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Gut Reactions:

Can gut microbial and environmental chemical interactions contribute to the obesity and diabetes epidemic ?

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Overview

- Global rates of obesity and Type II diabetes have increased dramatically
- Multiple environmental factors may contribute to these diseases:
  - Gut microbes, especially in the colon
  - Environmental chemicals (called obesogens and diabetogens)
- Studies suggest that person to person variation in the "gut microbiome" affects the toxicity / metabolism of many pharmaceuticals
- The majority of the environmental chemicals identified as "obesogens" or "diabetogens" also may be metabolized by gut microbes

Overview

- Interindividual variation in gut microbes may affect the absorption, distribution, metabolism, and excretion (ADME) of these chemicals
- Therefore, we propose that this interindividual variation in gut microbes may affect the body burden of obesogenic and / or diabetogenic chemicals
- SO, whether environmental chemicals affect obesity or diabetes may depend on your “gut reactions”

Global rates of obesity and diabetes

The Obesity and Diabetes Epidemics

- U.S. obesity rates rose from 14.5% to > 33% over in the last three decades (Flegal 1998, Flegal 2010)
- Body Mass Index (BMI) and diabetes incidence have risen in many areas world-wide (Finucane 2011, Danaei 2011
- Environmental factors may be important contributors to both of these diseases

The numbers

- The human "microbiome" has 3.3 million genes and 99% are of bacterial origin (Quin 2010)
- This is 150 times BIGGER than the human genome
- While many microbial species are shared, there is much variation in the microbial genes found between individuals ("interindividual" variation)
- Surprising, we know very little about the function of the microbiome

Gut microbes and obesity

- Studies of lean and obese twins suggested a "core" microbiome (Turnbaugh, 2009, and 2009a)
- A different study did not see specific microbial populations associated with obesity (Arumugam 2011)
- A study of intestinal by-pass patients suggested changes in obesity may affect gut ecology (Bjorneklett 1981)
- Studies in germ-free animals suggested a possible role of gut ecology in obesity (Backhed 2007, Fleissner 2010)

Gut microbes and obesity

- The role of microbes may include influencing:
  - Energy extraction (Turnbaugh 2006)
  - Fat storage regulation (Backhed 2004)
  - Endotoxemia-induced inflammation (Cani 2007, Cani 2008)
  - Dietary interactions (Backhed 2007, Fleissner 2010)
  - Satiety factors (Cani 2009, Ravussin 2011, Sanz 2010
  - Immune function (Vijay-Kumar 2010)
- Ratios of microbial families
  - Some, but not all studies in obese and lean humans have found differences in the ratios of Bacteroidetes to Firmicutes (Ley 2006, Armougom 2009)

Gut microbes and diabetes

- Bariatric surgery patients show dramatic changes in gut ecology (Furet 2010) as well as glycemic control (Ahima 2011, Meijer 2011)
- Antibiotic treated mice obese (ob/ob) mice have improved glucose tolerance (Membrez 2008)
- Type I diabetes – few studies done to date
  - Certain bacterial toxins can damage pancreatic cells (*Streptomyces toxin,* bafilomycin A1, Myers 2003).

Environmental Chemicals

- **Obesogens** can affect the delicate balance of controls in lipid metabolism, fat generation, and energy balance (see pg. 14-17 of review)
  - Tributyl tin is a developmental obesogen in animal studies; little information on current human exposures
  - PFOA, emerging evidence as developmental obesogen
  - DES, nonylphenol, and genestein (estrogenic compounds) show some evidence of affecting adipose or insulin pathways, often at low doses
  - Bisphenol A shows mixed evidence as an obesogen in rodent studies and weak evidence in human studies

Environmental Chemicals

- **Diabetogens** (see pgs. 13-14 of the review)
  - Arsenic is a known diabetogen (global associations)
  - PCBs, DDE, dioxins, chlordane, HCB, brominated flame retardants, and variety of other pesticides used in agriculture, have been associated with higher incidences of Type II diabetes in human epidemiological studies
  - PFOA (perfluoroctanoic acid) shows mixed evidence for diabetes risk in large-scale human studies (Ludin 2009, MacNeil 2009)

Disposition of Environmental Chemicals

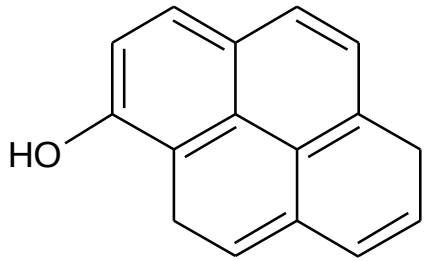
- Microbial affects on Absorption, Distribution, Metabolism and Excretion (ADME)
  - Change pollutant bioavailability
  - Direct “activation”
  - Production of endogenous toxins
  - Alter expression of host detoxification proteins
  - Change enterohepatic cycling

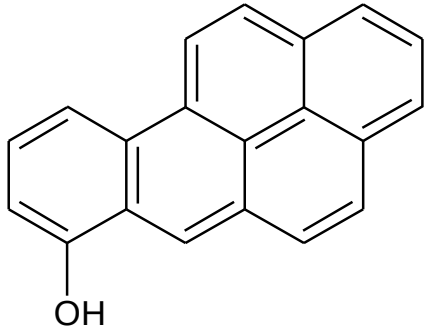
Disposition of Environmental Chemicals

- Changes in bioavailability
  - Leaky gut
    - Different microbes have different affects on permeability
  - Change in chemical form
    - Microbes can convert insoluble forms to bioavailable and bioactive forms (e.g. arsenic)

Disposition of Environmental Chemicals

- Direct activation by gut microbes
  - Gut microbes can convert PolyAromatic Hydrocarbons (PAHs) into estrogenic metabolites



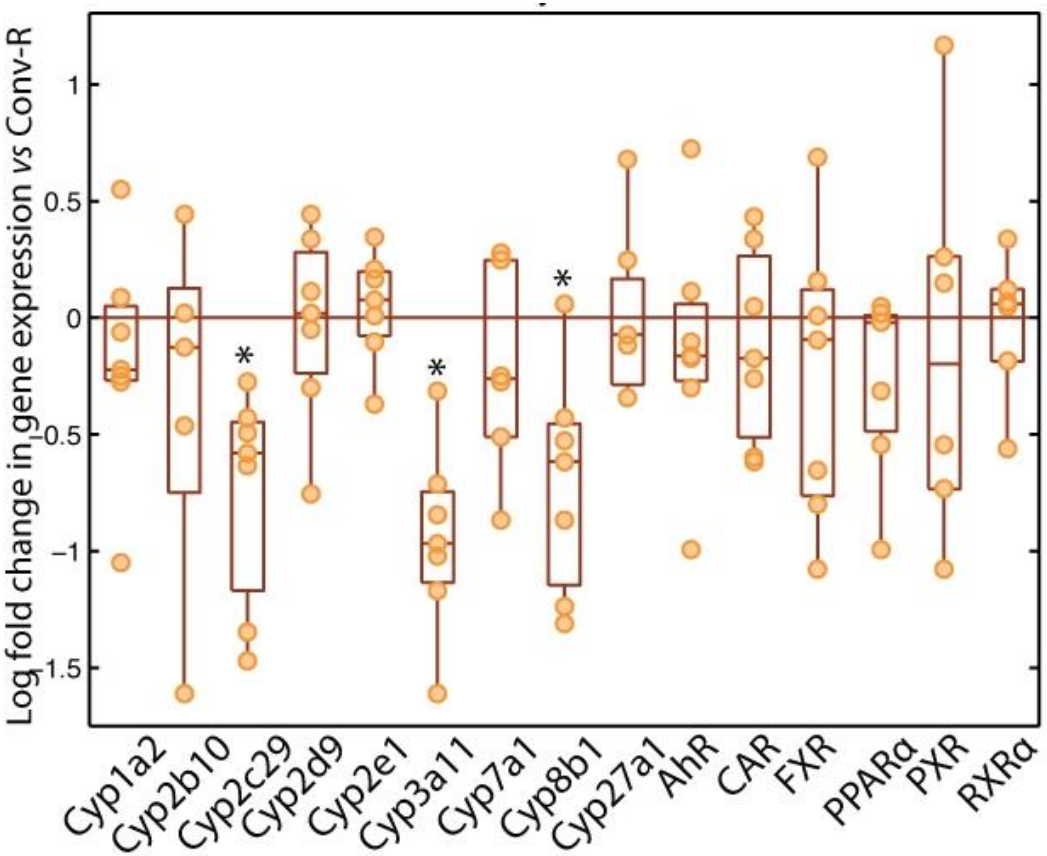


Van de Wiele 2005

Disposition of Environmental Chemicals

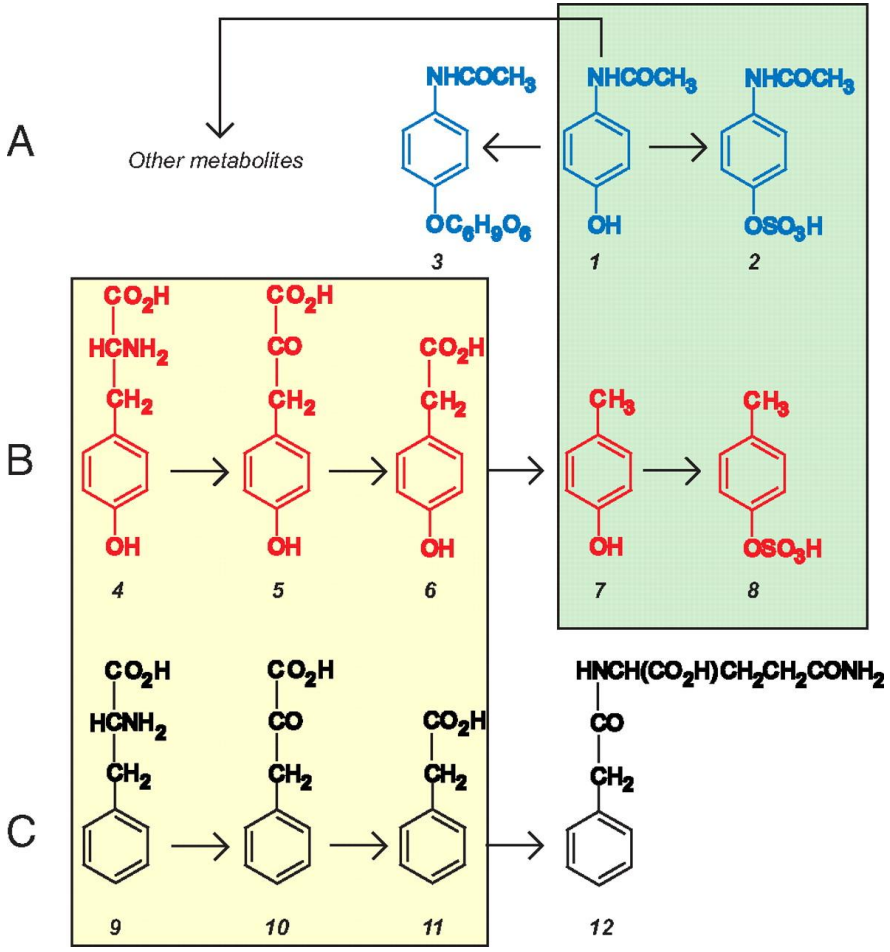
- Changes in host detoxification enzymes

Claus et al. 2011



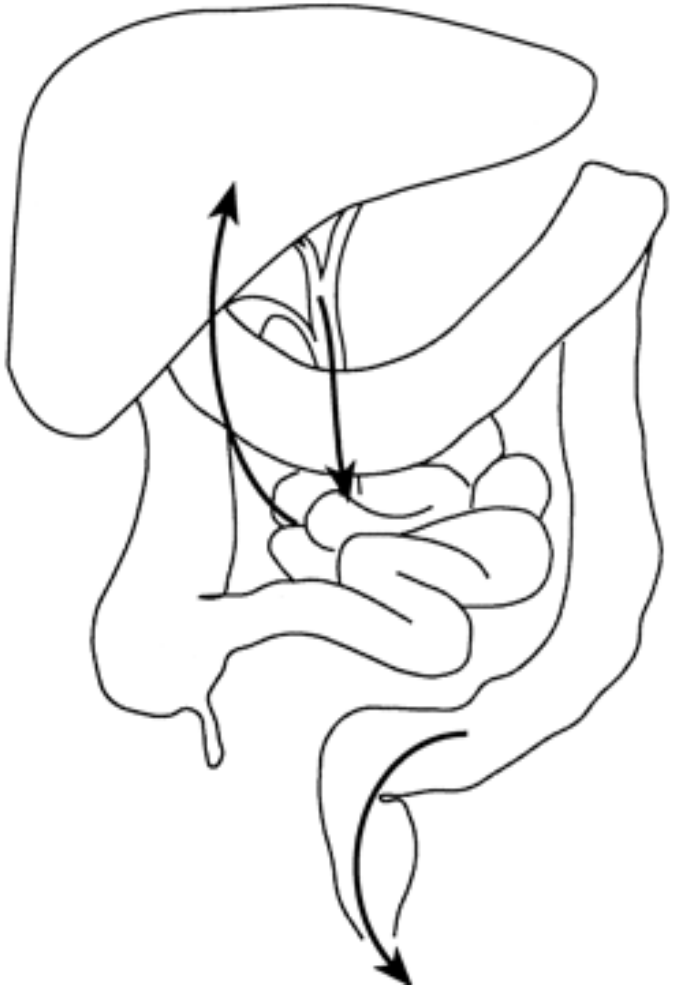
Disposition of Environmental Chemicals

- Production of endogenous toxins
  - Normal amino acids may be “activated” by certain gut microbes
  - This can rob the host of important detoxification capacity



Clayton et al. 2009

Disposition of Environmental Chemicals



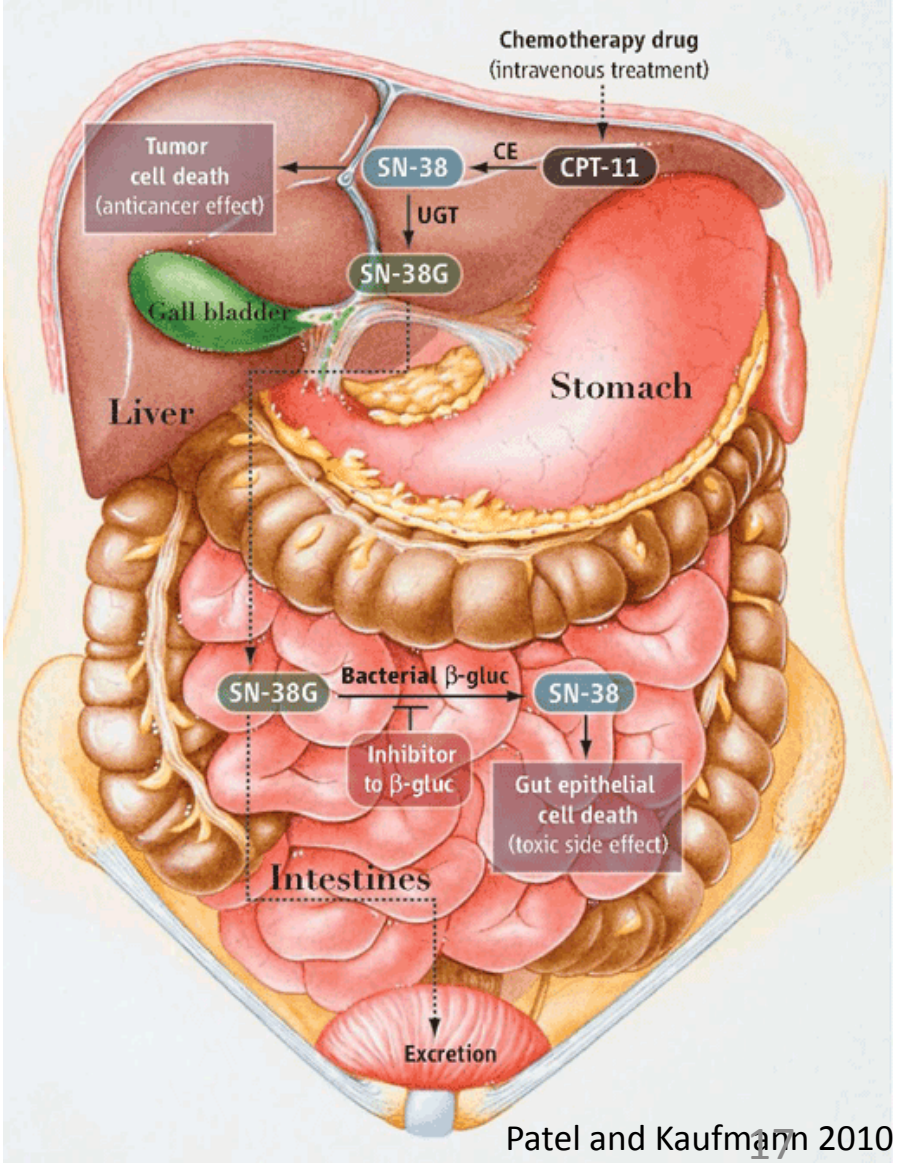
http://www.biology-online.org/

Altered Enterohepatic Cycling

- Ingestion followed by absorption in the small instestine
- Transport to the liver for 1st pass metabolism
- Metabolites secreted into the bile
- Metabolites reabsorbed from intestines or excreted.
  - e.g. Flame Retardants (Meijer 2006)

Gut Reactions can Produce Toxicants

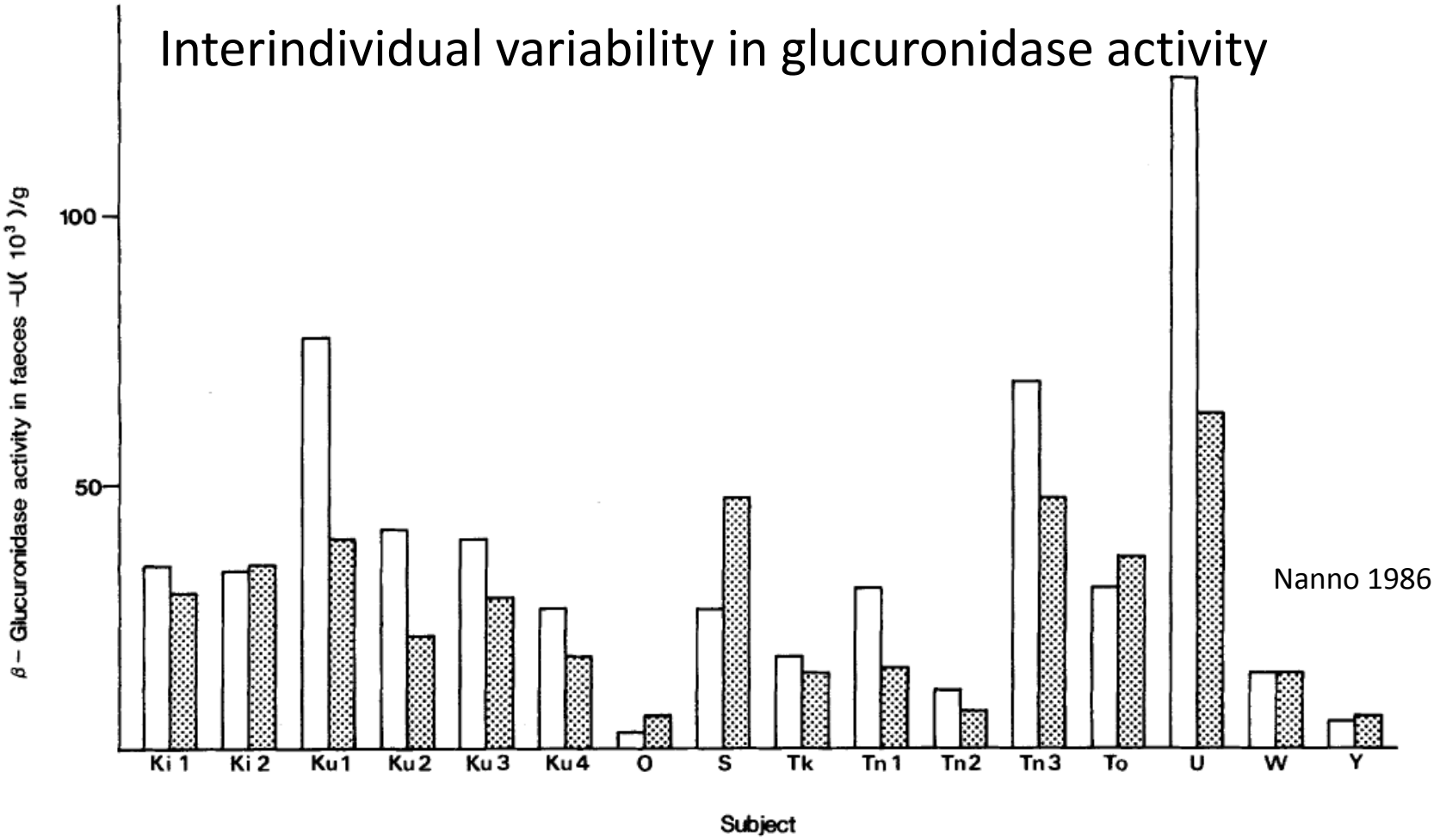
- The cancer prodrug CPT-11 is activated by the liver to SN-38.
- SN-38 kills tumors, but is glucuronidated (SN-38G)and excreted
- Gut microbes cleave the sugar from SN38G, producing SN38 which is toxic to gut epithelia



Patel and Kaufmann 2010

Disposition of Environmental Chemicals

Interindividual variability in glucuronidase activity



Nanno 1986

Figure. β-Glucuronidase activity in fresh human faeces. Each sample of faeces was diluted with the anaerobic diluent and its activity was assayed with p-nitrophenyl glucuronide (□) and phenolphthalein glucuronide (□). Numbers against subjects indicate that samples were collected from the same subjects on different days.

Chemicals that undergo Enterohepatic Circulation & Phase II metabolism*

Non-Pesticide POPs	Pesticides	Metals	Other Chemicals
Polybrominated flame retardants	Alachlor	Arsenic	Bisphenol A*
PCBs*	Aldrin*	Cadmium	DES*
Dibenzo-dioxins*	Amitraz*	Mercury	Genestein*
Dibenzo-furans*	Chlorpyrifos*	Tributyl tin	Nonylphenol*
	DDD, DDE, DDT*		Octylphenol*
	Dieldrin*, Endrin*		Some Phthalates*
	Heptachlor*		
	Hexachlorobenzene*		
	HCH, gamma & beta*		
	Trichlorofon*		

* Indicates chemicals that are glucuronide Phase II conjugates.

Data extracted from Supplemental Table 1 in Snedeker and Hay's 2011 EHP review article, http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.1104204#Supplemental%20Material

Conclusions

- The potential exists for gut microbes to affect the disposition of many obesogenic and diabetogenic environmental chemicals
- We know almost nothing about the interindivual variation of gut microbes
- Understanding and controlling gut microbes will be key to combating obesity and diabetes

Talk based on our review:

Do Interactions Between Gut Ecology and Environmental Chemicals Contribute to Obesity and Diabetes?

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http://dx.doi.org/10.1289/ehp.1104204

Includes a Supplemental Table on the "Phase II metabolism of obesogenic and diabetogenic chemicals." Table can be accessed at: http://ehp03.niehs.nih.gov/article/info%3Adoi%2F10.1289%2Fehp.1104204#Supplemental%20Material

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