Children are a product of their environment

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Health Care Without Harm

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Overview

- Dioxins: lessons learned
- DEHP: concerns for the future

Hospitals: a source, but not the primary source, of exposure to toxics

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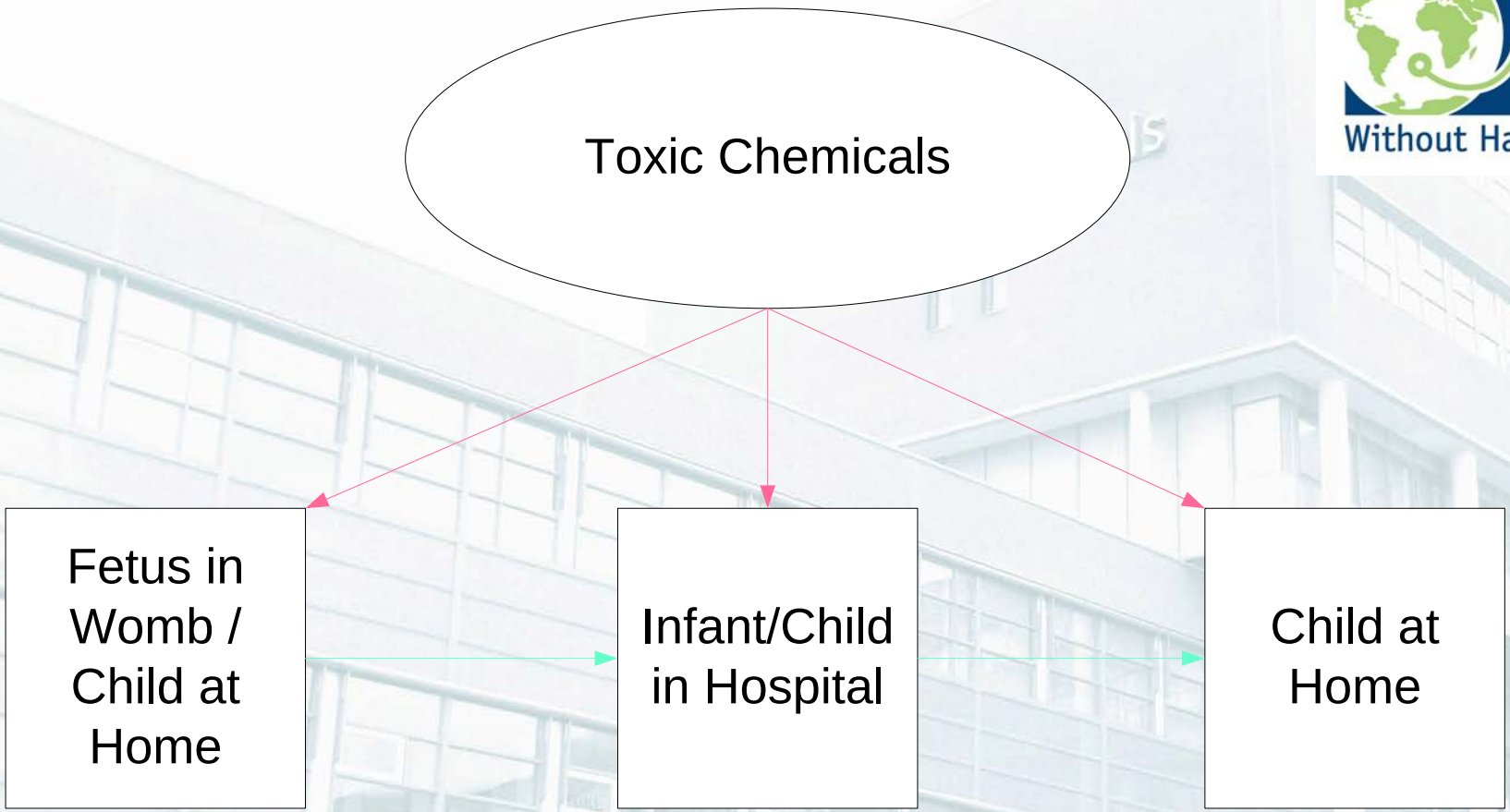

Sources of exposure to toxic chemicals in hospitals

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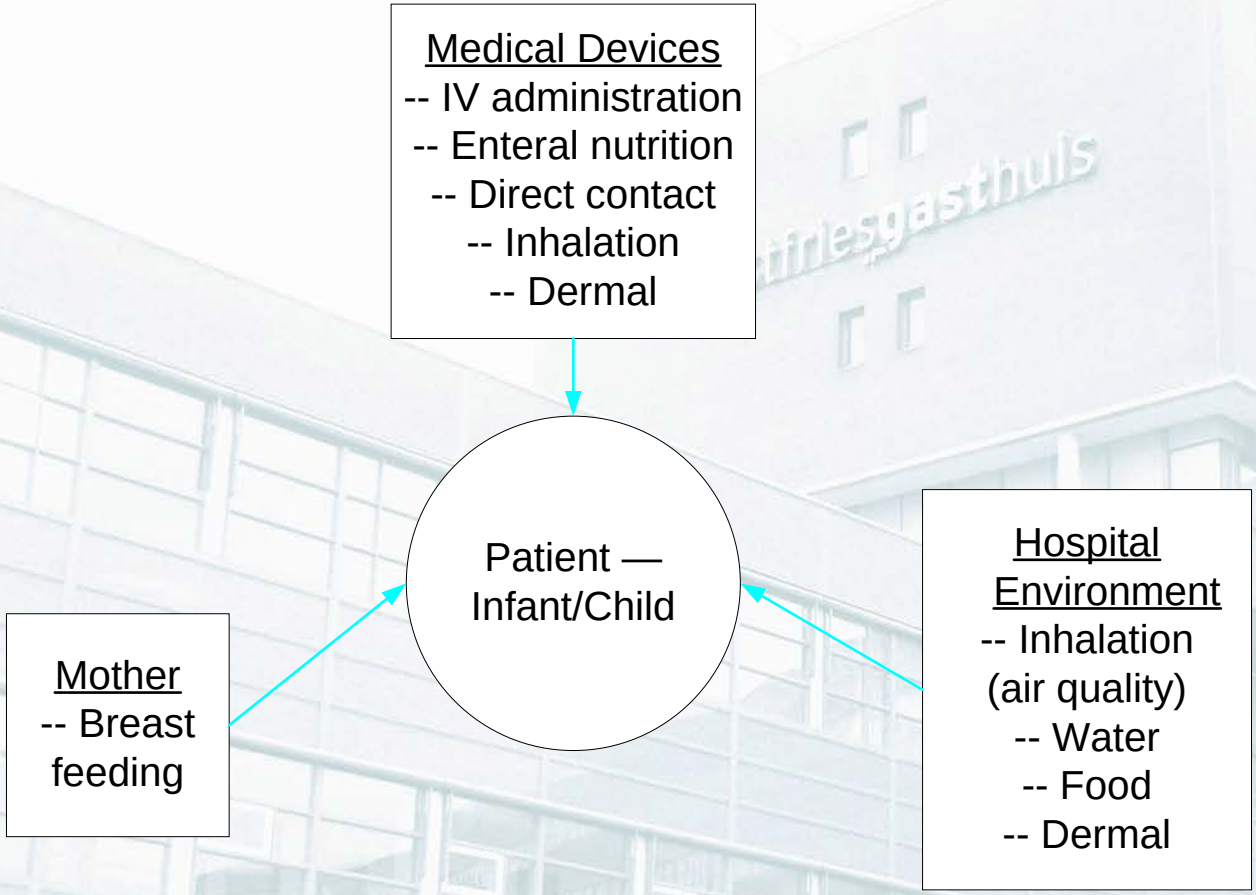

Most at risk

- Foetus, prematurely born, small for gestational age, seriously ill child
- Higher fat : water ratio but often less total body fat, long periods of exposure in hospital
- Often life-long accumulative exposure
- Organs (brain) still developing
- Less effective blood-brain and blood-testis barrier

Illustration dioxins & PCBs

- Prenatal exposure seems to have more health effects than postnatal
- Hydrophobic/lipophilic
- More daily intake per kilogram and more daily fat intake than adults
- Daily intake dioxins/PCBs about 25 times higher than adults

What are Dioxins and PCBs?

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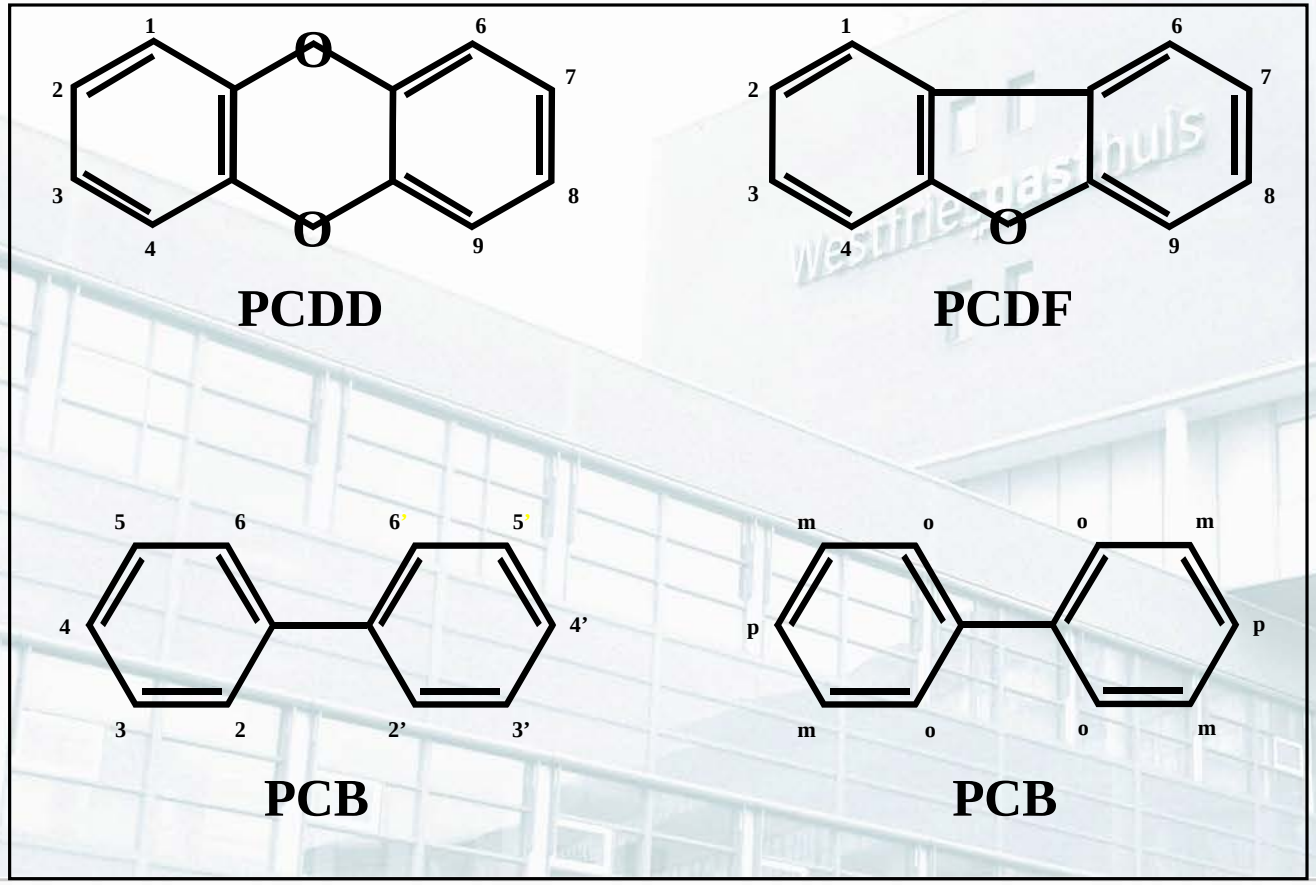
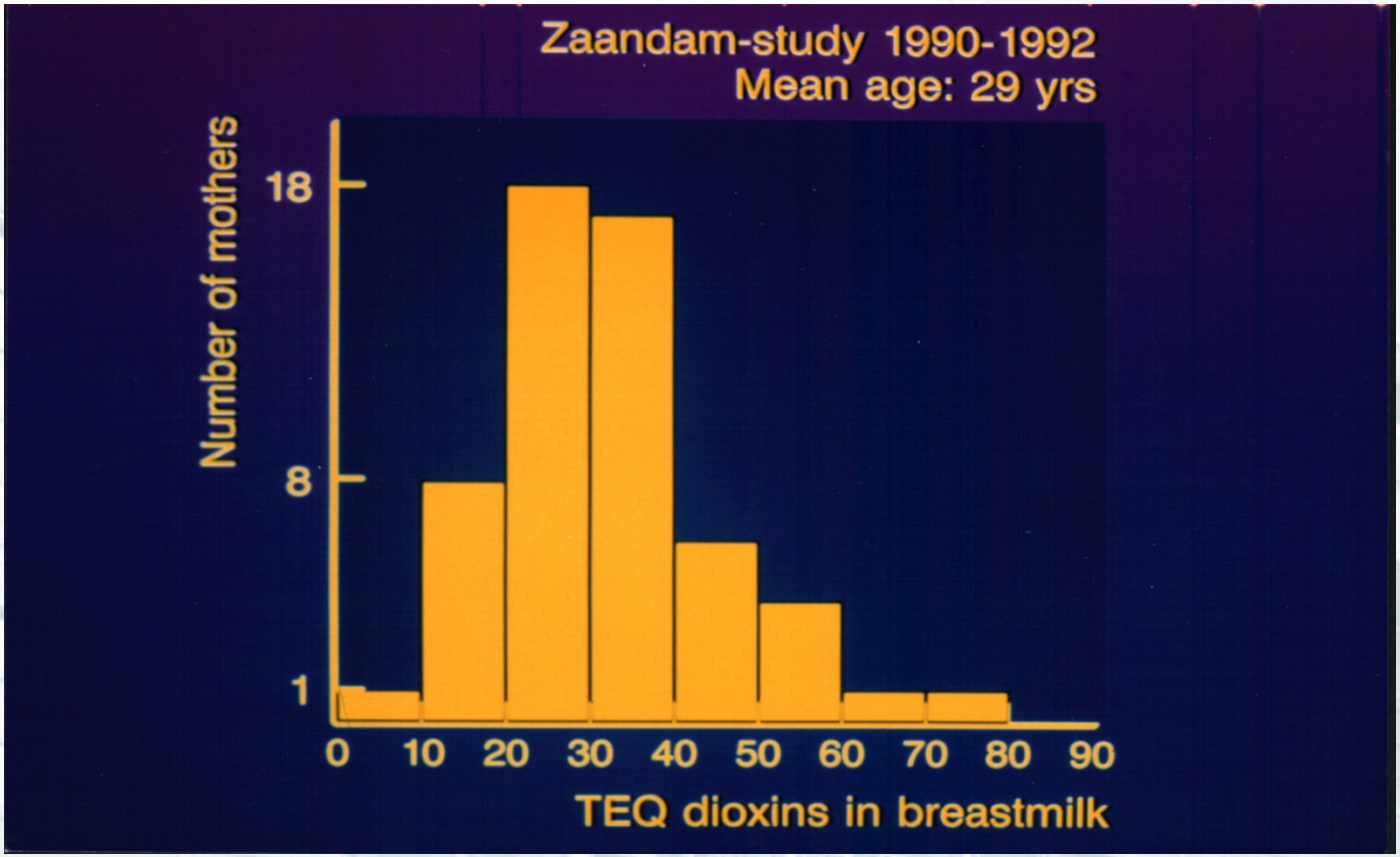


Dioxins

- Are of the most toxic substances known
- Colourless crystals or solids in pure form
- Not intentionally produced except for small quantities for research
- Extremely difficult to metabolise, thus accumulating, long half-life
- Stored in adipose tissue

- Exposure via placenta and breast milk
- Europe has high background exposure levels

Amsterdam/Zaandam Cohort



Birth Defects

- Increase in infant deaths and infant deaths with congenital disorders near solid waste incinerator
  - *Tango et al. J Epidemiol. 2004 May; 14(3): 83-93*
- Increase in hypospadias, phimosis, cryptorchidism, SGA, spontaneous abortions in polluted part of Russia
  - *Revich et al. Gig Sanit 2002; (1): 8-13*
- Increased miscarriages and premature birth; 60% congenital malformations after Agent Orange
  - *Le et al. Reprod Health Matters 2001; 9(18): 156-64*
- Increase in orofacial clefts
  - *ten Tusscher et al. Chemosphere 2000; 40: 1263-70*
- Other birth defects?

The Neonate

- Disregulation of thyroid function
  - *Pluim et al. Lancet 1992; 339: 1303, Environ Health Perspect 1993; 101(6): 504-8*
  - *Koopman-Esseboom et al. Pediatr Res 1994; 36(4): 468-73*
- Liver damage
  - *Pluim et al. Acta Paediatr 1994; 83(6): 583-7*
- Reduced platelet counts
  - *Pluim et al. Acta Paediatr 1994; 83(6): 583-7*
- Reduced numbers of granulocytes
  - *Pluim et al. Acta Paediatr 1994; 83(6): 583-7*
  - *Weisglas-Kuperus et al. Pediatric Res 1995; 38(3): 404-10*
  - *Nagayama et al. Chemosphere 1998; 37(9-12): 1781-7*

Toddlers and Pre-school-ers

- Precocious neuromotor development
  - *Ilsen et al. Chemosphere 1996; 33(7): 1317-26*
- Chickenpox at a younger age
  - *Weisglas-Kuperus et al. Environ Health Perspect 2000; 108(12): 1203-7*
- More middle-ear infections
  - *Weisglas-Kuperus et al. Environ Health Perspect 2000; 108(12): 1203-7*
- Less asthma
  - *Weisglas-Kuperus et al. Environ Health Perspect 2000; 108(12): 1203-7*

School Children

- More dental defects (caries and enamel)
  - *Alaluusua et al. Eur J Oral Sci 1996; 104(5-6): 493-7*

Decreased lung function associated with perinatal exposure to Dutch background levels of dioxins

Acta Paediatrica 90(11): 1292 - 1298

ten Tusscher, et al.

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Lung Function Assessment

41 healthy children (7–12 y, mean 8.2 y)

Prenatal exposure: 8.74 - 88.8 (mean 34.6) ng TEQ dioxin/kg fat, measured in breast milk

Postnatal exposure: 4.34 - 384.51 (mean 75.4) ng TEQ dioxin

Medical history of the children and their families

Spirometry

Lung Function Results

- Decreasing lung function with increasing prenatal exposure (p=0.045)
- Decreasing lung function with increasing postnatal exposure (p=0.0002)
- Increase in asthmatic complaints with increasing exposure (n=4)

Persistent Hematologic and Immunologic Disturbances in 8-Year-Old Dutch Children Associated with Perinatal Dioxin Exposure

Environmental Health Perspectives 111 (12): 1519-1523

ten Tusscher, et al.

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Immune System Effects

Reduction in allergy with increasing prenatal ($p=0.023$) and postnatal ($p=0.030$) exposure

Increasing $CD4^+$ (T-helper) cells with increasing postnatal exposure ($p=0.006$)

Immune System Effects

- Increase in autoimmune disease in rodents – humans?
  - *Holladay. Env Health Perspect 1999; 107(5): 687-91*
- Allergic disease aggravation by enhancing IgE-response
  - *Kimata. Int J Hyg Environ Health 2003; 206(6): 601-4*

Haematology

- Decreasing numbers of blood platelets with increasing postnatal exposure (p=0.04)
- Platelet production problem
- Stem cell damage?

Behavioural Problems

- Increase in social problems & aggression in two environments (home and school) with dioxins
  - *ten Tusscher et al. Thesis 2002*
- In boys less masculine play, in girls more masculine play, with increasing prenatal PCBs
  - *Vreugdenhil et al. Env Health Perspect 2002; 110(10): A593-8*

Brain Development

- Ultra modern and sensitive testing (MEG)
- Retardation in brain development of on average 3½ y
- Possible relation with behavioural problems

Adolescence and adulthood

- Increased incidence of non-Hodgkin lymphoma (RR 2.3) in vicinity of municipal solid waste incinerator
  - *Floret et al. Epidemiology 2003; 14(4): 392-8*
- Delay in genital and breast development in boys and girls with dioxins
  - *Den Hond et al. Health Perspect 2002; 110: 771-6*
  - *Leijs et al. Chemosphere 2008; 37(6): 999-1004*
- Possibly increase in endometriosis with dioxins
  - *De Felip et al. Toxicol Lett 2004: 150(2): 203-9*
  - *Leijs et al. Ph.D. thesis 2010*
- Adolescent colorectal cancer and dioxin?
  - *Pratt et al. Lancet 1987; 2(8562): 803*
- Increase in serum glucose and glucose: insulin ratio with dioxins (also prenatally)
  - *Leijs et al. Ph.D. thesis 2010*

Summary dioxin and PCB effects

- Birth defects
- Hormone disruption
- Decreased lung function
- Reduced production blood platelets
- Immunity interference
- Increased cancer risk
- Linked to diabetes
- Influence on the thyroid
- Liver damage
- Dental problems
- Behavioural problems
- Retardation sexual development
- Retardation in brain development

DEHP

- Softeners in plastic (PVC)
- Known for 30 years that it leaks out of medical devices
- Shown to leak from:
  - nasogastric tubes, respiratory tubes, endotracheal tubes, umbilical catheters, PVC blood bags, transfusion tubing systems, haemodialysis systems, cardiopulmonary bypass, continuous peritoneal dialysis, ECMO, infusion tubing
- Suspected of teratogenicity and endocrine disruption

DEHP and children

- highly lipophilic (over placenta, in breast milk)
- pancreatic lipase most important detoxifier
- much lower levels of pancreatic lipase in neonates
- greater absorption in children
- vulnerable developmental windows

NICU exposure to DEHP

- 6 premature infants expected to have i.v. infusion for > 2 weeks included
- 7 urine samples per infant
- DEHP metabolites (mEHHP, mEOHP, mEHP) measured by CDC

- 41 samples (1 sample no urine extractable)
- 33 samples positive for all 3 metabolites

Cohort

Results

Discussion

- geometric mean mEHP (100 ng/mL) prems
  - significantly higher than 19 toddlers 12 – 18 months (4.6 ng/mL)
  - 26 fold higher than US median for children 6 – 11 yrs
- mEHHP and mEOHP 1-2 order of magnitude higher than US population (62 adults and children)
- no correlation with specific procedure, GA, birth weight

In utero exposure vs gestational age

- Cord blood samples obtained in 84 consecutive newborns (82 singletons, 2 twins)
- General practice hospital
- 39 males, 45 females
- 11 preterm, 3 VSGA, 4 SGA
- No in vitro fertilisation
- Sampling with glass devices

Results

- Logistic regression:
  - Significant inverse relation mEHP & GA at birth (38.16 ± 2.34 vs 39.35 ± 1.35 wks)
  - OR 1.5 (CI 1.013-2.21) presence/absence mEHP

Exchange transfusion

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Transfusion. 1993 Jul;33(7):598-605.

Exposure of newborn infants to di-(2-ethylhexyl)-phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters.

Plonait SL, Nau H, Maier RF, Wittfoht W, Obladen M.

Department of Neonatology, Klinikum Rudolf Virchow, Free University of Berlin, Germany.

Abstract

Infants in the neonatal intensive care unit are regularly exposed to the plasticizer di-(2-ethylhexyl)-phthalate (DEHP) following exchange transfusion or extracorporeal membrane oxygenation. Whether such exposure leads to increased morbidity is not known, although elevated levels of DEHP have been associated with necrotizing enterocolitis and cholestasis. The hypothesis that infants undergoing exchange transfusion are exposed to toxic levels of DEHP and the presumed metabolite 2-ethylhexanoic acid (EHXA) was tested by measuring serum levels of DEHP in 16 newborn infants (gas -liquid-chromatography) and urine concentrations of EHXA in 6 of these infants (gas chromatography-mass spectrometry). DEHP levels were undetectable (< 1 microgram/mL) before exchange but ranged from 6.1 to 21.6 micrograms per mL of serum (average, 12.5 +/- 6.2 micrograms/mL) after a single exchange transfusion. DEHP uptake did not result in cholestasis. EHXA peak levels were 127 to 416 ng per mL of urine, with a median of 174 ng per mL. Concentrations of EHXA were lower than anticipated, which indicates that EHXA is not a major metabolite in the neonatal infant.

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Urinary di-(2-ethylhexyl)phthalate metabolites in athletes as screening measure for illicit blood doping: a comparison study with patients receiving blood transfusion

Núria Monfort, Rosa Ventura,* Ana Latorre, Viviana Belalcazar, Mercè López, and Jordi Segura*

Volume 50, January 2010 TRANSFUSION 145

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CONCLUSION: Elevated concentrations of urinary DEHP metabolites represent increased exposure to DEHP. High concentrations of DEHP metabolites present in urine collected from athletes may suggest illegal blood transfusion and can be used as a qualitative screening measure for blood doping.

DEHP as doping marker

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TABLE 1. Distribution of concentrations of DEHP metabolites among different population groups

Group	Number	Metabolite	Concentrations (ng/mL) Percentile 10th	25th	50th	75th	90th	Maximum
Control	30	MEHP	4.6	8.7	11.7	20.1	27.1	47.7
		MEHHP	9.3	12.8	27.7	47.8	64.6	90.9
		MEOHP	8.9	14.2	34.7	43.1	75.8	105.3
Transfused patients (0-24 hr)	24	MEHP	21.6	51.8	202.9	387.7	620.3	3535.5
		MEHHP	45.6	93.7	236.6	572.5	896.4	5174.1
		MEOHP	39.6	98.1	226.5	393.0	951.9	2362.2
Transfused patients (24-48 hr)	25	MEHP	8.2	34.3	200.9	274.2	536.3	628.7
		MEHHP	16.1	26.6	101.1	318.6	763.3	1972.4
		MEOHP	8.0	26.9	74.1	178.9	452.2	1002.4
Nontransfused patients (0-24 hr)	39	MEHP	2.7	4.6	13.4	26.1	50.6	255.6
		MEHHP	4.7	10.5	21.0	52.2	66.0	289.8
		MEOHP	4.4	15.9	26.8	55.9	71.1	430.7
Nontransfused patients (24-48 hr)	37	MEHP	5.6	13.8	19.1	32.4	46.8	129.5
		MEHHP	9.9	18.2	41.6	64.0	114.8	199.3
		MEOHP	13.8	26.2	69.9	92.0	179.1	331.8

Bits and pieces

- Endotracheal tubes show 6 – 12 % loss of DEHP during use → most probably into the lungs
- Priming of ECMO circuits with saline increased circuit degradation
- DEHP found in lung tissue in preterms after mechanical ventilation

DEHP

- “normal” daily exposure 3-30 mcg/kg BW/day
- NICU enteral nutrition 40-140 mcg/kg BW/day
- NICU parental nutrition up to 2500 mcg/kg BW/day !!
- Total daily intake in all children (< 19 yrs) > adults

Bear in mind

- DEHP toxicity shown in animal studies (long term toxicity & tissue deposition)
- DEHP exposure is life-long, ubiquitous environmental contaminant
- No longer in toys for children < 3 yrs (EU 1999/815/EG)
- US FDA consider NICU patients at particular risk

American Medical Association

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H-135.945 Encouraging Alternatives to PVC/DEHP Products in Healthcare

AMA: (1) encourages hospitals and physicians to reduce and phase out polyvinyl chloride (PVC) medical device products, especially those containing Di(2-ethylhexyl)phthalate (DEHP), and urge adoption of safe, cost-effective, alternative products where available; and (2) urges expanded manufacturer development of safe, cost-effective alternative products to PVC medical device products, especially those containing DEHP. (BOT Action in response to referred for decision Res. 502, A-06)

Summarising

- Clear indications of DEHP exposure from medical devices
- Animal studies show negative health effects
- Exposure scenario in plastic laden environment
- Increased exposure in infants

Precautionary Principle

- Safer alternatives for almost all products
- We need to actively choose better alternatives
- Choose PVC-free/DEHP-free
- “When in doubt, throw it out”

Concluding

- Our children are already being exposed to chemicals in concentrations that are too high
- POPs remain in our bodies for many years
- It is not wise to risk the health and development of our children

Take home message

- Let us learn from our mistakes and implement these lessons with other chemicals, especially when treating our patients
- **First do no harm !!!**
- Thank you for your attention!