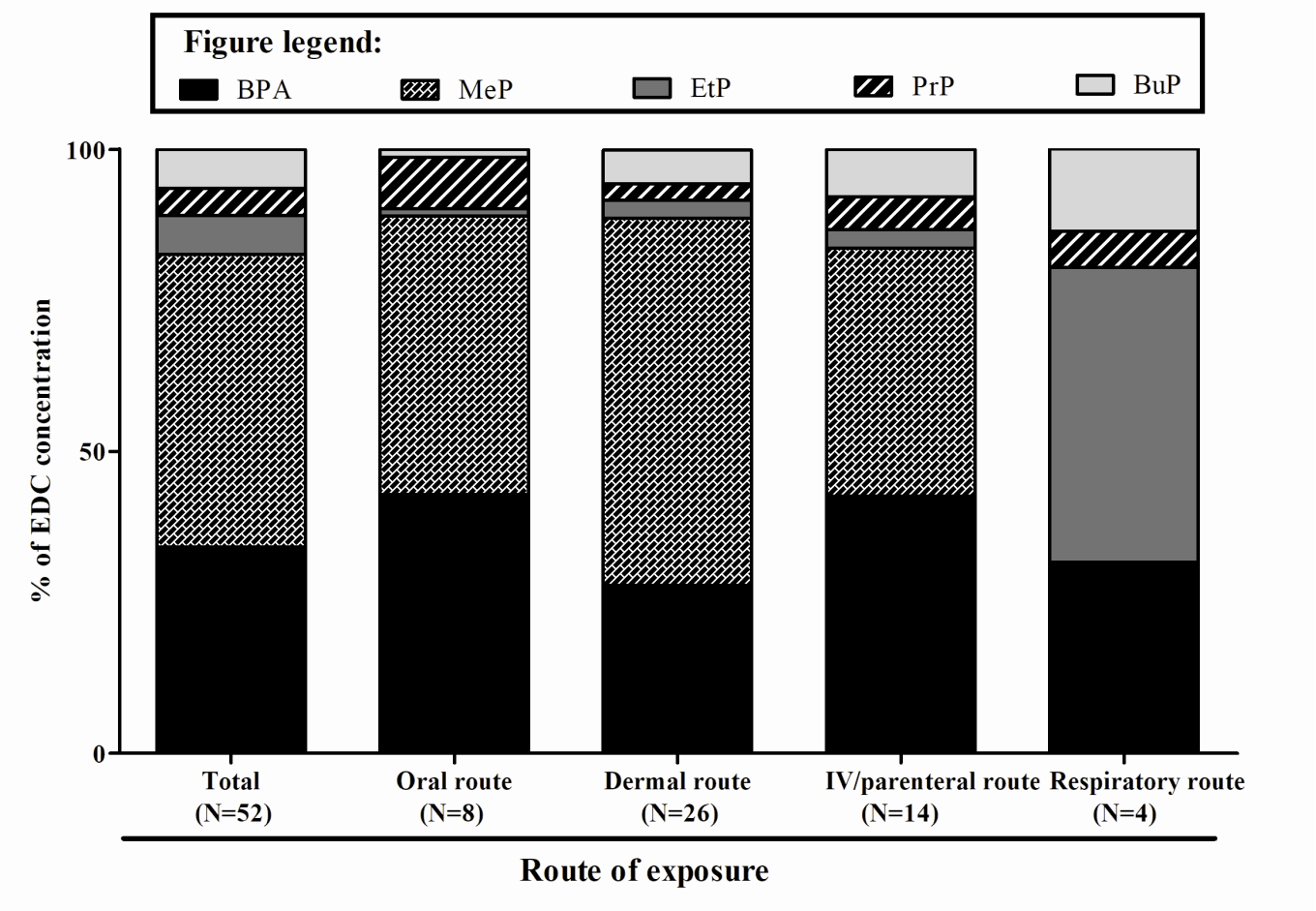
∑PBs
>100 ng/g

- Light therapy protection glasses
- Patterned transparent film dressing
- Winged intravenous catheter
- Intravenous infusion extension set
- Textile tape

Results

MePB 40-60%

BPA 30%



Mean relative concentration of each compound (%) according to exposure route

Results

Levels of EDCs according to main routes of exposure

ORAL

- BPA: 5/8 items, highest levels:

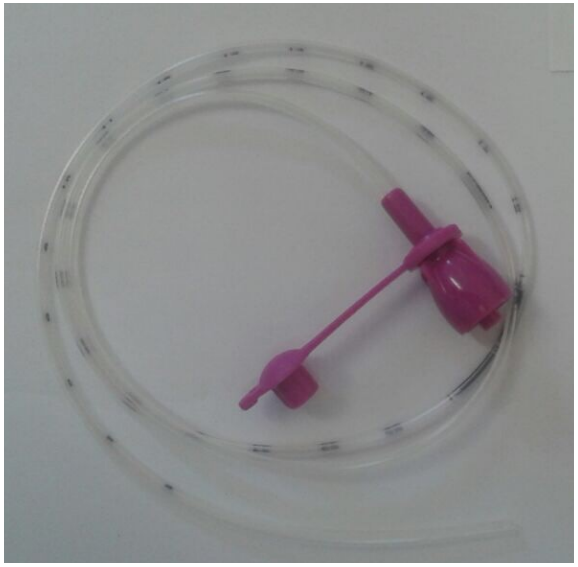
✓**Gastro-duodenal feeding tube** (301 ng/g)

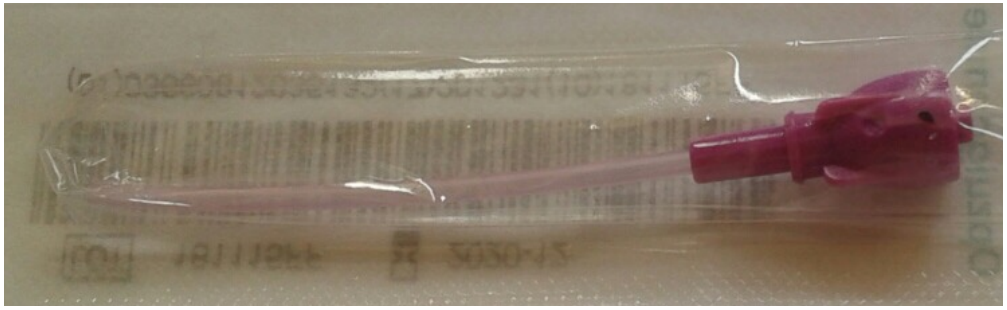
✓**Feeding sampling straw** (108 ng/g)

- Most frequently detected PB: MePB
- PBs: 5/8 items, highest levels (∑PBs):

✓**Small dummy nipple** (90.8 ng/g)

✓**Gastro-duodenal feeding tube** (73.8 ng/g)





Results

DERMAL

- BPA: 17/26 items, highest levels:
  - ✓ **Patterned transparent film dressing** (688 ng/g)
  - ✓ **Sterile gloves** (140 ng/g)
- Most frequently detected PBs: MePB and EtPB.
- PBs: 24/26 items, highest levels (MePB):
  - ✓ **Light therapy protection glasses** (481 ng/g)
  - ✓ **Patterned transparent film dressing** (208 ng/g)
  - ✓ **Textile tape** (108 ng/g)

Results

INTRAVENOUS AND PARENTERAL

- BPA: 7/14 items, highest levels:

✓**Three-way stopcock (clear section)** (7053 ng/g)

✓**Single-lumen umbilical vein catheter** (103 ng/g)

✓**IV infusion system extension set** (113 ng/g)

- Most frequently detected PBs: MePB and PrPB.
- PBs: 11/14 items, highest levels (∑PBs):

✓**Winged IV catheter** (149 ng/g)

✓**IV infusion system extension set** (126 ng/g)

Results

INHALATION

- BPA: 2/4 items:

✓**Endotracheal tube** (95.4 ng/g)

✓**Nasal prong** (33.9 ng/g)

- At least 2 PBs detected in each item, highest levels (∑PBs):

✓**Nasal cannula** (117 ng/g)

Conclusions

1) First report on the **presence of BPA and PBs** in materials in contact with newborns in NICUs, and first evidence that the contents of NICU materials exert **hormonal activities**.

2) Our findings indicate that:
   - Several NICU materials may act as potential sources of exposure to BPA and PBs for the **extremely vulnerable neonates** admitted to NICUs.
   - These newborns may be exposed to BPA and PBs *via* inhalation, oral, dermal, and intravenous/parenteral routes, with the possibility that other hospitalized infants may be similarly exposed.

3) NICU infants are a potential **high-risk population** following exposure to EDCs. There is an urgent need to:
   - Investigate the **potential short- and long-term implications** of our findings for the health of these highly vulnerable neonates.
   - **Eliminate or decrease** the use of **plastics** containing BPA and other EDCs in devices and feeding equipments in NICUs.

Thanks for your attention!

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