# Emerging Pollutants: From source to health effects to policy


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# Preamble

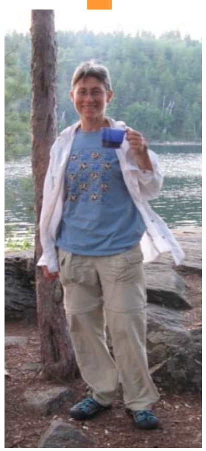
- Extremely high production volume (HPV) chemicals (> 1 million tonnes/year) are inevitably in us
- Some are known to disrupt endocrine function at low exposures
- Are population-wide exposures putting some/all at risk?

# Per Capita Material Flows

Tons/capita/year

Airborne waste
5.1

Input goods
6



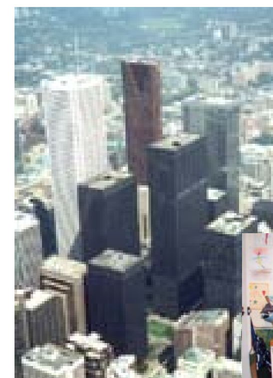
Liquid waste
0.8

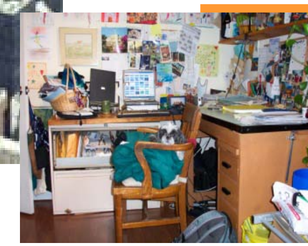
Stock ~0

Solid waste
0.1

Airborne waste
19

Input goods
89





Sewage
61

Stock 266

Solid waste
3

Brunner & Rechberger 2001

# Consumption Trends

MATOS & WAGNER

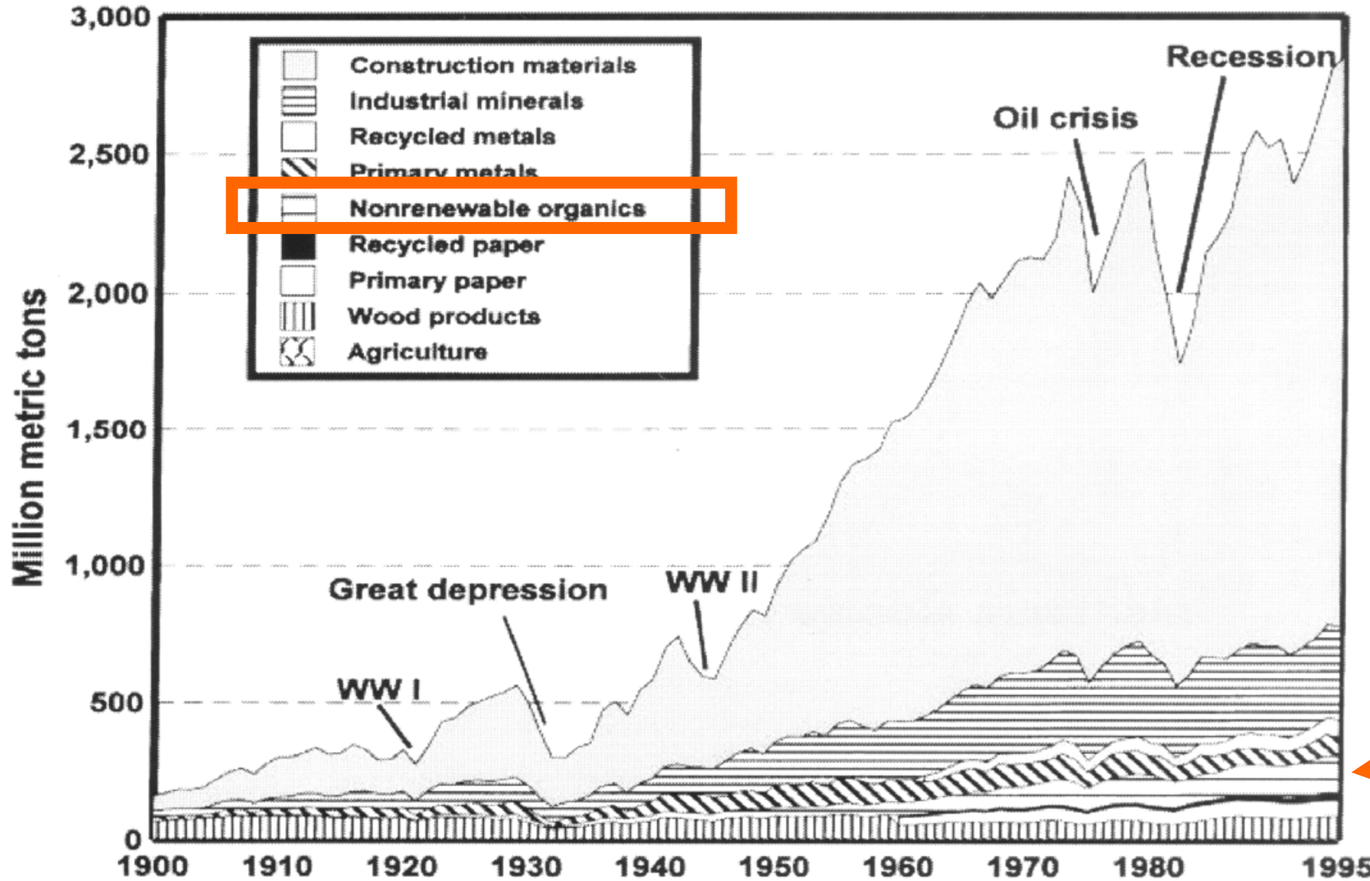



*Figure 1* Measurement of the amount of raw materials consumed in the United States. WWI, World War I; WWII, World War II (5).

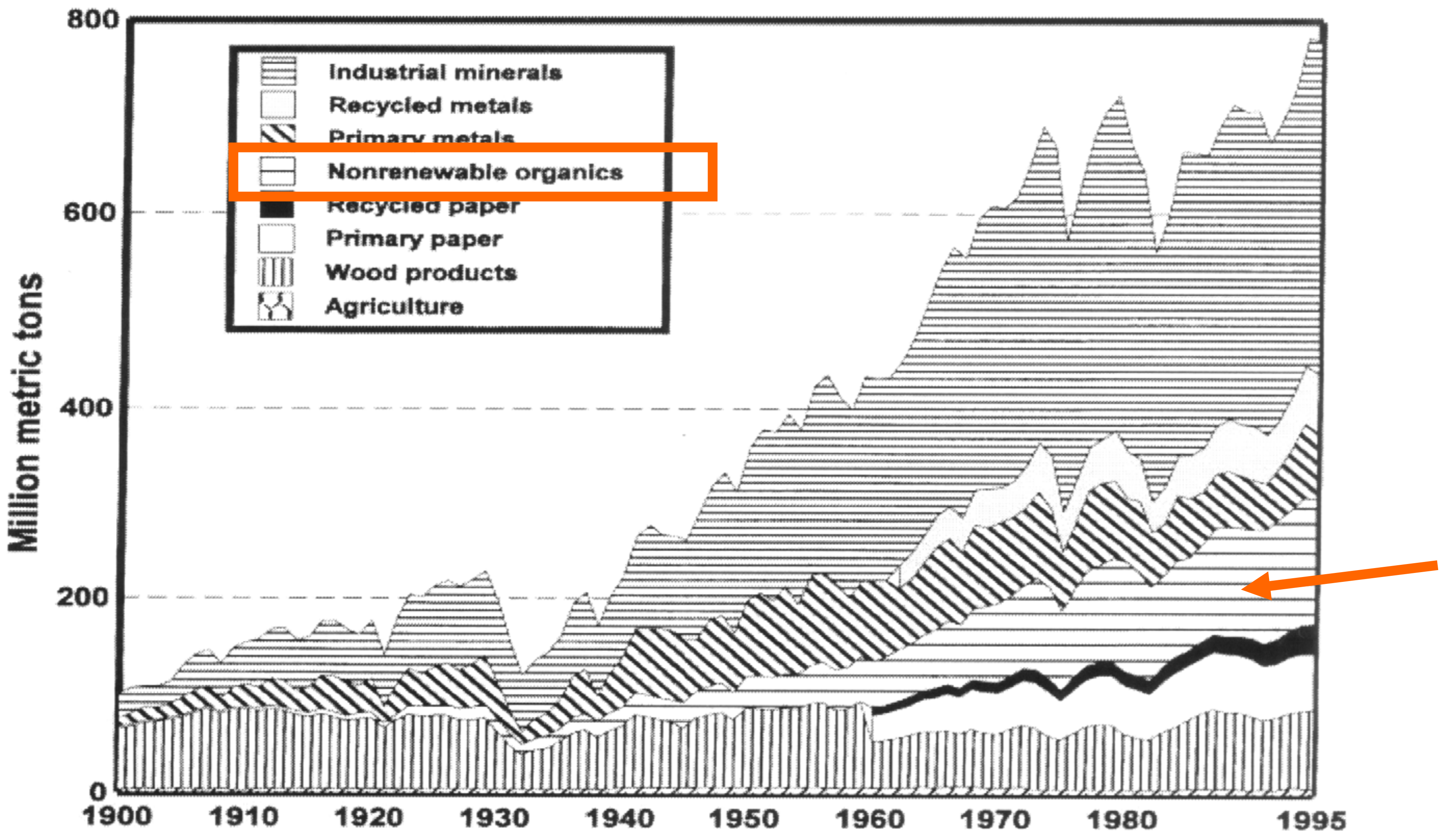



*Figure 3* Measurement of the amount of raw materials (excluding crushed stone and construction sand and gravel) consumed in the United States.



Matos & Wagner. 1998. Ammu. Rev. Energy Environ. 23:107-122.

# Growth in Chemical Production

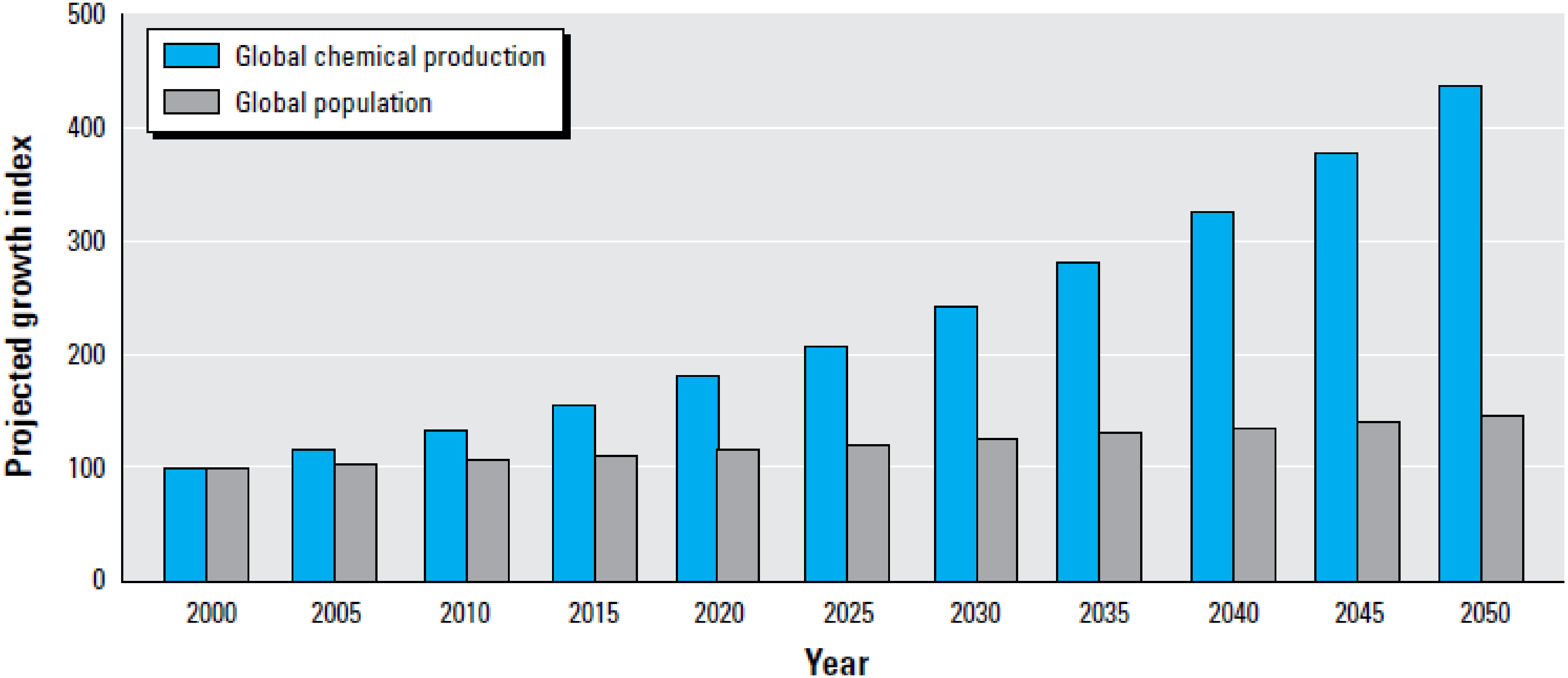
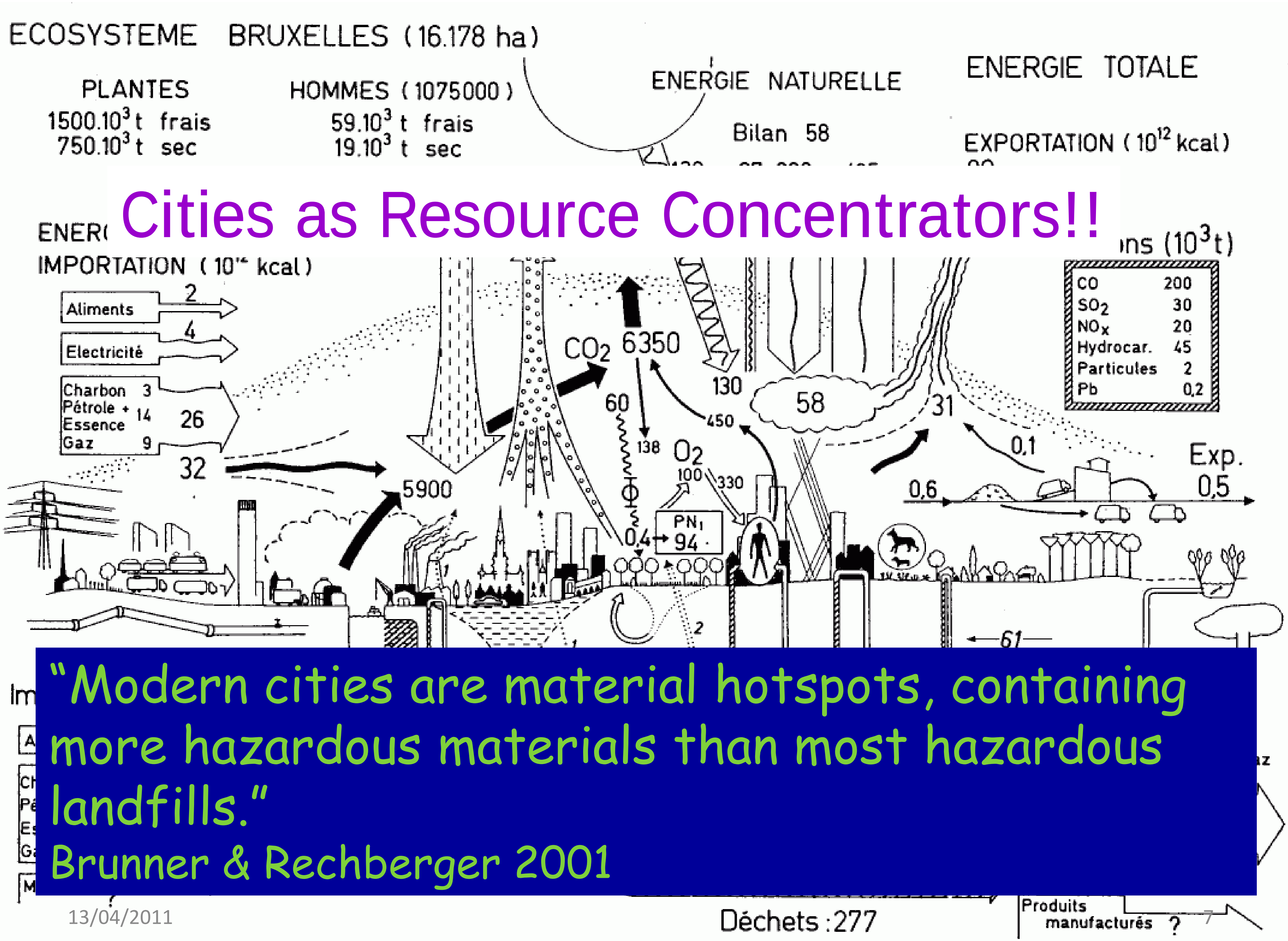



**Figure 2.** Global chemical production is projected to grow at a rate of 3% per year, rapidly outpacing the rate of global population growth, estimated at 0.77% per year. On this trajectory, chemical production will double by 2024, indexed to 2000 (American Chemistry Council 2003; OECD 2001; United Nations 2004).

Wilson & Scharzman 2009, Environ Health Perspectives

# Cities as Resource Concentrators!!

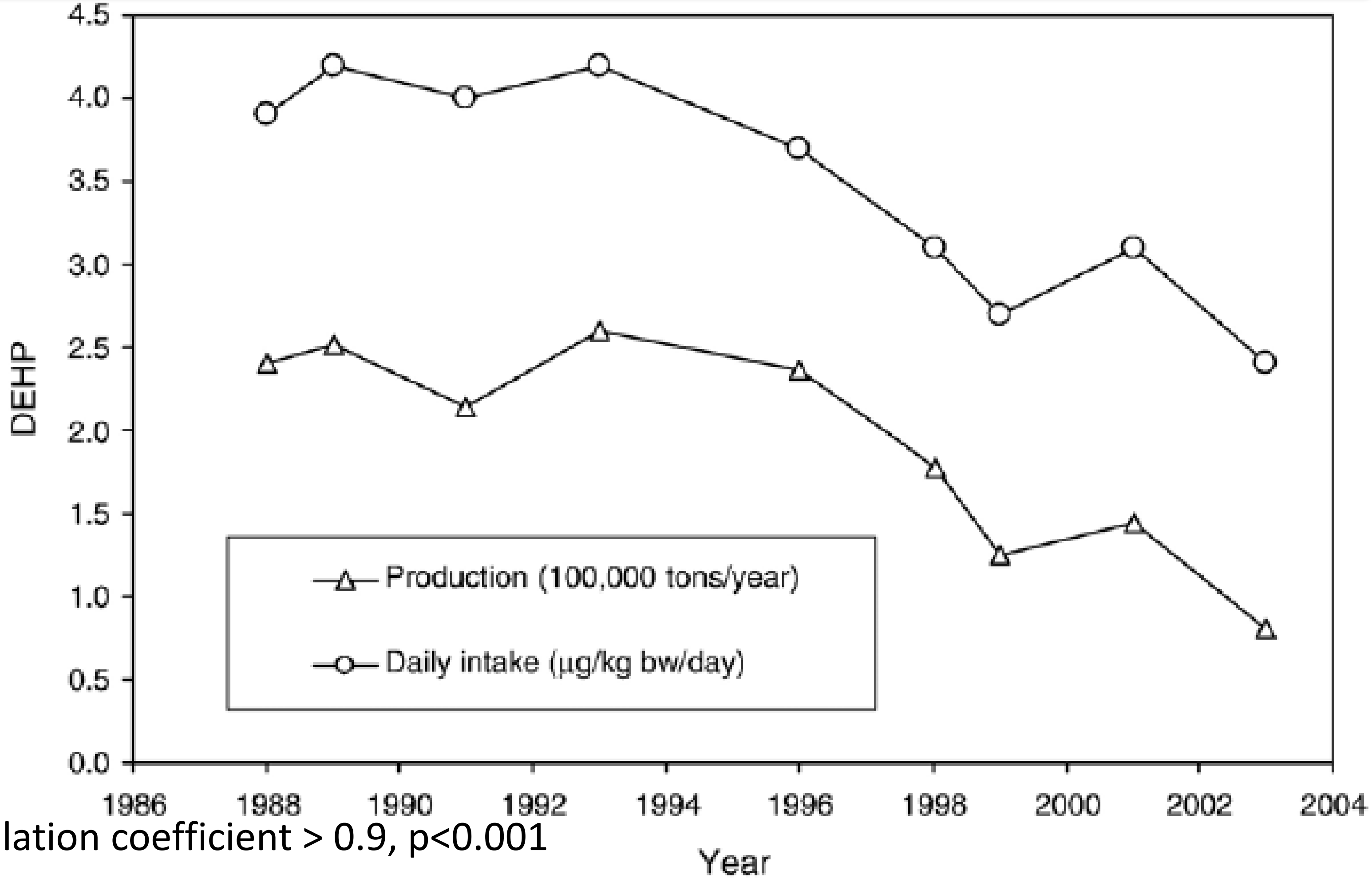



“Modern cities are material hotspots, containing more hazardous materials than most hazardous landfills.”

Brunner & Rechberger 2001

| Chemical | Production (g/c.d) | Rate % | Exp to Prod Ratio, ppm |
|---|---|---|---|
| BPA | 9.13<br>US | 6-10%/y | 0.23 (adult) |
| DEHP | 6.54<br>Germany | ~1000X<br>‘77-’88 | 46 (adult) |
| PBDEs | 0.07<br>North America | 33% (’91-’99) | 2 (adult)<br>28 (infant) |
| PCBs | 0.06<br>Canada | 57% (‘60-’64 vs ‘65-’69) | 3 (adult) |

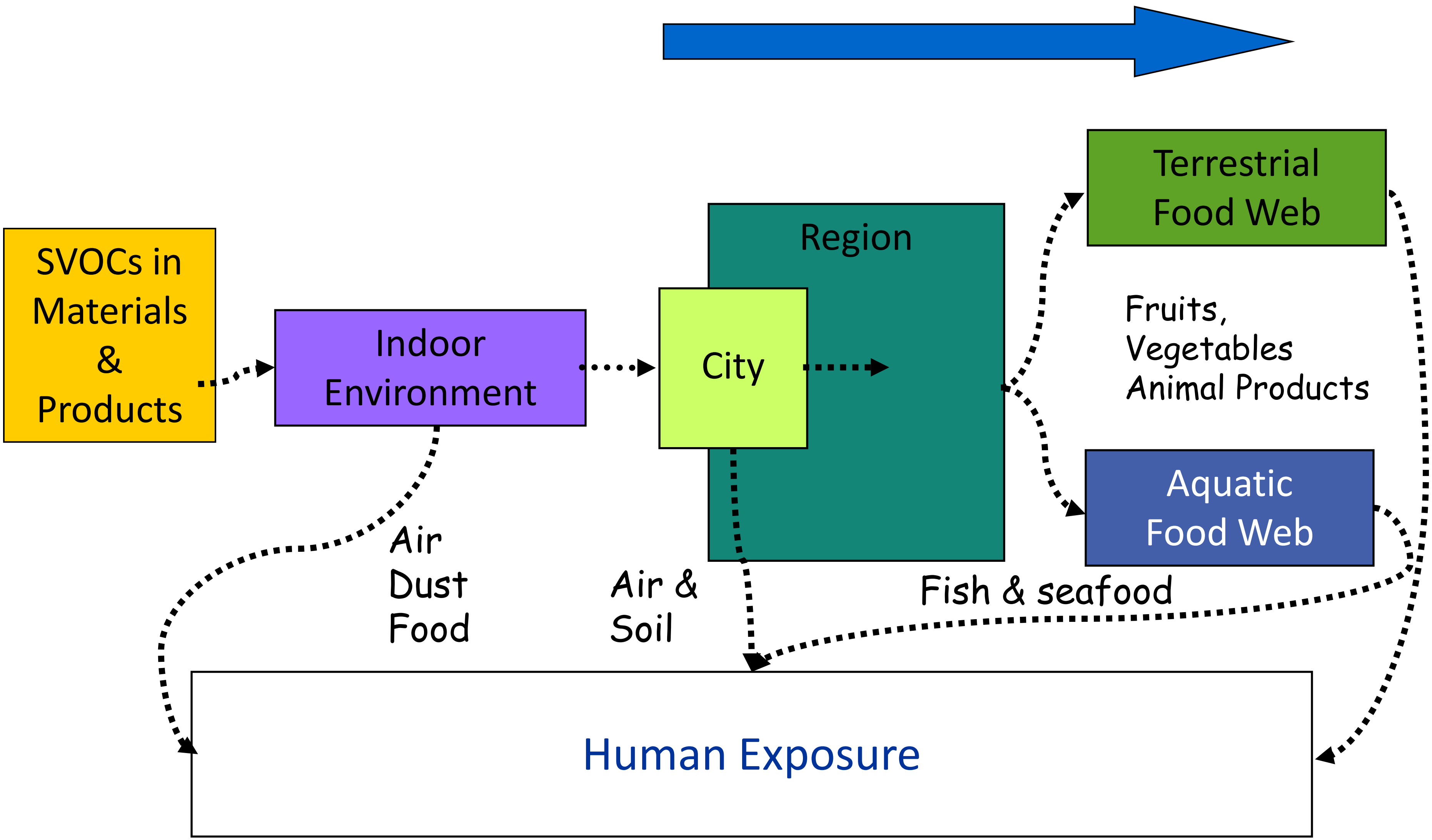
# Population Scale Correlation between Intake and Production



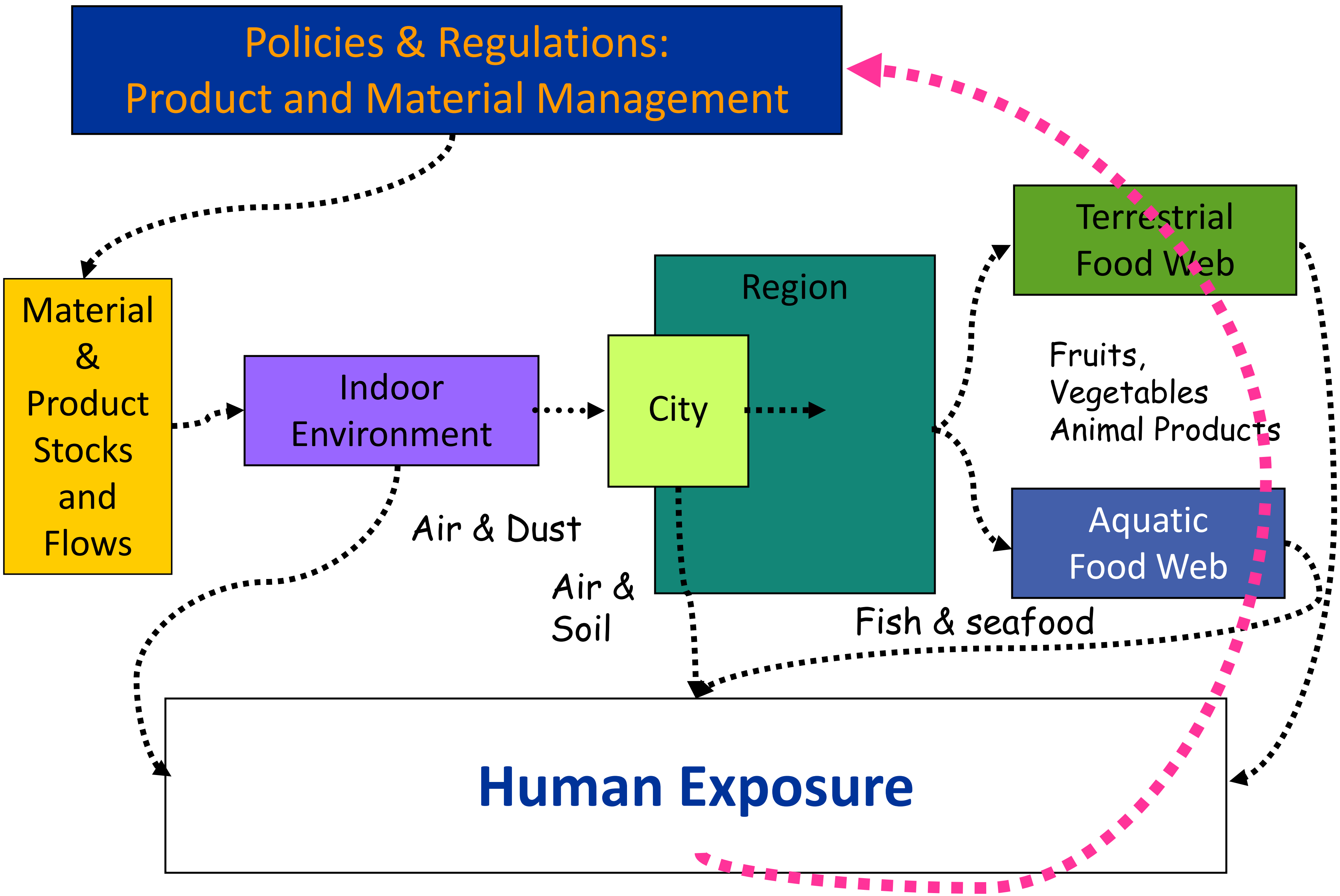

Correlation coefficient > 0.9, p<0.001

Helm D.2007 Correlation between production amounts of DEHP and daily intake. Sci Total Environ 388:398-391.

# If Persistent & not metabolised

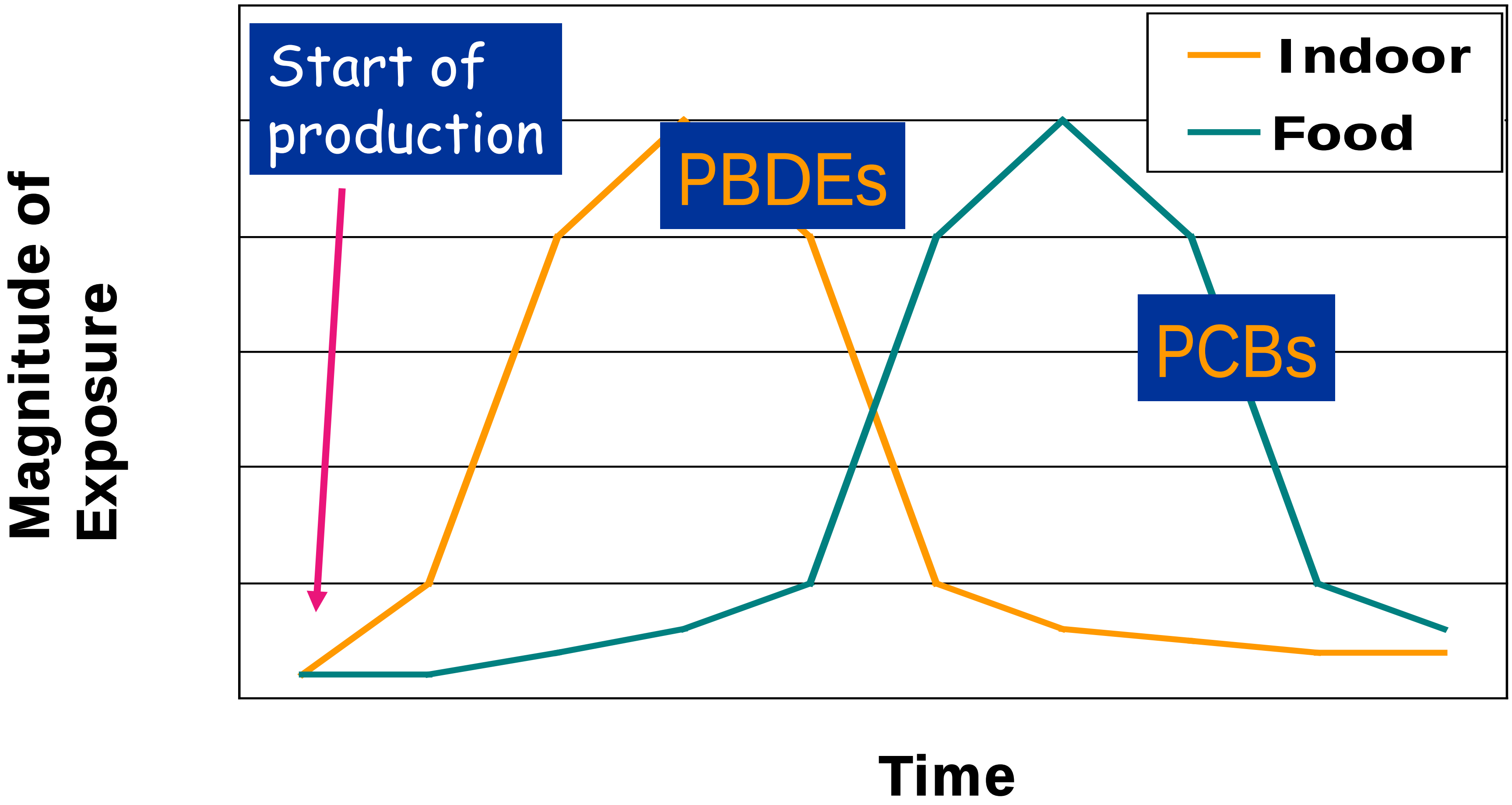



Diamond & Harrad. 2009. The chemicals that will not go away: implications for human exposure to reservoirs of POPs. *Persistent Organic Pollutants: Current Issues and Future Challenges*. S.J. Harrad Chichester, UK, Wiley.

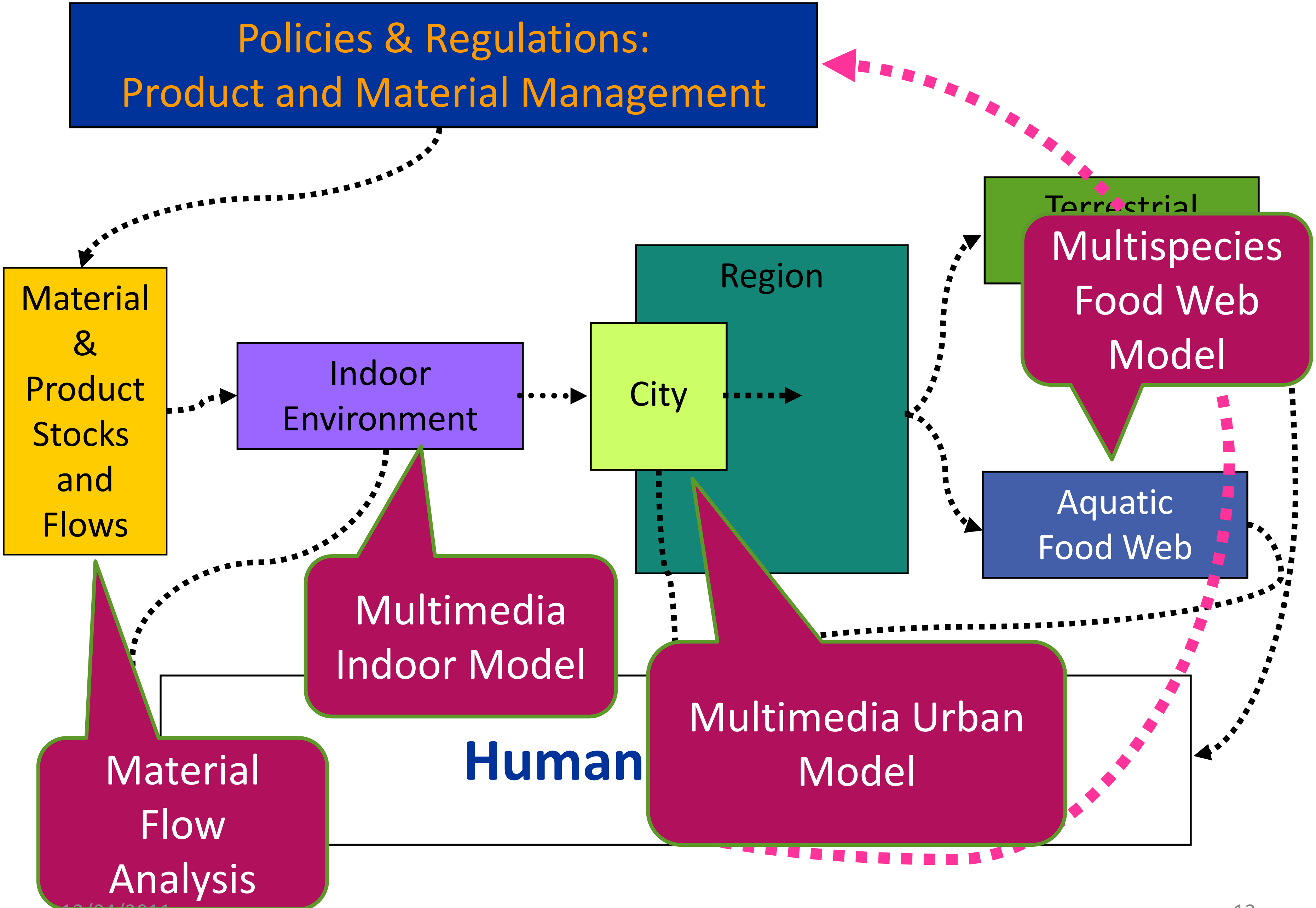



Diamond & Harrad. 2009. The chemicals that will not go away: implications for human exposure to reservoirs of POPs. *Persistent Organic Pollutants: Current Issues and Future Challenges*. S.J. Harrad Chichester, UK, Wiley.

# Contaminant Exposure




Harrad & Diamond 2006 *Atmos Environ* 40:1187-1188


Policies & Regulations:
Product and Material Management
Material & Product Stocks and Flows
Indoor Environment
City
Region
Terrestrial
Multispecies Food Web Model
Aquatic Food Web
Multimedia Indoor Model
Multimedia Urban Model
Human
Material Flow Analysis

# Source ⇨ Emission ⇨ Fate ⇨ Exposure ⇨ Toxicity⇨ Policy

1. Phthalates
    - Exposure
    - Toxicity
2. Polybrominated diphenyl ethers (PBDEs) & Polychlorinated biphenyls
    - Material Flow Analysis (MFA)
    - Indoor Environment
    - Urban Environment
3. PBDEs & Bisphenol A
    - Food web transfer
    - Policy

# Plastics

- Manufactured as a material that could be molded to different shapes
- Earliest mass produced plastic was Bakelite
  - Very hard, durable plastic
  - Black (could not take pigment)

http://cgi.ebay.ca/VINTAGE-GYPSY-JAZZ-GUITAR-PICK-CATALIN-BAKELITE_W0QQitemZ310209646065QQcmdZViewItemQQptZGuitar_Accessories?hash=item4839ef8df1

http://www.google.ca/imgres?imgurl=http://blog.blacknight.ie/images/black-phone.jpg&imgrefurl=http://blog.blacknight.com/updated-telephone-numbers.html&h=282&w=425&sz=90&tbnid=cNcr9CZrLrRS_M:&tbnh=84&tbnw=126&prev=/images%3Fq%3Dblack%2Btelephone&usg=__CfwZ0xqRE6Kpkn34FYk5fDLgT1Y=&ei=4gyyS7LPN8P58Aa845HJAQ&sa=X&oi=image_result&resnum=1&ct=image&ved=0CAsQ9QEwAA

http://www.vam.ac.uk/vastatic/microsites/1331_modernism/files/97/1931_germany_chermayeff.jpg

# Flexible Plastic

- Durable (won’t break, crack, yellow over time)
- Take colours
- Easily molded
- Inexpensive
- Light weight

http://media.giantbomb.com/uploads/0/2750/238166-beachball_large.jpeg

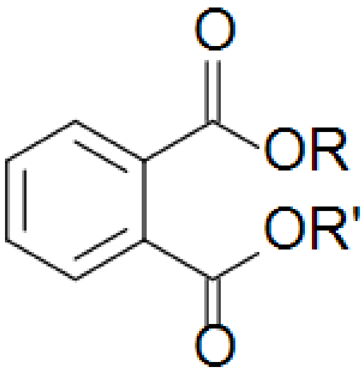
http://www.vam.ac.uk/images/image/15519-large.jpg

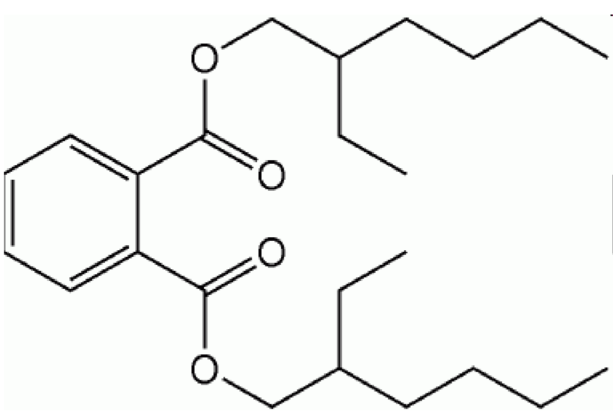
http://www.vestaldesign.com/blog/wp-content/uploads/plastic-bottle-blowing-hand.jpg

# Outline

1. What are phthalates, what are their uses, what products are they in?
2. How do phthalates move around the environment? (fate)
3. How are we exposed to phthalates?
4. What are some of the toxicological concerns about this exposure?
5. How do we minimize our exposure?
   - Individual action,
   - Policies & regulations

# What are phthalates?



Di(2-ethylhexylphthalate) or DEHP

- Esters of phthalic acid
- R can be short (C1-4) or long (C8-11) alkyl groups
- Global production
  - ~3.5-4 billion kg/yr in 2003 (Lin et al. 2003)
  - ~ 6 billion kg/yr in 2004 (Rudel & Perovich 2009)

http://en.wikipedia.org/wiki/Phthalate

# Common Phthalates

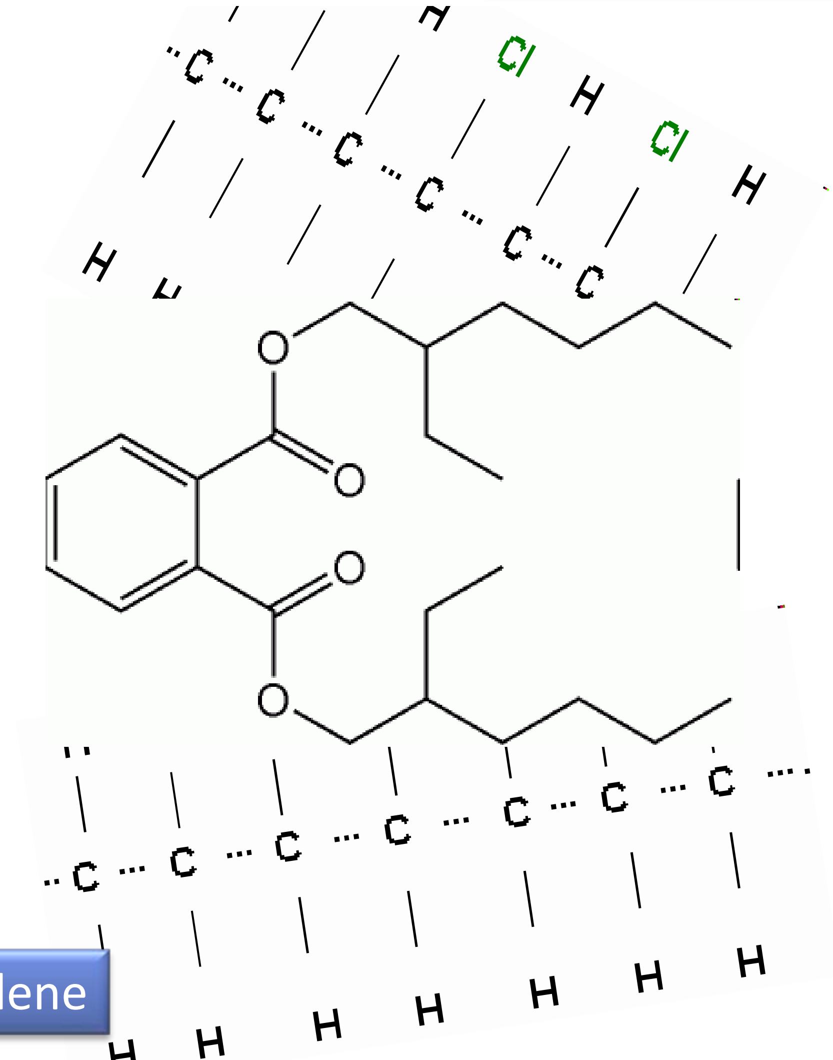
| Abbreviation | Ester Groups | Formula | CAS No. | Molecular Weight |
|---|---|---|---|---|
| DMP | Dimethyl | $C_{10}H_{10}O_4$ | 131-11-3 | 194.2 |
| DEP | Diethyl | $C_{12}H_{14}O_4$ | 84-66-2 | 222.2 |
| DiBP | Diisobutyl | $C_{16}H_{22}O_4$ | 84-69-5 | 278.4 |
| DnBP | Di-n-butyl | $C_{16}H_{22}O_4$ | 84-74-2 | 278.4 |
| BBzP | Butylbenzyl | $C_{19}H_{20}O_4$ | 85-68-7 | 312.4 |
| DEHP | Di-(2-ethylhexyl) | $C_{24}H_{38}O_4$ | 117-81-7 | 390.6 |
| DINP | Diisononyl | $C_{26}H_{42}O_4$ | 28553-12-0 | 418.6 |
| | | | 68515-48-0 | (418.6–432.6) |
| DIDP | Diisodecyl | $C_{28}H_{46}O_4$ | 26761-40-0 | 446.7 |
| | | | 68515-49-1 | (432.7–446.7) |

Wormuth et al. 2006 Risk Analysis 26(3): 803-824

# Phthalate Uses

- Plasticizer
  - Increase flexibility & transparency
- esp with polyvinyl chloride
- Lubricant
- Solvent
- Emulsifier
- Added 10-60% by wt

Polyvinyl chlorinde



Polyethylene

http://www.americanchemistry.com/s_chlorine/docs/images/pvc_poly2.gif

# Phthalate Uses

- DEHP, BBZP Building materials vinyl tiles, vinyl wall paper, shower curtains, vinyl clothing
- DnBP Consumer products
  - Cosmetics, fragrances, shampoos, moisturizers, hair spray
- Medical equipment
  - IV & tubing
- Food wrappers
- Gloves used in food handling
- Agricultural crop covers
- “Inert” carrier in pesticide mixtures

http://www.directwallpaper.co.uk/products.html

http://www.home-improvement-time.com/2008/09/06/sierra-plank-konecto-flooring-vinyl-tiles/

http://www.thecoolhunter.net/article/detail/1533

http://niceskin.org/index.php?pageNum_product=11&case=search&ps=Colorescience-Lip-Polish-Wand-Softer-Shade-Of-Pale&pscat=Make+Up

http://commons.wikimedia.org/wiki/File/Regular_strength_enteric_coated_aspirin_tablets.jpg

http://plasticulture.cas.psu.edu/IMAGES/field/imagepages/image4.htm

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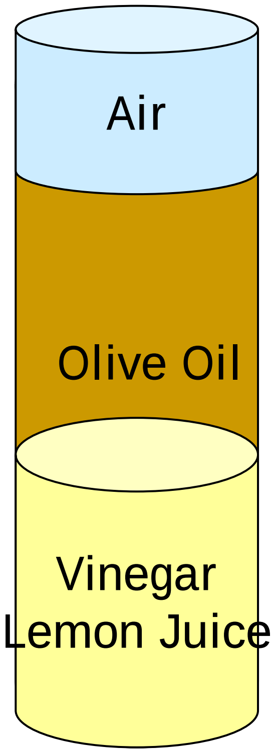
# Tangent

http://oncampus.macleans.ca/education/2009/10/06/after-the-fork-in-the-road/

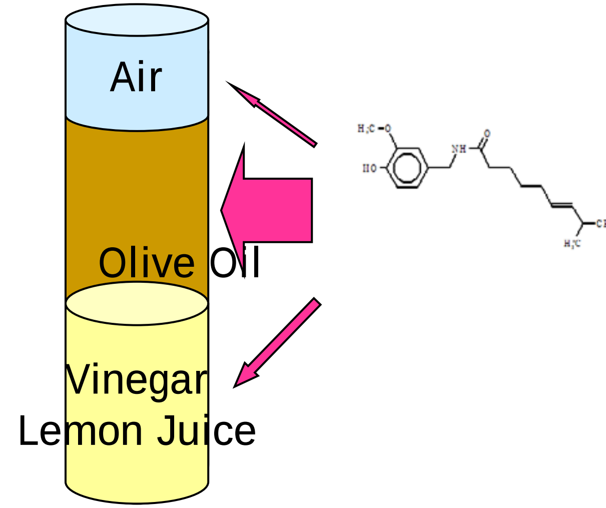
# Introduction - Fugacity

- Partitioning – Distribution of chemicals among environmental compartments
- Chemicals do not partition in the environment to achieve equal concentrations, but to achieve chemical equilibrium
- Fugacity
  - escaping tendency of a chemical
  - In units of pressure (Pa)
  - Comes from the Latin *fugere*, describing a “fleeing” or “escaping” tendency
  - Coined in 1901 by G.N. Lewis, a UC-Berkeley professor
  - Don Mackay, a former U of T engineering professor first applied it to modeling contaminants in the late 1970s
  - Commonly used in contaminant fate modelling



# Fugacity capacity

- capacity of an environmental compartment to hold a chemical
- Function of the solubility of the chemical in a phase

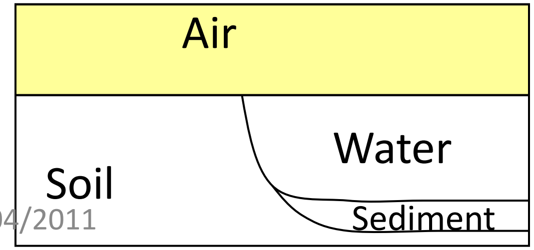



# Equilibrium:

- State at which there is no tendency to change
- Fugacity in each compartment is equal
- Regardless of where and how a chemical is discharged or found in the environment, all chemicals will strive to obtain a characteristic distribution or equilibrium among environmental compartments

At chemical equilbrium:

$$f_{air} = f_{water} = f_{soil/sed} = f_{biota}$$




If:

$$f_{air} > f_{water} = f_{soil/sed} = f_{biota}$$

How will chemical move?

# Chemical Transport

- The case of the killer vinyl shower curtains

ENVIRONMENTAL | DEFENCE

*protecting the environment and human health*

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2008 June 12 — Print

## Vinyl Shower Curtains Release Toxic Chemicals

***New report shows as many as 100 chemicals released from PVC shower curtains***

Toronto - As many as 100 toxic chemicals associated with adverse health effects are released into the air from polyvinyl chloride (PVC ) shower curtains. These chemicals make up that "new shower curtain smell" unique to PVC vinyl shower curtains and shower curtain liners, according to *"Volatile Vinyl: The New Shower Curtain's Chemical Smell."* The new study is released today by the US-based Center for Health, Environment & Justice (CHEJ) and in Canada by Environmental Defence and the Canadian Environmental Law Association (CELA).

http://www.environmentaldefence.ca/pressroom/viewnews.php?id=419

# Molecular Diffusion

High Fugacity ⇨⇨⇨ Low Fugacity

http://cn1.kaboodle.com/hi/img/2/0/0/34/e/AAAAArSBf8cAAAAAADTlqg.jpg

Rate

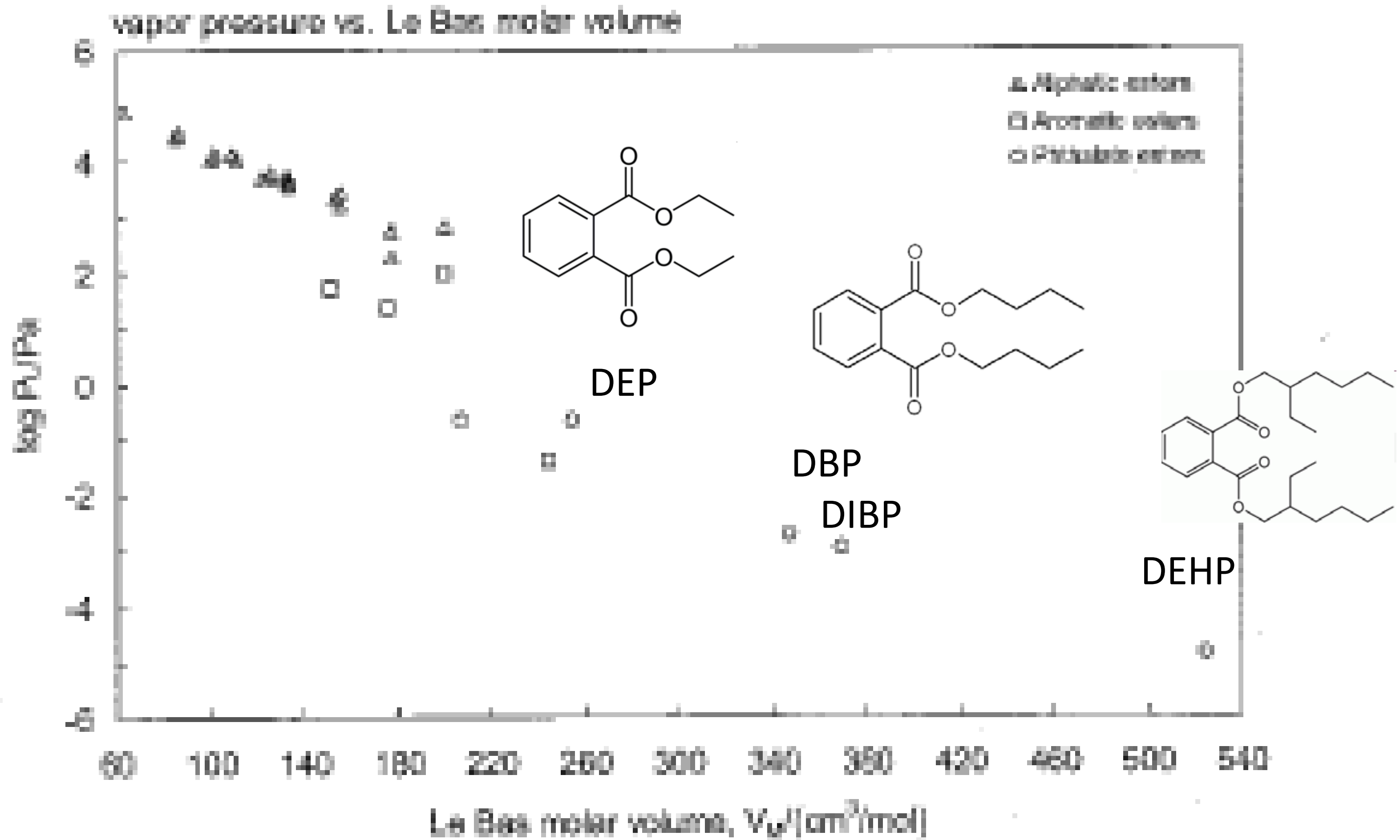
- Fick's 1st Law

  $N \approx \Delta f\ (Pa) \cdot MTC\ (m/s)$

- Molecular weight
- Temperature
- Sorbents such as other plastics that don't contain compound

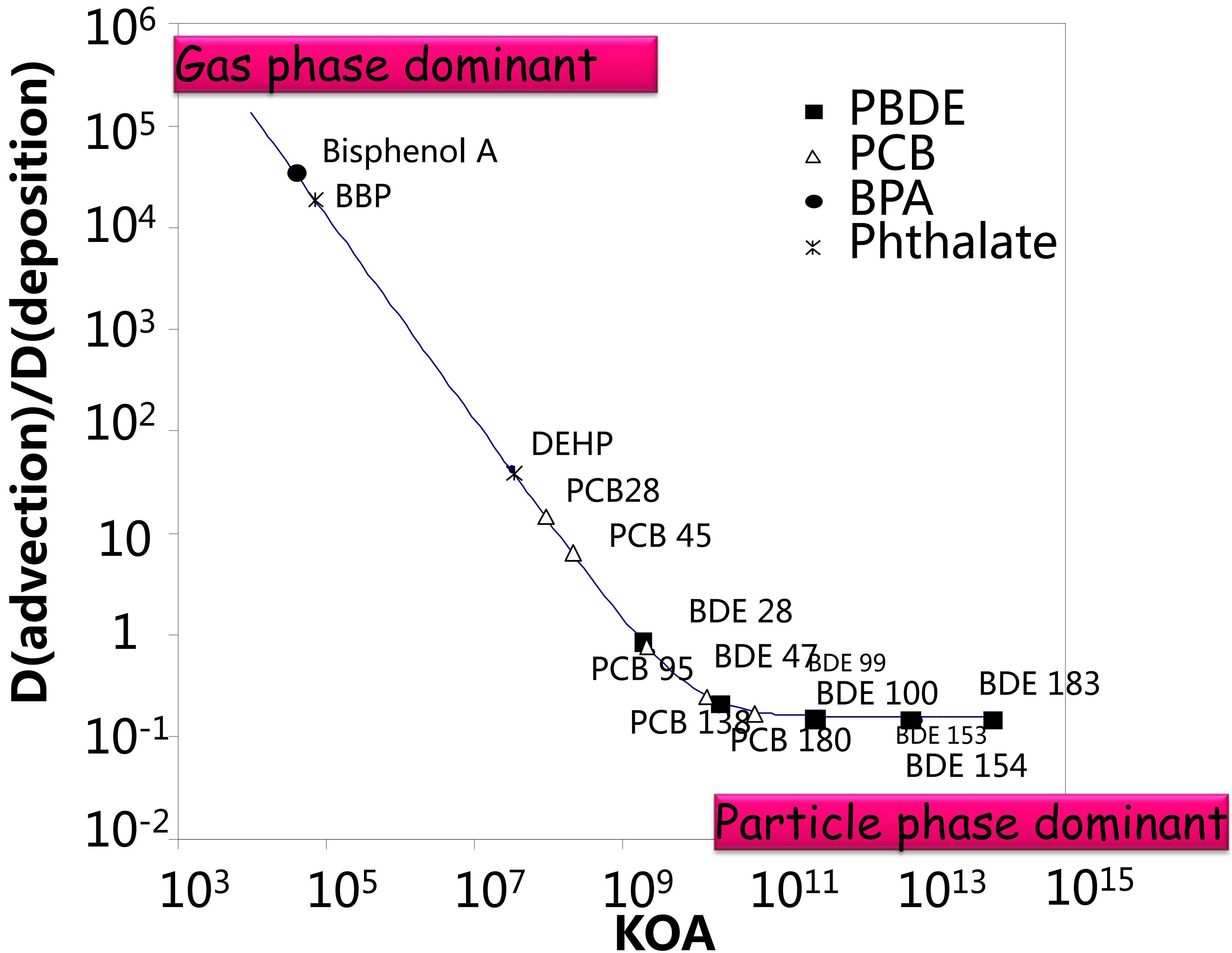
# Phthalates & VP

0.22




1.15E-3 Pa

Mackay et al. 2006



Gas phase dominant
Particle phase dominant
PBDE
PCB
BPA
Phthalate
Bisphenol A
BBP
DEHP
PCB28
PCB 45
BDE 28
PCB 95
BDE 47
BDE 99
BDE 100
BDE 183
PCB 138
PCB 180
BDE 153
BDE 154
D(advection)/D(deposition)
KOA
10^6
10^5
10^4
10^3
10^2
10
1
10^-1
10^-2
10^3
10^5
10^7
10^9
10^11
10^13
10^15

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# Summary of Routes of Exposure



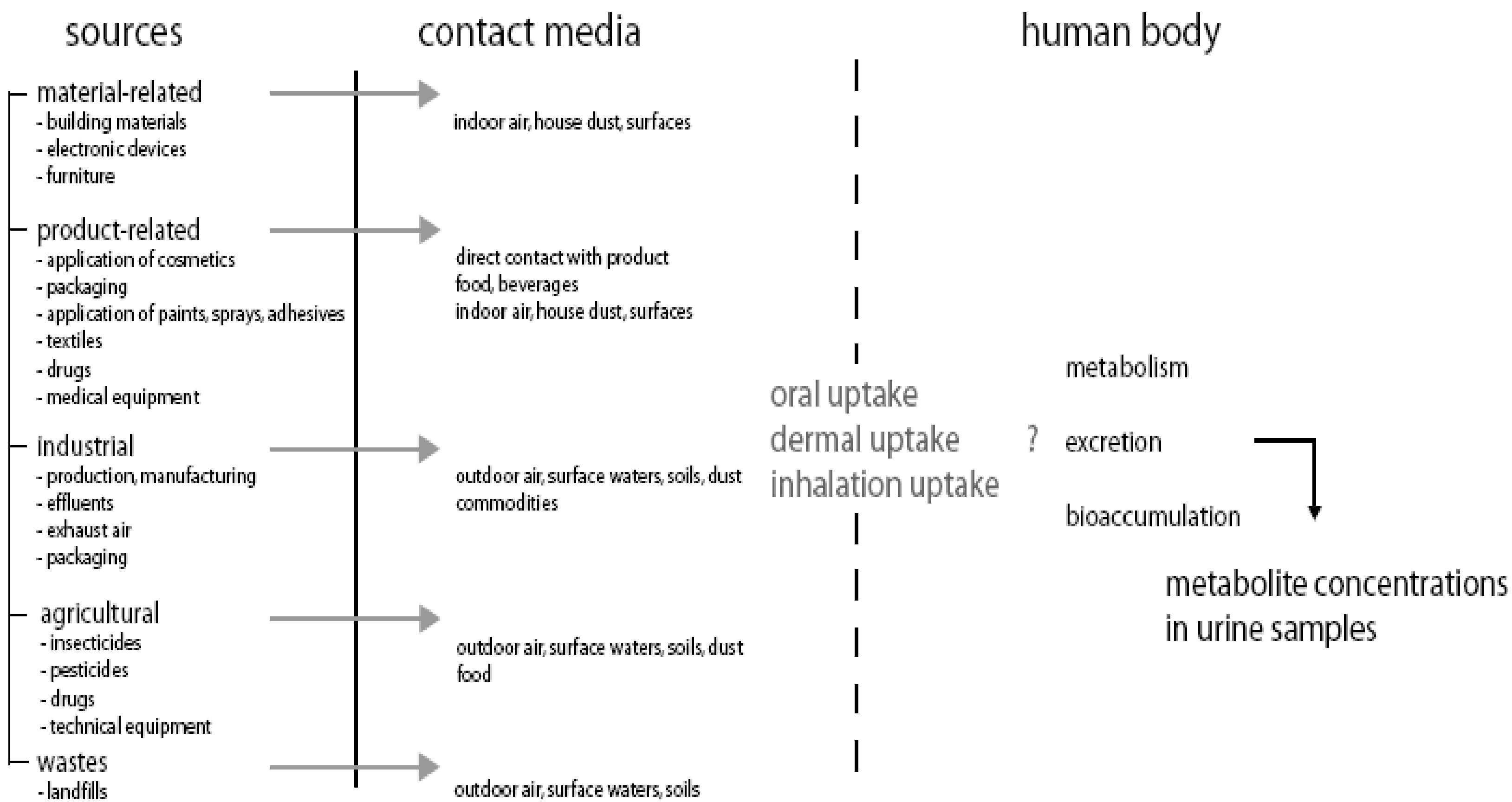



**Fig. 1.** Consumers are exposed to phthalates via different sources. Measurements of concentrations of phthalate metabolites in urine samples have demonstrated the ubiquitous consumer exposure to these plasticizers.

Wormuth et al. 2006 Risk Analysis 26(3): 803-824

# How are we exposed?

Food

Medications

Home

- Air
  - Inhalation
  - Dermal
  - Saliva
- Dust

Hand-to-mouth

- All intake routes?
- Representative intake rates?
- Reliable measured concentrations?

Biomarker

- Urine
- Blood

-How representative is the sample?
-All metabolites?
-Back-calculation to intake?

# Forward & Reverse Dosimetry

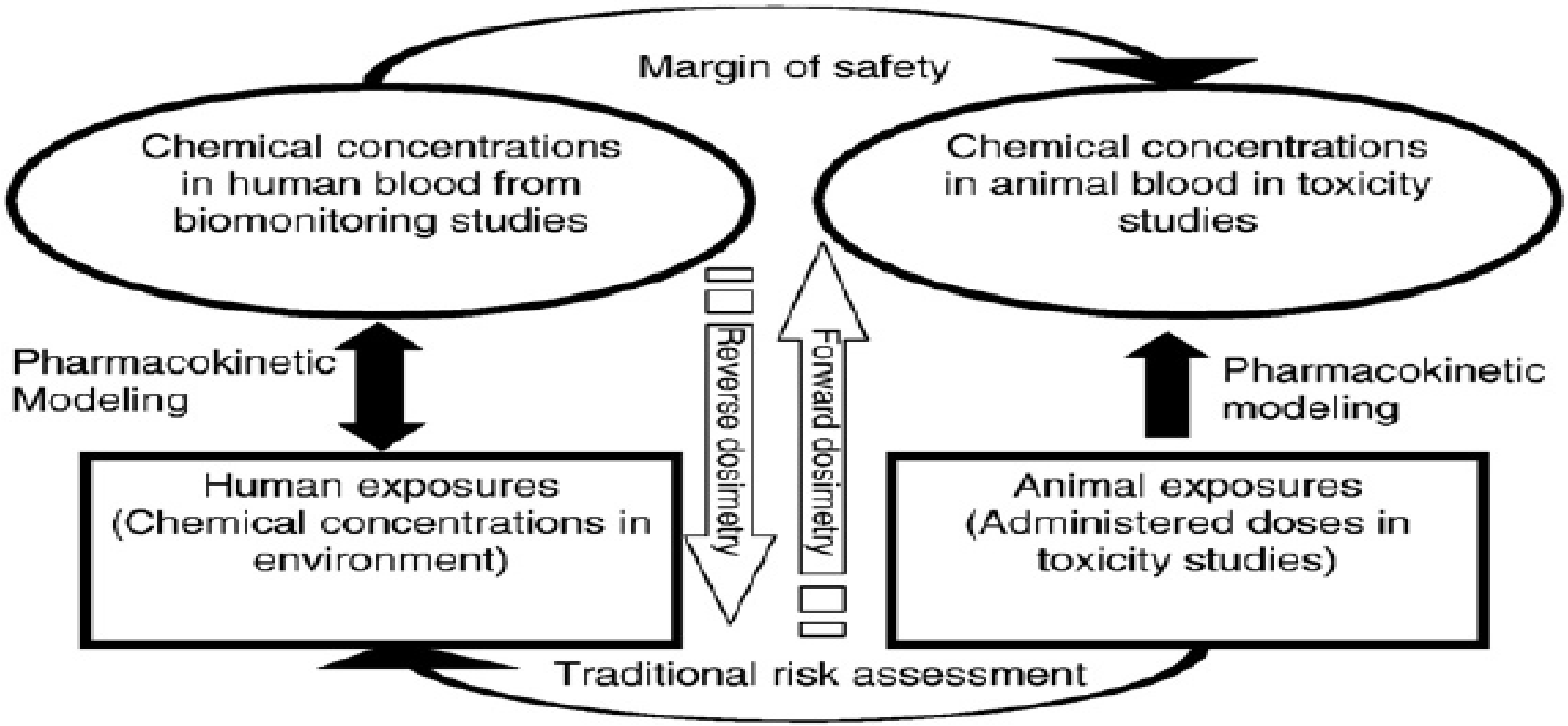



**Fig. 2.** Interpretation of Biomonitoring Data. To be put in context, the relationship of human biomonitoring data to animal toxicity data must typically be determined. Biomonitoring provides a measure of internal exposure. Traditional risk assessment is based on measures of external exposure, such as mg/kg/day ingested. In forward dosimetry, pharmacokinetic studies in the experimental animal can be used to support a direct comparison of internal exposures, providing an estimate of the margin of safety. Alternatively, reverse dosimetry can be performed to estimate the external exposure in the human for comparison with an animal-based health standard, such as a Reference Dose (RfD).

Clewell et al. 2008. Quantitative interpretation of human biomonitoring data. Toxiol App Pharm 231:122-133.

# Forward Dosimetry: Phthalate Exposure Assessment

- Compilation of phthalates in foods, air, dust
- Compilation of how much of each food is consumed, air inhaled, etc.
- Example:
  - Wormuth et al. 2006 European exposure assessment

# Phthalates in our Foods

**Table 5** The five products (nos. 1–5) with the highest DINP concentration and a product substantially contaminated by a small DINP content in the gasket (no. 6)

| Product | Jar size(g) | In food (mg/kg) DINP | In food (mg/kg) ESBO | DINP in gasket(%) |
|---|---|---|---|---|
| 1 Satay sauce | 220 | 270 | | 30 |
| 2 [illegible] | [illegible] | [illegible] | | [illegible] |
| 3 Sauce | 180 | 180 | | 33 |
| 4 Peppers stuffed with feta cheese | 310 | 178 | | 19 |
| 5 Seasoned garlic in oil | 175 | 160 | | 17 |
| 6 Anchovies | 80 | 55 | 440 | 1.2 |

ucts laid in oil (the olives at the bottom being at position 18 of the complete ranking). Mostly concentrations are lower because of the significantly larger jar content.

All nine foods in jars with lids with substantial amounts of DINP in the gasket contained this phthalate at concentrations above 120 mg/kg (average of 175 mg/kg). The top five are listed in Table 5. Another four products with small amounts in the gasket contained 10–55 mg/kg DINP. The bottom line shows an example: as little as 1.2% DINP in the gasket (next to 37% ESBO) was sufficient to contaminate the food at a concentration of 55 mg/kg. Hence, 9 mg/kg (SML conventionally derived from the TDI) would be reached in a product of this type with 0.2% DINP in the gasket.

with DEHP as principal plasticizer, the concentrations varied between 28 and 45%. In another 14 gaskets, they were between 0.2 and 1.4%.

DEHA was never the principal plasticizer. It was present in nine gaskets, namely eight times in a range between 2.2 and 14% and once at 0.2%. Interestingly it was often combined with other esters of 2-ethyl hexanol, such as DEHP or Ehol-16/Ehol-18. Acetylated partial glycerides were found in 16 gaskets, namely twice as the main plasticizer beside ESBO (25 and 21%), four times between 2 and 8.5% and ten times between 0.8 and 1.3%.

**Table 7** The seven products with the highest DEHP concentration

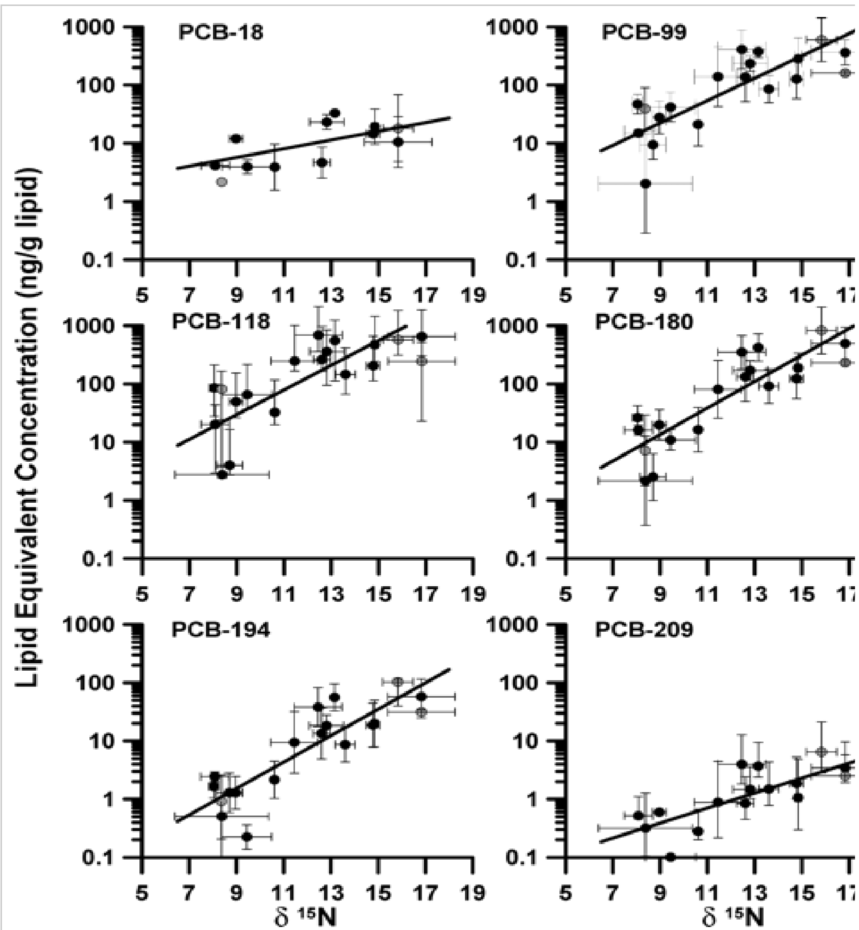
| Product | Jar size (g) | DEHP in food (mg/kg) | DEHP in gasket (%) |
|---|---|---|---|
| 1 Curry paste | 300 | 825 | 45 |
| 2 Mixed pickle in oil | [illegible] | [illegible] | [illegible] |
| 3 Pesto | 185 | 660 | 27 |
| 4 Tomato paste | 185 | 615 | 31 |
| 5 Biryani Paste | 300 | 510 | 28 |
| 6 Olive paste | 90 | 435 | 32 |
| 7 Tomato paste | 190 | 392 | 28 |
| 8 Tuna in oil | 167 | 360 | 30 |

**Table 6** The five products (nos. 1–5) with highest DIDP concentration and some other products of interest (nos. 6–9)

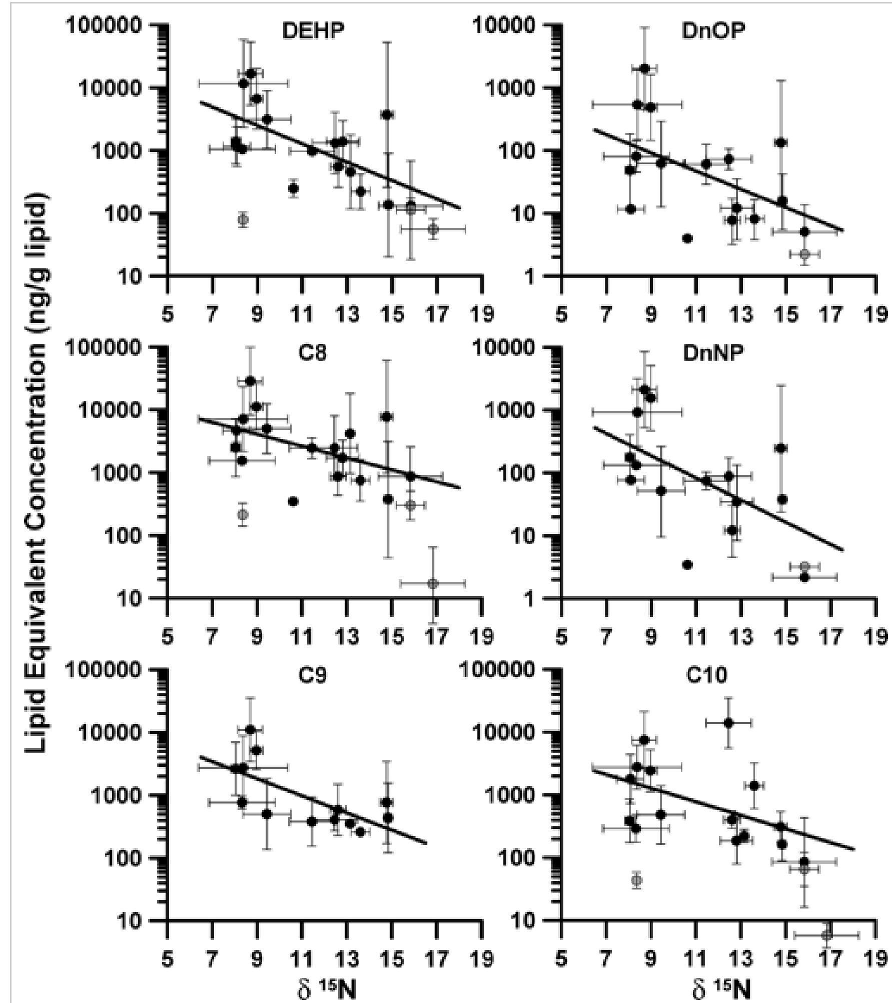
| Product | Jar size (g) | Fat content (%) | In the food (mg/kg) ESBO | DIDP | DEHA | ATBC | OA | EA | DIDP in gasket (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 Olive sauce | 175 | | | 740 | | | 30 | 27 | 27 |
| 2 Pesto | 180 | | | 430 | 55 | | | | 24 |
| 3 Mango pickles in oil | 350 | | | 380 | | | | | |
| 4 Tomato sauce with spices | 400 | 6.5 | | 170 | | | | | 19 |
| 5 Tomato sauce with meat | 400 | 6.5 | | 150 | | | | | 20 |
| 6 Tomato sauce with cheese | 400 | 6.5 | | 15, 200 | | | | | 20 |
| 7 Sauce tartar | 120 | 33 | | <5 | | | | | 24 |
| 8 Meat marinade | 250 | 12 | | <5 | | | | | 29 |
| 9 Anchovies in oil | 90 | | 540 | 30 | | 60 | 48 | 20 | 0.5 |

Kankhauser et al. 2006. PVC plasticizers/additives migrating from the gaskets of metal closures into oily food: Swiss market survey June 2005. Eur Food Res Technol 223:447-453.

# Phthalates don't bioaccumulate



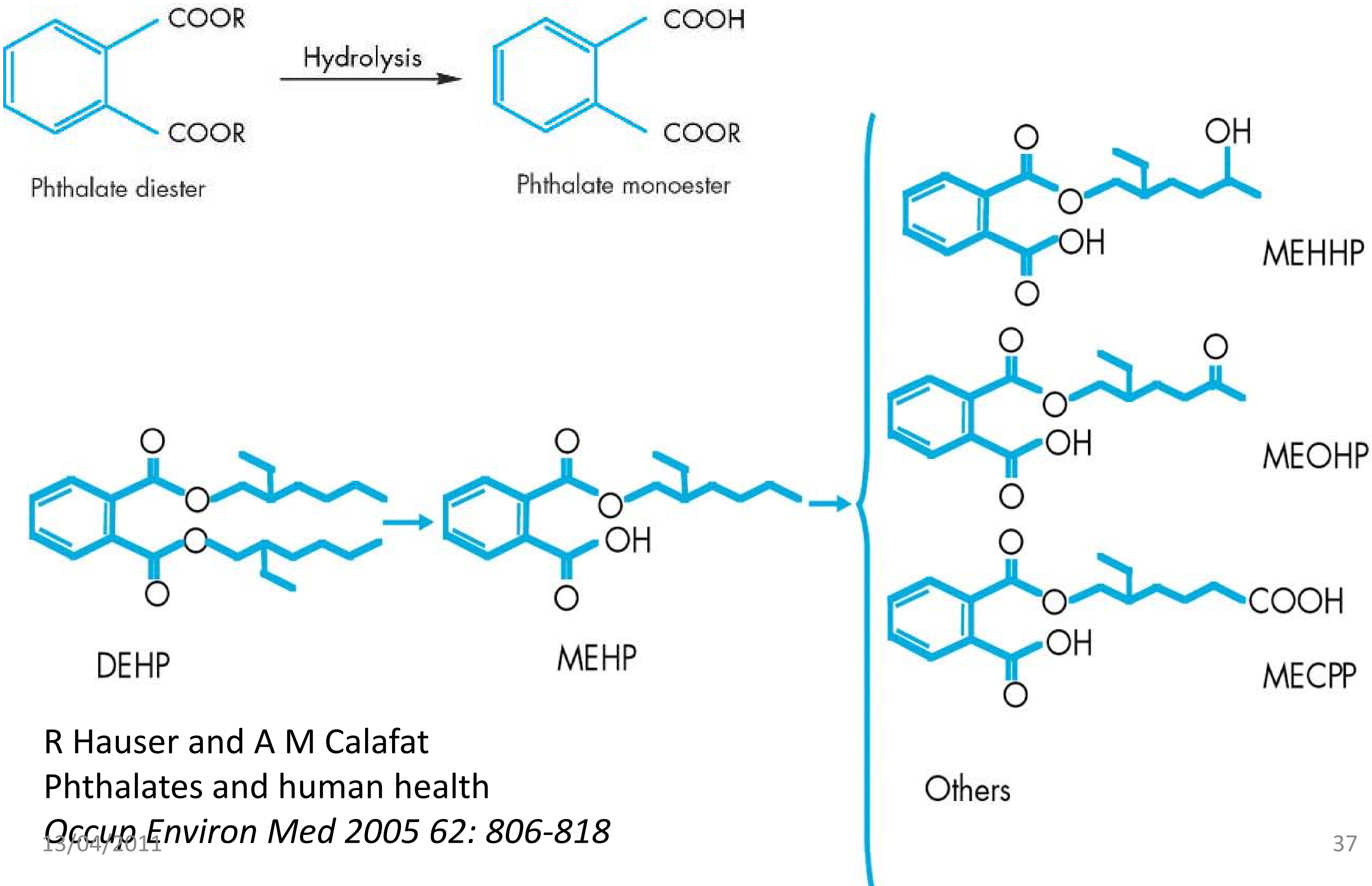

PCBs




C8-10 Phthalates

MacIntosh et al. 2004 Environ Sci Technol 38:2011-2020

# Phthalate Metabolism




R Hauser and A M Calafat
Phthalates and human health
*Occup Environ Med 2005 62: 806-818*

# Consumption Rates (European)

**Table III.** Amounts of Food Consumed Daily; Amounts of Ingested Soil, Dust, and Personal Care Products (g/day)

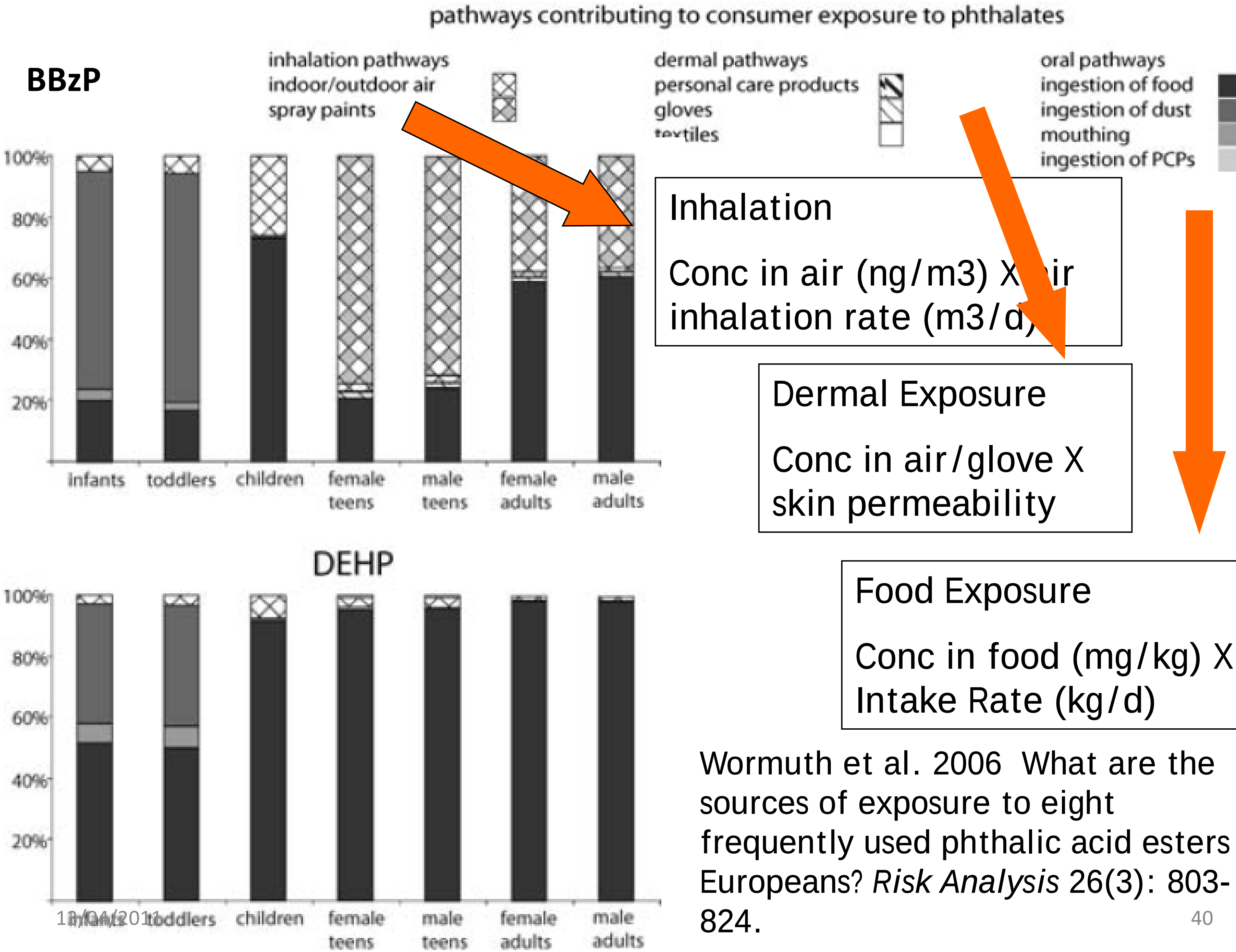
| | Infants | | Toddlers | | Children | | Female Teens | | Male Teens | | Female Adults | | Male Adults | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Food | Mean | *CF* | Mean | *CF* | Mean | *CF* | Mean | *CF* | Mean | *CF* | Mean | *CF* | Mean | *CF* |
| Pasta, rice | 17.0 | 0.070 | 25.0 | 0.654 | 24.2 | 0.589 | 56.0 | 0.693 | 64.1 | 0.637 | 59.7 | 0.869 | 74.6 | 0.863 |
| Cereals | 52.0 | 0.580 | 21.7 | 0.727 | 18.1 | 0.689 | 23.6 | 0.930 | 21.9 | 0.890 | 25.5 | 0.753 | 29.3 | 0.750 |
| Breakfast cereals | | | | | | | | | | | 58.1 | 0.500 | 74.6 | 0.460 |
| Bread | 30.4 | 0.648 | 39.6 | 0.737 | 41.8 | 1.000 | 87.5 | 0.993 | 123.7 | 0.980 | 94.8 | 0.903 | 130.3 | 0.898 |
| Biscuits, crispy bread | 5.0 | 0.175 | 15.2 | 0.872 | | | | | | | 15.1 | 0.680 | 21.3 | 0.630 |
| Cakes, buns, puddings | 21.5 | 0.514 | 10.0 | 0.466 | 25.9 | 0.879 | 31.4 | 0.970 | 55.4 | 0.980 | 38.6 | 0.860 | 45.9 | 0.842 |
| Bakeries, snacks | 2.2 | 0.251 | 7.7 | 0.656 | 9.1 | 0.781 | 80.7 | 0.817 | 102.7 | 0.883 | 8.7 | 0.591 | 10.6 | 0.595 |
| Milk, milk beverages | 386.3 | 0.645 | 307.3 | 0.902 | 276.5 | 0.987 | 150.0 | 0.980 | 212.6 | 0.980 | 154.6 | 0.730 | 188.3 | 0.740 |
| Cream | | | | | 2.5 | 0.170 | 14.6 | | 4.1 | | 5.0 | 0.190 | 4.8 | 0.185 |
| Ice cream | 17.0 | 0.055 | 18.3 | 0.579 | 17.8 | | 11.4 | | 25.8 | | 13.8 | 0.329 | 15.2 | 0.324 |
| Yogurt | 38.0 | 0.225 | 43.1 | 0.698 | 26.3 | 0.485 | 52.0 | | 39.2 | | 42.2 | 0.651 | 36.0 | 0.596 |
| Cheese | 7.5 | 0.375 | 5.6 | 0.572 | 7.6 | 0.574 | 51.8 | 1.000 | 77.6 | 0.990 | 31.8 | 0.927 | 34.1 | 0.937 |
| Eggs | 6.3 | 0.083 | 6.3 | 0.288 | 9.4 | 0.412 | 9.7 | 0.990 | 15.4 | 0.990 | 25.4 | 0.861 | 31.1 | 0.877 |
| Spreads | 3.0 | 0.280 | | | | | | | | | 29.6 | 0.330 | 35.4 | 0.370 |
| Animal fats | 3.0 | 0.280 | 2.2 | 0.264 | 2.3 | 0.284 | 3.7 | 0.880 | 3.8 | 0.840 | 7.0 | 0.794 | 16.5 | 0.789 |
| Vegetable oils | 3.0 | 0.280 | 7.1 | 0.394 | 10.3 | 0.474 | 21.1 | 0.437 | 26.5 | 0.410 | 13.6 | 0.799 | 17.6 | 0.811 |
| Meat, meat products | 21.5 | 0.290 | 27.3 | 0.368 | 28.8 | | 68.0 | 1.000 | 76.4 | 1.000 | 88.5 | 0.948 | 117.1 | 0.949 |
| Sausage | 26.0 | 0.033 | 9.5 | 0.448 | 9.0 | 0.484 | 15.3 | 0.880 | 29.4 | 0.940 | 34.8 | 0.855 | 42.7 | 0.864 |
| Poultry | 14.7 | 0.444 | 4.5 | 0.329 | 8.2 | 0.447 | 13.5 | | 23.6 | | 37.0 | 0.825 | 59.5 | 0.874 |
| Fish | 5.2 | 0.096 | 10.0 | 0.325 | 5.1 | | 22.9 | 0.940 | 30.8 | 0.930 | 47.6 | 0.781 | 55.5 | 0.768 |
| Vegetables | 35.8 | 0.478 | 56.1 | 0.916 | 72.0 | 0.830 | 144.1 | 0.970 | 137.0 | 0.910 | 187.3 | 0.998 | 198.2 | 0.998 |
| Potatoes | 21.9 | 0.390 | 54.8 | 0.783 | 53.4 | 0.927 | 58.6 | 0.533 | 66.7 | 0.600 | 96.7 | 0.930 | 122.5 | 0.912 |
| Fruits | 117.3 | 0.659 | 91.6 | 0.841 | 113.2 | 0.826 | 90.9 | 0.840 | 103.4 | 0.763 | 223.4 | 0.972 | 220.5 | 0.967 |
| Nuts, nut spreads | 1.5 | 0.069 | | | 1.5 | | | | | | 4.8 | 0.542 | 6.1 | 0.522 |
| Preserves, sugar | 3.0 | 0.170 | 6.8 | 0.557 | 7.6 | 0.638 | 3.9 | | 8.8 | | 11.2 | 0.591 | 14.8 | 0.675 |
| Confectionery | 6.0 | 0.130 | 13.3 | 0.633 | 30.9 | 0.719 | 17.4 | 0.990 | 22.2 | 1.000 | 24.3 | 0.808 | 29.3 | 0.801 |
| Spices | | | | | 5.1 | | 7.8 | | 7.8 | | 22.7 | 0.991 | 31.6 | 0.992 |
| Soups, sauces | | | | | 1.7 | 0.815 | 2.7 | | 2.7 | | 36.2 | 0.650 | 41.3 | 0.643 |
| Juices | 72.0 | 0.110 | 64.2 | 0.380 | 59.2 | 0.400 | 60.0 | 0.730 | 78.0 | 0.570 | 93.7 | 0.728 | 101.9 | 0.713 |

Wormuth et al. 2006 What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Analysis* 26(3): 803-824.

# Phthalate Conc in Foods

Table IV. Phthalate Concentrations in Various Foods (mg/kg) as Used in the Scenario Calculations

| | DMP | | | DEP | | | DiBP | | | DnBP | | | BBzP | | | DEHP | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Food | Min | Mean | Max | Min | Mean | Max | Min | Mean | Max | Min | Mean | Max | Min | Mean | Max | Min | Mean | Max |
| Pasta, rice | 0 | 0 | 0 | 0 | 0 | 0.01700 | 0.00150 | 0.021 | 0.158 | 0.002 | 0.010 | 0.36 | 0 | 0 | 0.025 | 0.0000 | 0.012 | 0.17 |
| Cereals | 0 | 0 | 0 | 0 | 0.00650 | 0.02000 | 0.01000 | 0.109 | 0.180 | 0.074 | 0.565 | 2.10 | 0.013 | 0.015 | 0.017 | 0.0700 | 0.574 | 1.70 |
| Breakfast cereals | 0 | 0 | 0 | 0 | 0.00650 | 0.02000 | 0.01000 | 0.109 | 0.180 | 0.074 | 0.565 | 2.10 | 0.013 | 0.015 | 0.017 | 0.0700 | 0.574 | 1.70 |
| Bread | 0 | 0 | 0 | 0 | 0.00600 | 0.01740 | 0 | 0.060 | 0.232 | 0.007 | 0.032 | 5.13 | 0 | 0 | 0.440 | 0.0261 | 0.068 | 1.96 |
| Biscuits, crispy bread | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.007 | 0.020 | 0 | 0.130 | 0.42 | 0 | 0.028 | 0.088 | 0.1020 | 0.547 | 1.10 |
| Cakes, buns, puddings | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.007 | 0.020 | 0 | 0.130 | 0.42 | 0 | 0.028 | 0.088 | 0.1020 | 0.547 | 1.10 |
| Bakeries, snacks | 0 | 0 | 0 | 0 | 0 | 0 | 0.04800 | 0.154 | 0.260 | 0 | 0.011 | 1.17 | 0 | 0 | 0.530 | 0.0094 | 0.214 | 4.42 |
| Milk, milk beverages | 0 | 0 | 0.02800 | 0 | 0 | 0.01000 | 0 | 0 | 0.016 | 0 | 0.015 | 0.03 | 0 | 0 | 0.000 | 0.0085 | 0.040 | 0.17 |
| Cream | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.002 | 0.010 | 0 | 0.037 | 0.70 | 0 | 0.005 | 0.030 | 0.1800 | 0.224 | 0.32 |
| Ice cream | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.1650 | 0.242 | 0.39 |
| Yoghurt | 0 | 0.01167 | 0.03500 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.051 | 0.09 |
| Cheese | 0 | 0 | 0 | 0 | 0.00233 | 0.00700 | 0 | 0 | 0 | 0 | 0.056 | 0.30 | 0 | 0.014 | 0.039 | 0.0410 | 0.496 | 1.23 |
| Eggs, egg spreads | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.050 | 0.100 | 0.034 | 0.067 | 0.10 | 0.010 | 0.050 | 0.090 | 0.2830 | 0.442 | 0.60 |
| Animal fats | 0 | 0 | 0 | 0 | 0.00900 | 0.01800 | 0.01200 | 0.030 | 0.048 | 0 | 0.046 | 0.19 | 0 | 0.011 | 0.056 | 0.9130 | 1.447 | 2.83 |
| Vegetable oils | 0 | 0 | 0 | 0 | 0.00500 | 0.00925 | 0 | 0.020 | 0.067 | 0 | 0 | 0.88 | 0 | 0 | 0.357 | 0 | 0.404 | 2.08 |
| Meat, meat products | 0 | 0 | 0 | 0 | 0 | 0.01760 | 0 | 0.007 | 0.053 | 0.024 | 0.075 | 0.11 | 0 | 0 | 0.072 | 0.0248 | 0.207 | 0.76 |
| Sausages | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.027 | 0.001 | 0.004 | 0.17 | 0 | 0 | 0.005 | 0.0380 | 0.064 | 0.75 |
| Poultry | 0 | 0 | 0 | 0 | 0.00500 | 0.01000 | 0 | 0.030 | 0.060 | 0 | 0.100 | 0.20 | 0 | 0.015 | 0.030 | 0.2850 | 0.518 | 0.70 |
| Fish, seafood | 0 | 0.00030 | 0.01678 | 0 | 0.00254 | 0.00851 | 0.00015 | 0.001 | 0.025 | 0.005 | 0.008 | 0.38 | 0 | 0.002 | 0.005 | 0.0023 | 0.013 | 0.29 |
| Vegetables | 0 | 0 | 0 | 0 | 0.00667 | 0.00667 | 0 | 0 | 0 | 0 | 0.033 | 0.03 | 0 | 0 | 0 | 0 | 0.140 | 0.14 |
| Potatoes | 0 | 0 | 0 | 0 | 0.00900 | 0.00900 | 0 | 0.005 | 0.005 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.076 | 0.08 |
| Fruits | 0 | 0 | 0 | 0 | 0 | 0 | 0.00800 | 0.030 | 0.052 | 0.016 | 0.028 | 0.05 | 0 | 0 | 0 | 0.0300 | 0.069 | 0.12 |




Inhalation

Conc in air (ng/m3) X air inhalation rate (m3/d)

Dermal Exposure

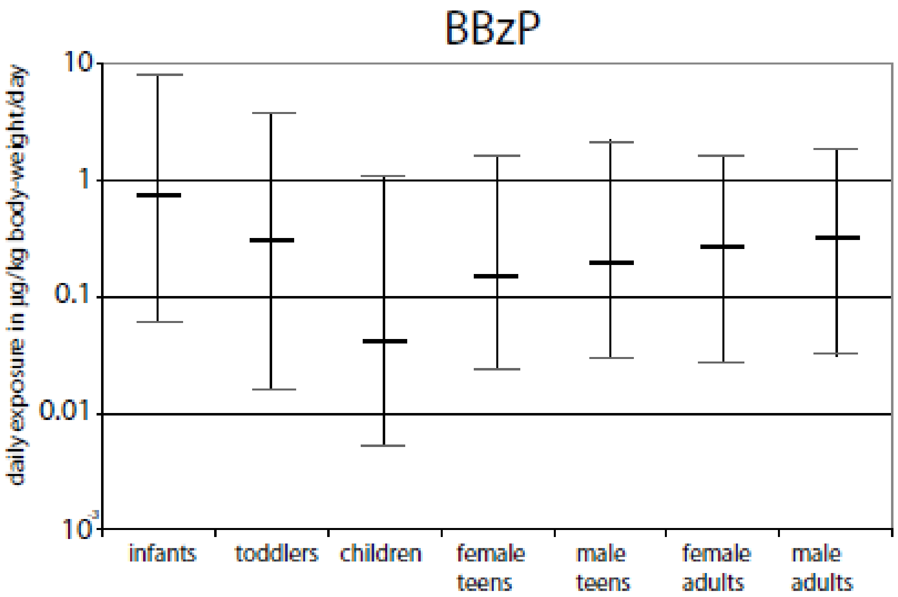
Conc in air/glove X skin permeability

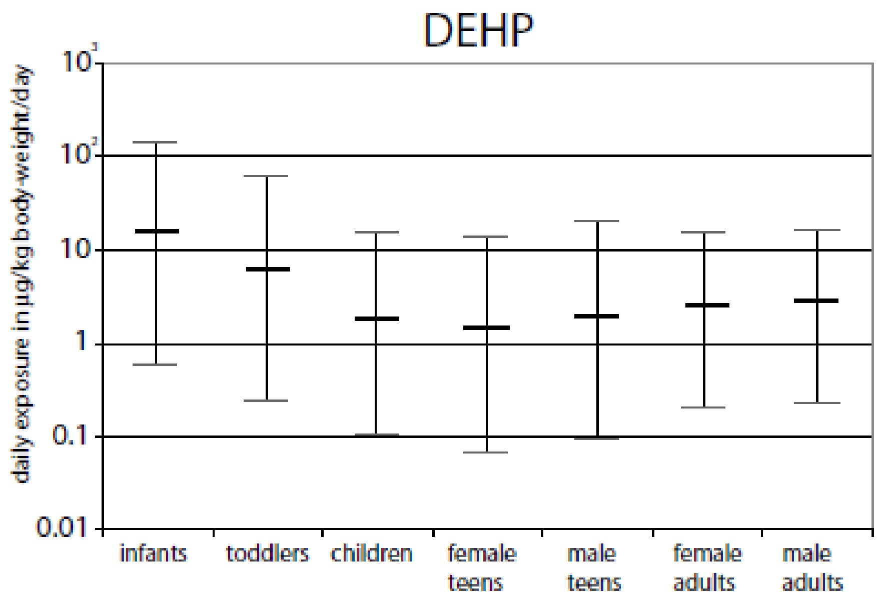
Food Exposure

Conc in food (mg/kg) X Intake Rate (kg/d)

Wormuth et al. 2006 What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Analysis* 26(3): 803-824.

# Summary of Forward Dosimetry Calculation




Wormuth et al. 2006 What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Analysis 26(3): 803-824.

# Reverse Dosimetry: Phthalate Exposure

| μg phthalate met/g creatinine | BBzP | DEHP |
|---|---|---|
| 6-11 yrs | 38.1 | 5.38 |
| 12-19 yrs | 17.9 | 3.62 |
| 20+ yrs | 12.7 | 3.81 |
| Females | 15.7 | 4.43 |
| Males | 12.7 | 3.32 |
| Mexican Americans | 12.4 | 4.16 |
| Non-hispanic blacks | 16.7 | 4.59 |
| Non-hispanic whites | 13.9 | 3.63 |

Geometric means of creatinine corrected urine, ug/g creatinine, 01-02 data, CDC 2005. Silva et al. 2004 Environ Health Perspectives 112:331-338; Mono-ester metabolite.

# Reverse: Exposure Reconstruction for NHANES III Data on Di-n-Butyl Phthalate (DnBP)

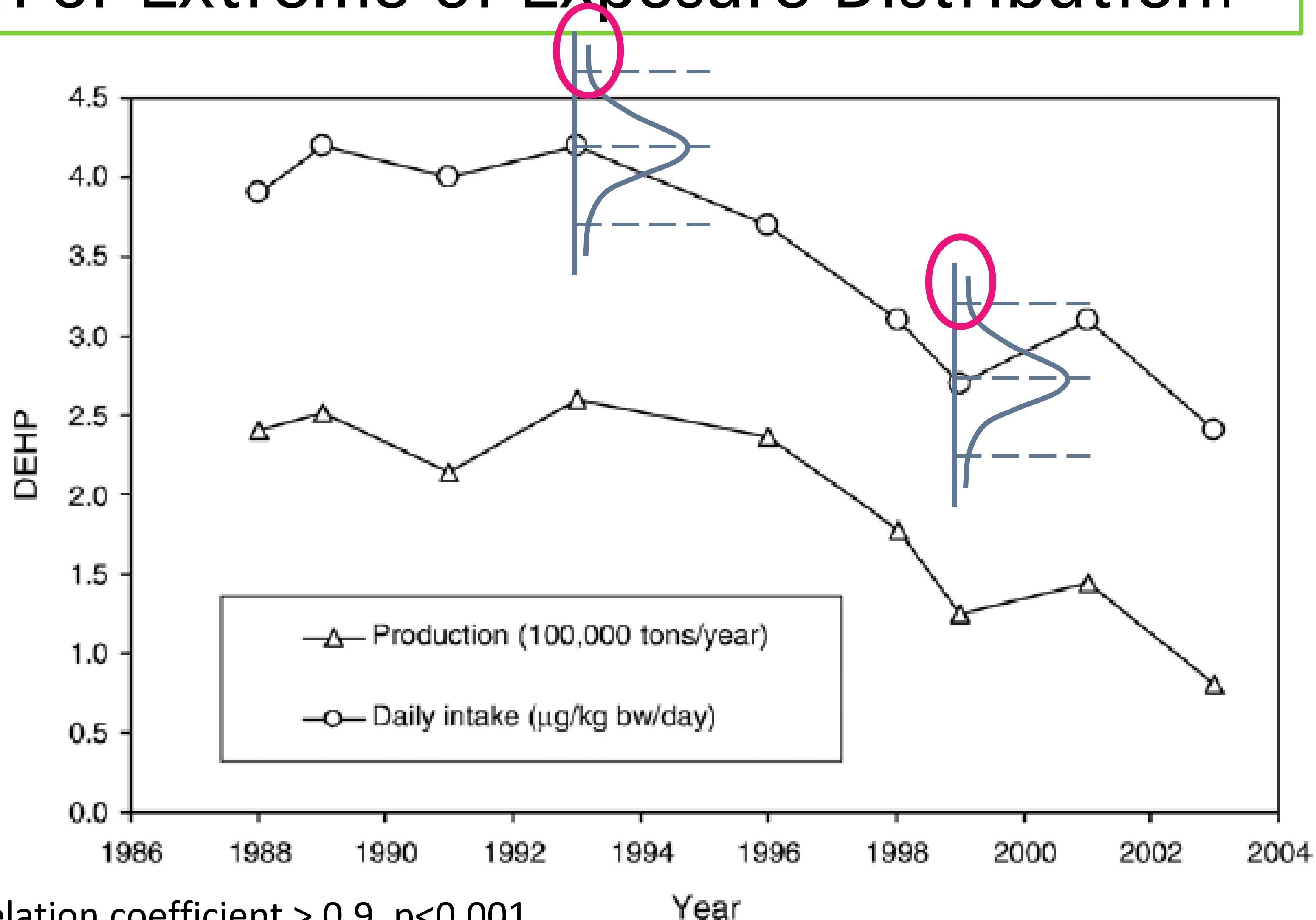
| Percentile | NHANES III Concentration in Urine (µg/L) | Predicted Intermittent Exposure* (µg/kg/day) | Predicted Continuous Exposure (µg/kg/day) |
|---|---|---|---|
| 10% | - | 0.30 | |
| 25% | - | 0.45 | 0.25 |
| 50% | 20.4 | 1.17 | 0.8 |
| 75% | 40.4 | 3.78 | 1.4 |
| 90% | 73.6 | 5.46 | 3.0 |
| 95% | 108 | 7.74 | 4.2 |

*Assumed to be sum of three ingestion events per day

**Compares well with 24-hour urine data in German study (Wittassek et al., 2007): average = 1.9 µg/kg/day, 95% = 5.3 µg/kg/day**

Clewell 2009

# Mean or Extreme of Exposure Distribution?




Correlation coefficient > 0.9, p<0.001

Helm D.2007 Correlation between production amounts of DEHP and daily intake. *Sci Total Environ* 388:398-391.

# Mean or Extreme of Exposure Distribution?

Table 4. Daily intakes ($\mu g$ (kg body weight)$^{-1}$ $d^{-1}$) of phthalates for the German and US American general population deduced from urinary metabolite concentrations; values are median (95th percentile) (maximum).

| study | Marsee *et al.* (2006) | Kohn *et al.* (2000)[a] | Koch *et al.* (2003*a*) | Wittassek *et al.* (2007*a*)[b]; Koch *et al.* (2007)[b] | Wittassek *et al.* (2007*b*) | RfD[f] | TDI[g] |
|---|---|---|---|---|---|---|---|
| country of origin | USA | USA | Germany | Germany | Germany | | |
| sample origin | pregnant women, SFF II[c] | NHANES III | general population | GerES IV | ESBHum[d] | | |
| sampling year | 1999–2002 | 1988–1994 | 2002 | 2001–2002 | 1988–2003 | | |
| urine | spot | spot | first morning | first morning | 24 h | | |
| *n* | 214 | 289 | 85 | 239 | 632 | | |
| age (years) | n.a. | 20–60 | 7–63 | 2–14 | 20–29[e] | | |
| DEP | 6.64 (112) (1260) | 12 (110) (320) | 2.32 (22.1) (69.3) | — | — | 800 | — |
| BBzP | 0.5 (2.47) (15.53) | 0.88 (4.0) (29) | 0.6 (2.5) (4.5) | 0.42 (2.67) (13.9) | 0.26 (1.6) (27.3) | 200 | 500 |
| DnBP | 0.84 (2.33) (5.86) | 1.5 (7.2) (110)[h] | 5.22 (16.2) (22.6) | 4.07 (14.9) (76.4) | 4.1 (19.1) (116) | 100 | 10 |
| DiBP | 0.12 (0.41) (2.90) | — | — | — | 1.4 (5.7) (29.0) | — | — |
| DEHP | 1.32 (9.32) (41.1)[i] | 0.71 (3.6) (46) | 4.6 (17.0) (58.2)[j] | 4.3 (15.2) (140)[j] | 3.5 (10.1) (39.8)[j] | 20 | 50 |
| DiNP | — | <LOD (1.7) (22) | — | — | 0.29 (1.7) (20.2)[k] | — | 150 |

Koch and Calafat 2009. Human body burdens of chemicals used in plastic manufacture. *Phil. Trans. Royal Soc B* 364:2063-2078.

# The Most Highly Exposed


http://www.deathreference.com/images/medd_02_img0090.jpg

# Outline

1. What are phthalates, what are their uses, what products are they in?
2. How do phthalates move around the environment? (fate)
3. How are we exposed to phthalates?
4. What are some of the toxicological concerns about this exposure?
5. How do we minimize our exposure?
   - Individual action,
   - Policies & regulations

# Phthalate Toxicity – a moving target

- Early studies
  - Hepatic cancer & teratogenesis at high doses
  - Cancer found to involve PPARα (peroxisome proliferator activated receptor)
    - therefore not relevant for humans
- Newer studies have found liver tumors, pancreatic acinar adenomas
    - Factors other than PPARα
- Some types of PPAR agonists involved in inflammatory response

National Academies of Sciences 2008

# Toxicity – a moving target

- Early studies
  - Did not find teratogenesis
- Recent studies
  - Do find teratogenic effects on male reproductive system
- Effects in offspring depend on timing of exposure
- Effects more subtle (not included in early study protocols)

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# Summary Risk Assessments

NTP* Summary

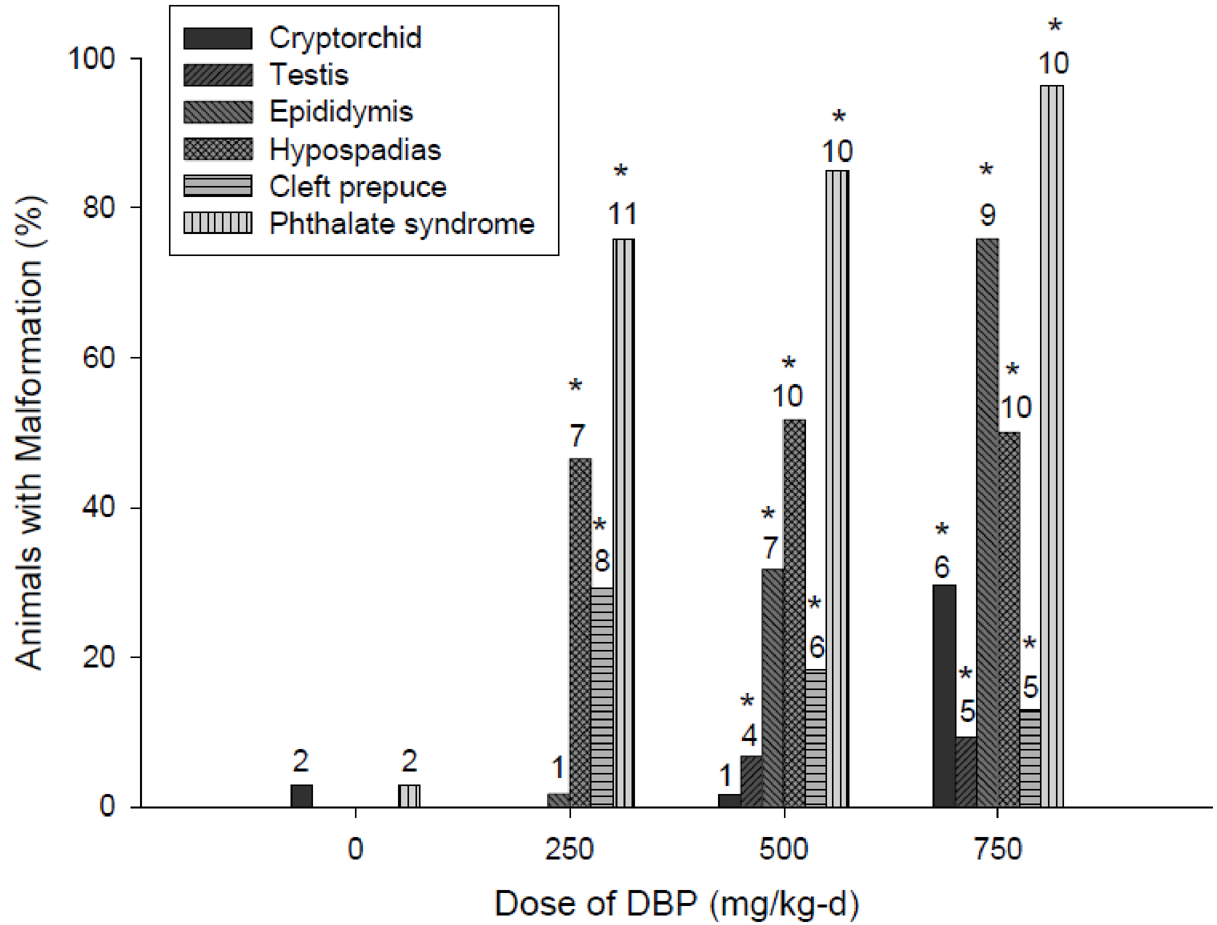
- DEHP, DBP & BBP hazardous to human reproduction & development
- DiNP & DiDP hazardous to human development
- DnHP & DnOP – insufficient data to determine risk

REACH**

- DEHP, DBP & BBP classified as human reproductive toxins (effects on fertility & development
- DiNP & DiDP – no risk
- DnOP yet to be assessed

US Nation Toxicology Program

European Registration, Evaluation, Authorization & Restriction of Chemicals




* P < 0.05 (Fisher's exact)

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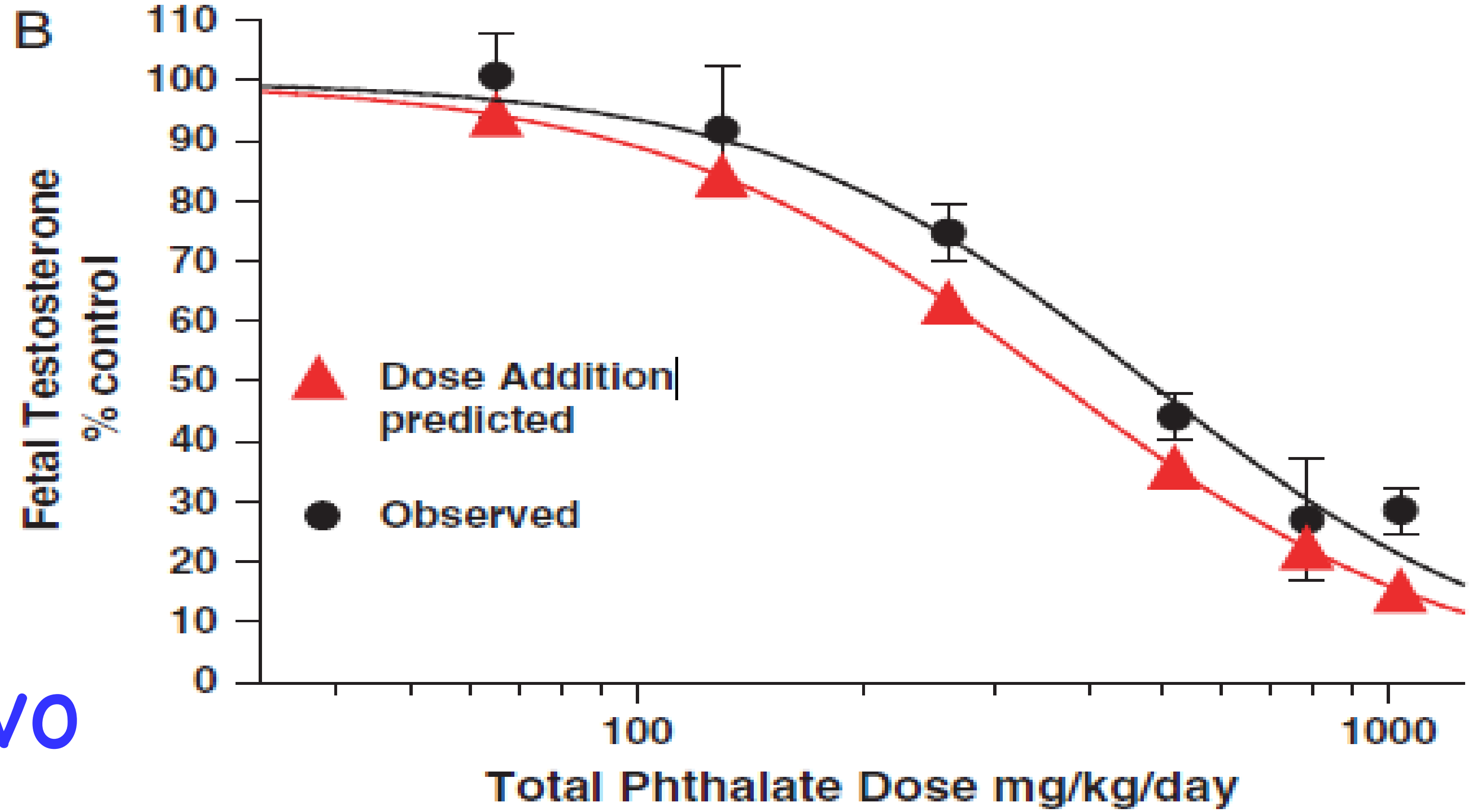
Phthalate Risk Assessment 2008

**FIGURE 3-3** Effect of DBP given over 3 days on reproductive tract malformations. Pregnant Sprague-Dawley rats were given DBP on GD 15-17, critical window for induction of phthalate syndrome, at 0, 250, 500, or 750 mg/kg-d by gavage in corn oil (5 mL/kg-d). Reproductive tract malformations were assessed in male offspring at postnatal day 100. Litters (10-12) were evaluated in each dose group; numbers of litters responding are indicated above bars. Control animals exhibited only cryptorchidism. Only when exposure occurred over GD 15-17 was the full suite of reproductive tract malformations that make up the phthalate syndrome observed. Other short-term (2-d) dosing regimens over GD 15-20 will produce specific reproductive malformations but not the full suite of malformations (Carruthers and Foster 2005).

Sprague- Dawley rats exposed on gestational days 8- 18.
Testicular testosterone production.
Total 1300 mg phthalate/kg/d, DPP, BBP, DBP, DEHP and DiBP

# Dose Additivity




In Vivo

Howdeshell et al. 2008 Toxicol Sci 105:153-165

# Mode of Toxicological Action

- Mono-ester metabolites appear to be toxic agent
- Classified as peroxisome proliferators
  - Mediated by nuclear transcription of peroxisome proliferator-activated receptors (PPARs)
- Some types of PPAR agonists involved in inflammatory response
  - Mechanism underlying association between asthma and rhinitis in kids & phthalate concentrations in dust? E.g., Bornehag et al. 2004 EHP

# Reproductive & Development Toxicity

- BBzP, DiBP, DnBP, DPeP, DEHP, DiNP

As an Endocrine Modulator*

- Modulate endogenous production of fetal testicular testosterone
- Influence insulin-like Factor 3 & follicle-stimulating hormone production
- Results in functional & structural impairment of male reproduction & development
  - Production of steroid hormones & spermatozoa, reduced fertility

* A chemical that mimics or interferes with the biosynthesis, binding and/or action of natural hormones and thus disrupts physiological processes that are hormonally controlled (Jobling et al. 1995)

# Phthalate Syndrome

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Phthalate Risk Assessment 2008

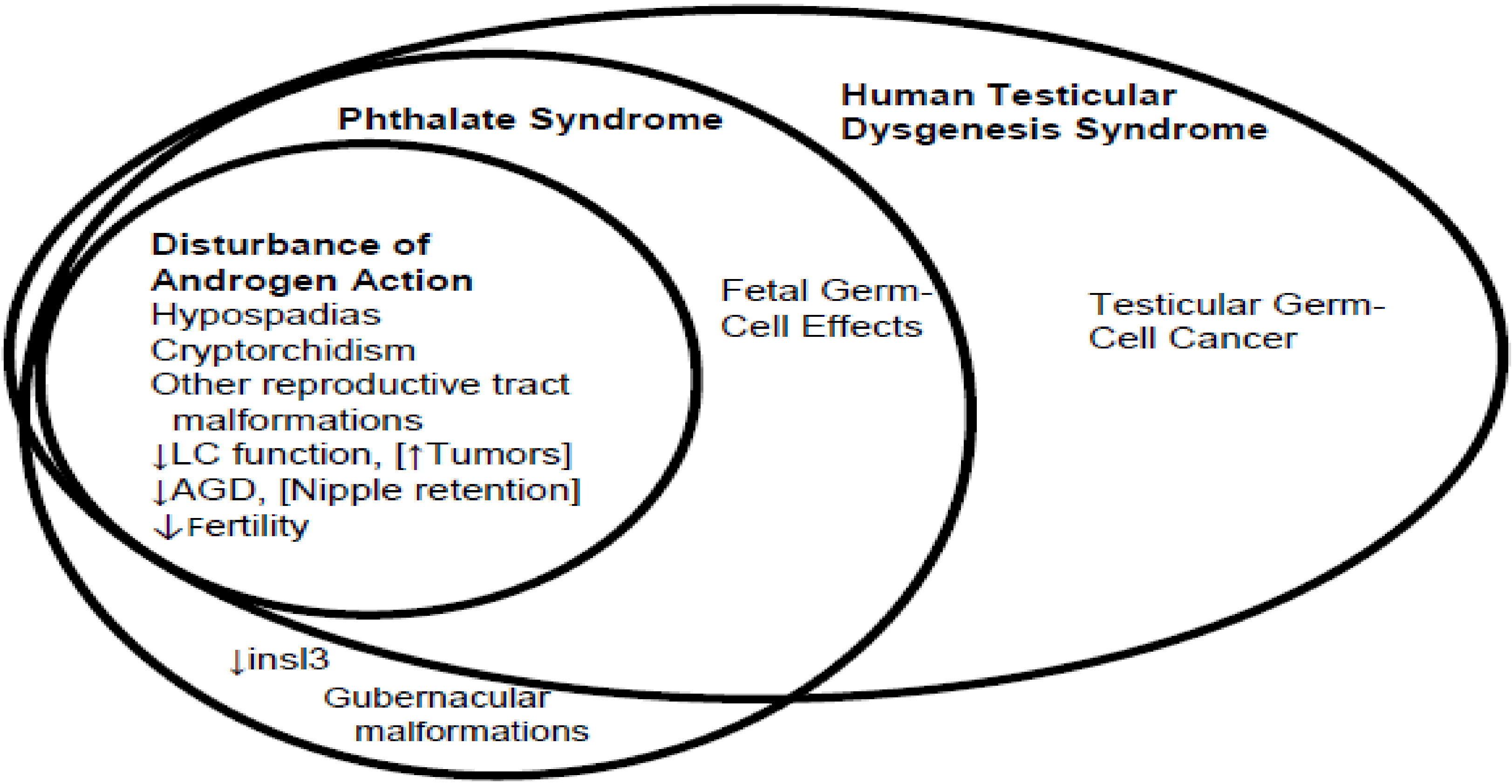


**FIGURE S-1** Relationship of phthalate syndrome in rats to effects associated with agents that perturb androgen action and produce androgen insufficiency and to the hypothesized testicular dysgenesis syndrome in humans. Outcomes in brackets are restricted to findings in experimental animals. AGD, anogenital distance; insl3, insulin-like factor 3; LC, Leydig cell; ↑, increase; and ↓, decrease.

# Summary of Reproductive Effects

**TABLE 3-1** Reproductive and Developmental Effects of DBP in the National Toxicology Program Reproductive Assessment by Continuous Breeding Study (1991)

| Effect Noted | $F_0$ Generation | $F_1$ Generation |
|---|---|---|
| Decrease in fertility | – | + |
| Decrease in litter size (of fertile animals) | + | + |
| Decrease in testes weight (and histopathology) | – | + |
| Decrease in pup weight | + | + |
| Decrease in sperm count | – | + |
| Cryptorchidism | Not applicable | + |
| Male reproductive tract malformations (epididymide, external genitalia) | Not applicable | + |
| Female reproductive tract weight (and histopathology) | – | – |
| Estrus cyclicity | – | – |

Note: +, positive response; –, negative response.

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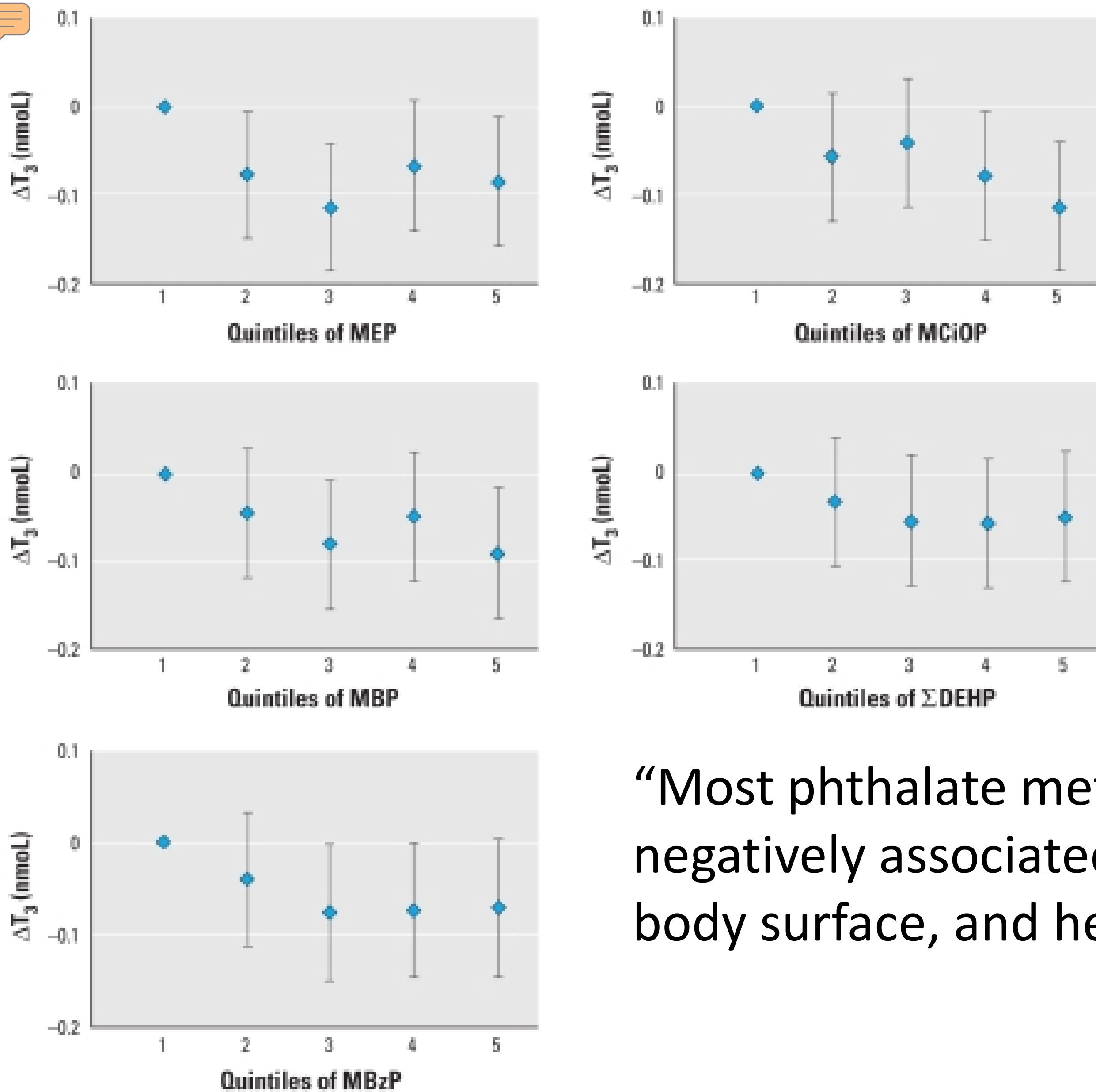
Phthalate Risk Assessment 2008

# Relationship between Phthalate Metabolites & Thyroid Hormones in kids (4-9 yrs old)

Boas et al. 2010 Environ Health Perspec 118:1458-1464.




“Most phthalate metabolites were negatively associated with height, weight, body surface, and height gain in both sexes.”

Regression coefficients (95% confidence intervals) for a change in total $T_3$ ($\Delta T_3$) associated with quintiles of MEP, MCiOP, MBP, MBzP, and sum of DEHP metabolite concentrations (∑DEHP) (adjusted for sex and age; *n* = 758).

# Consistency between human & rat symptoms

**TABLE 3-2** Comparison of Human Male Reproductive Effects of Concern with Effects of in Utero Phthalate Exposure in Rats

| Human Reproductive Effects with a Possible in Utero Origin | Effects of in Utero Phthalate Exposure in Rats |
|---|---|
| Infertility | √ |
| Decreased sperm count | √ |
| Cryptorchidism | √ |
| Reproductive tract malformations | √ |
| Hypospadias | √ |
| Testicular tumors[a] | √ [a] |

[a]Testicular tumors in rats are Leydig-cell-derived, not germ-cell-derived as in humans.

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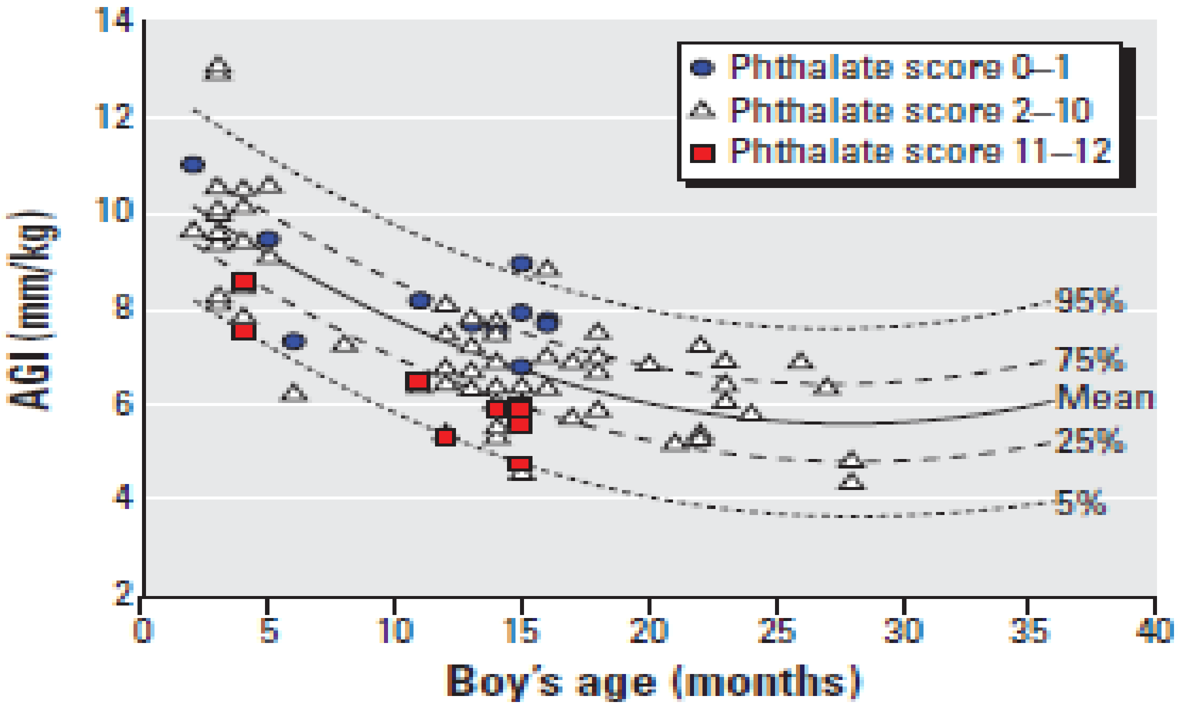


Shorter than expected anogenital distance in boys 2-36 months old significantly related to urinary phthalate (metabolite) concentration

**Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).**

**Table 7.** Concentrations of four phthalate metabolites in three groups of women (ng/mL).

| Monoester metabolite | Percentile | This study: Short AGI | This study: Others | NHANES[a] |
|---|---|---|---|---|
| MBP | 50th | 24.5 | 12.1 | 30.0 |
| | 75th | 44.8 | 28.0 | 59.5 |
| MBzP | 50th | 16.1 | 7.2 | 16.0 |
| | 75th | 27.5 | 17.8 | 35.8 |
| MEP | 50th | 225 | 90.4 | 174 |
| | 75th | 551 | 281 | 425 |
| MiBP | 50th | 4.8 | 2.1 | —[b] |
| | 75th | 12.1 | 4.3 | —[b] |

[a]Females only (CDC 2003). [b]MBP in the NHANES analysis includes both MBP and MiBP; in this study these metabolites were measured separately.

Swan et al. 2005 Environ Health Perspec 113(8):1056-1061

# Phthalate Syndrome

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Phthalate Risk Assessment 2008

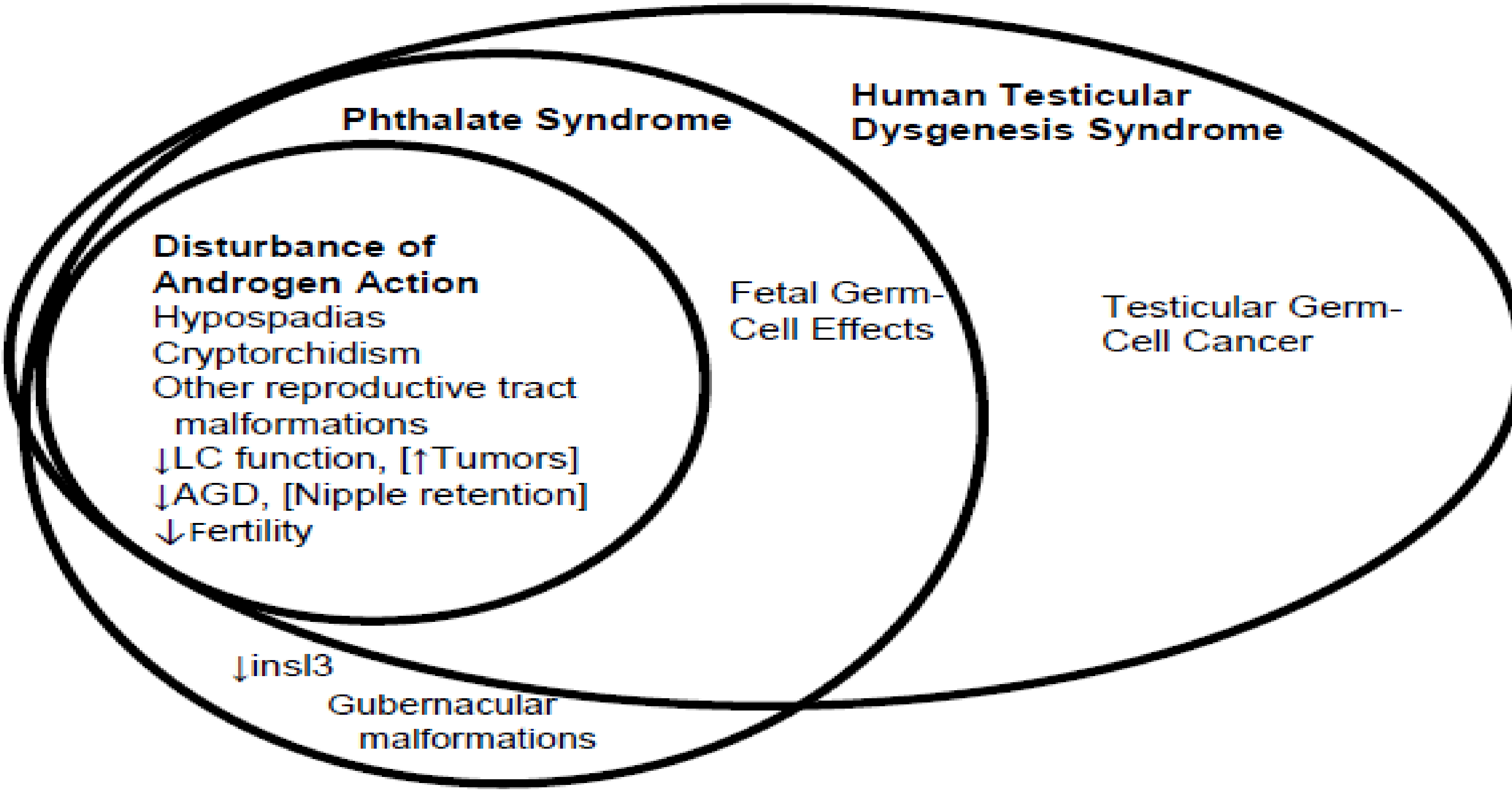


**FIGURE S-1** Relationship of phthalate syndrome in rats to effects associated with agents that perturb androgen action and produce androgen insufficiency and to the hypothesized testicular dysgenesis syndrome in humans. Outcomes in brackets are restricted to findings in experimental animals. AGD, anogenital distance; insl3, insulin-like factor 3; LC, Leydig cell; ↑, increase; and ↓, decrease.

# Margin of Exposure

**The estimated 95th percentile of the population exposure distribution is 0.0077 mg/kg/day**

**Margin of Exposure**

NOAEL = 30 mg/kg/day

MOE = 30/0.0077 = 3896

**Comparison with RfD**

Proposed RfD = 0.3 mg/kg/day (UF 100)

MOE = 0.3/0.0077 = 38.96

Clewell 2009

# Outline

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# Regulation & Policy

Individual Level

- Minimize phthalates in dust?
- Minimize phthalate products in home?

Chemical Management

- Risk management of particular phthalates? E.g., DEHP in kids toys

Industry

- What chemicals should be produced?

Societal Level

- Healthy kids living in healthy homes & playing outside
- Chemical use

# Canadian Environmental Protection Act

- DEHP (1994) declared toxic
- DBP (1994) OK
- BBP (2000) OK
- DnOP (1993, 2003) insufficient info
- DiNP & DiDP – not assessed

# Regulations

EU & USA

- DEHP, BBP, DBP, DiNP, DiDP, DnOP banned from soft kids toys & childcare products

EU

- Banned DEHP & DBP in cosmetics, restrictions in products coming into contact with food

Canada

- Restrict use of DEHP & DiNP in products used by kids 0-4 yr intended to be mouthed
- Imports??
- Hazardous Products Act, June 2009 proposal to harmonize with US & EU

# Consumer Action in Market Place



Largely imported materials, goods & products

# Summary

1. What are phthalates, what are their uses, what products are they in? everywhere, in many products!
2. How do phthalates move around the environment? (fate) not persistent, relatively volatile
3. How are we exposed to phthalates? food (from packaging), consumer products, other??
4. What are some of the toxicological concerns about this exposure? Endocrine disruptor, "phthalate syndrome"
5. How do we minimize our exposure?
   - Individual action
   - Policies & regulations