



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 (perfluorooctanoic 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



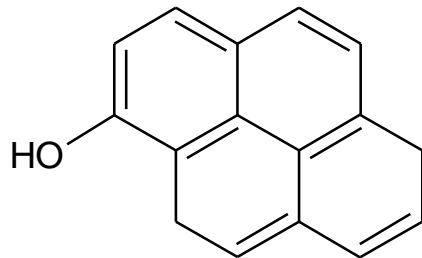
Disposition of Environmental Chemicals

- 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)

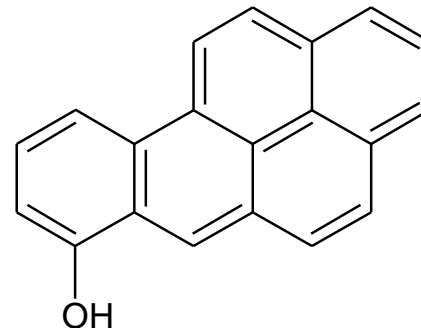


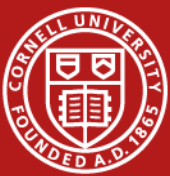
Disposition of Environmental Chemicals

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



Van de Wiele 2005

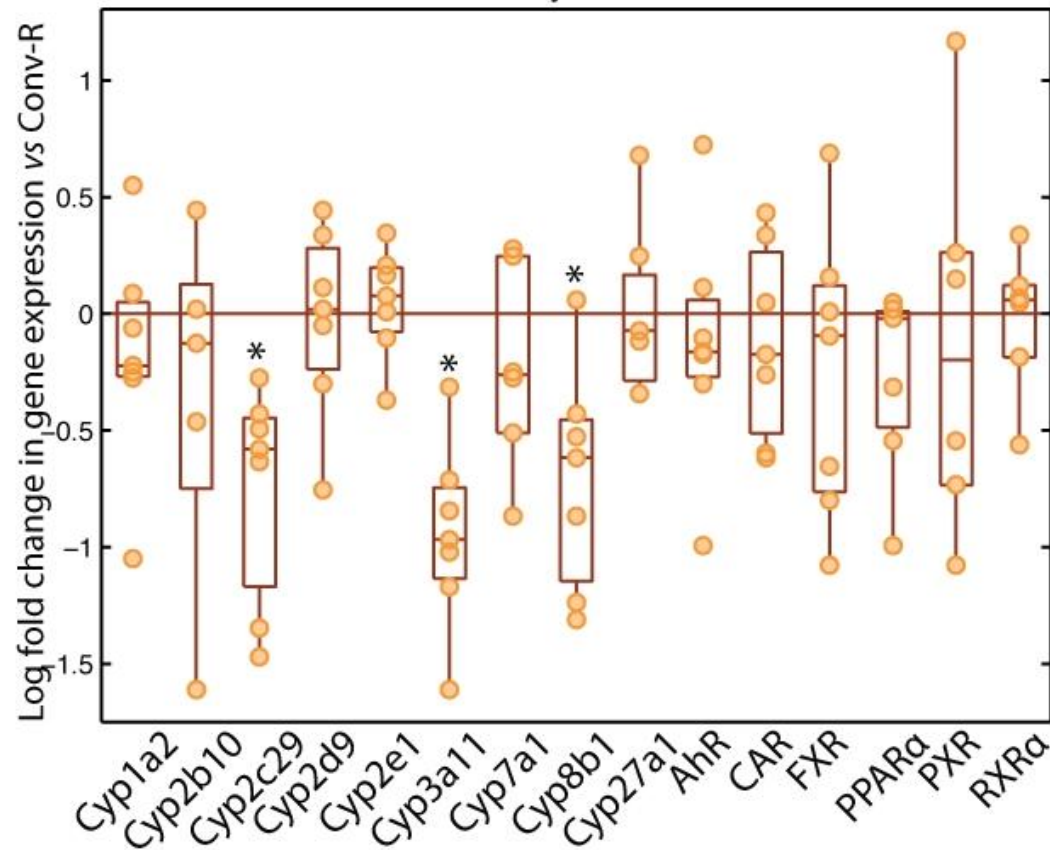




Disposition of Environmental Chemicals

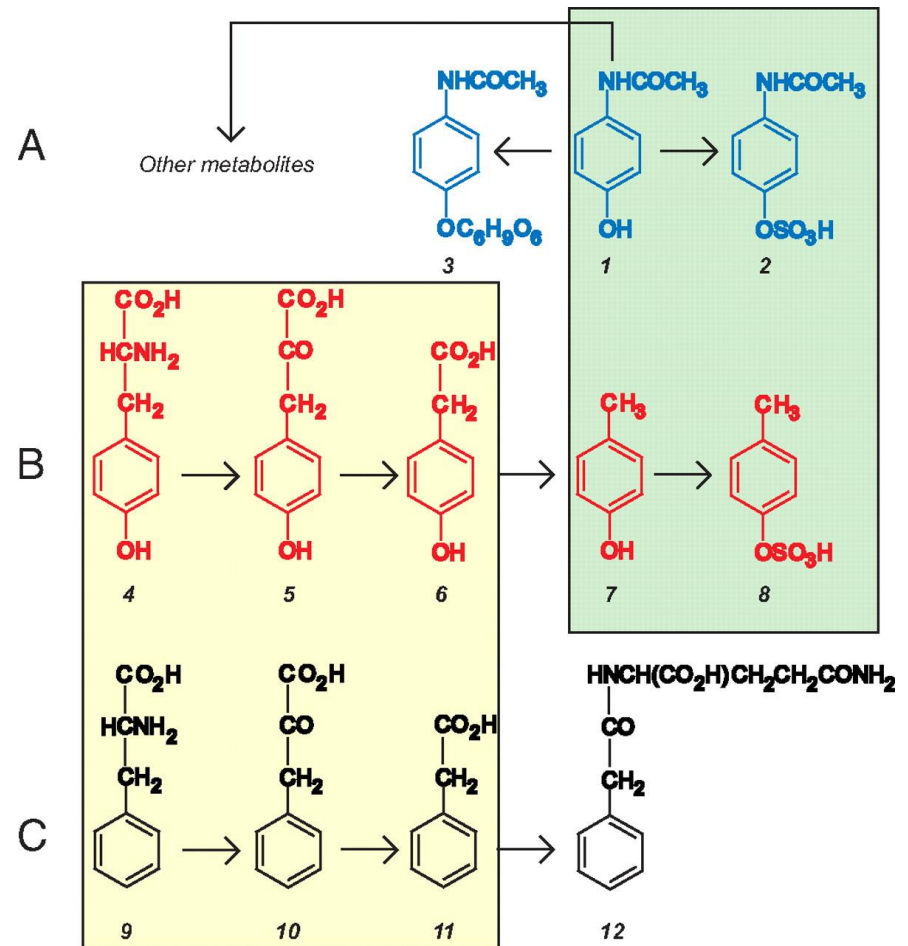
- Changes in host detoxification enzymes

Claus et al. 2011



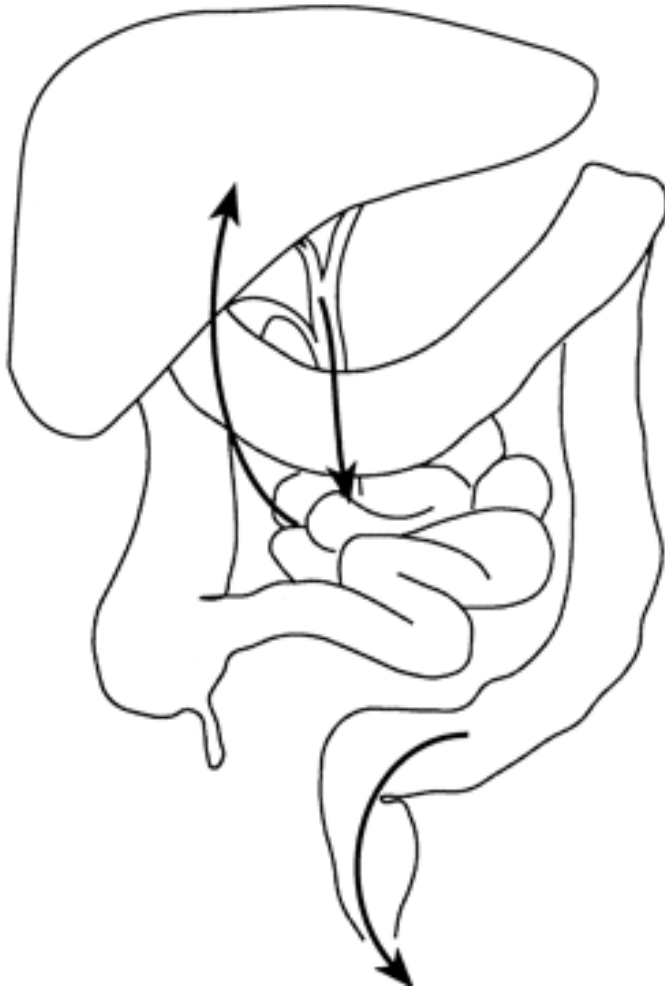
Disposition of Environmental Chemicals

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





Disposition of Environmental Chemicals

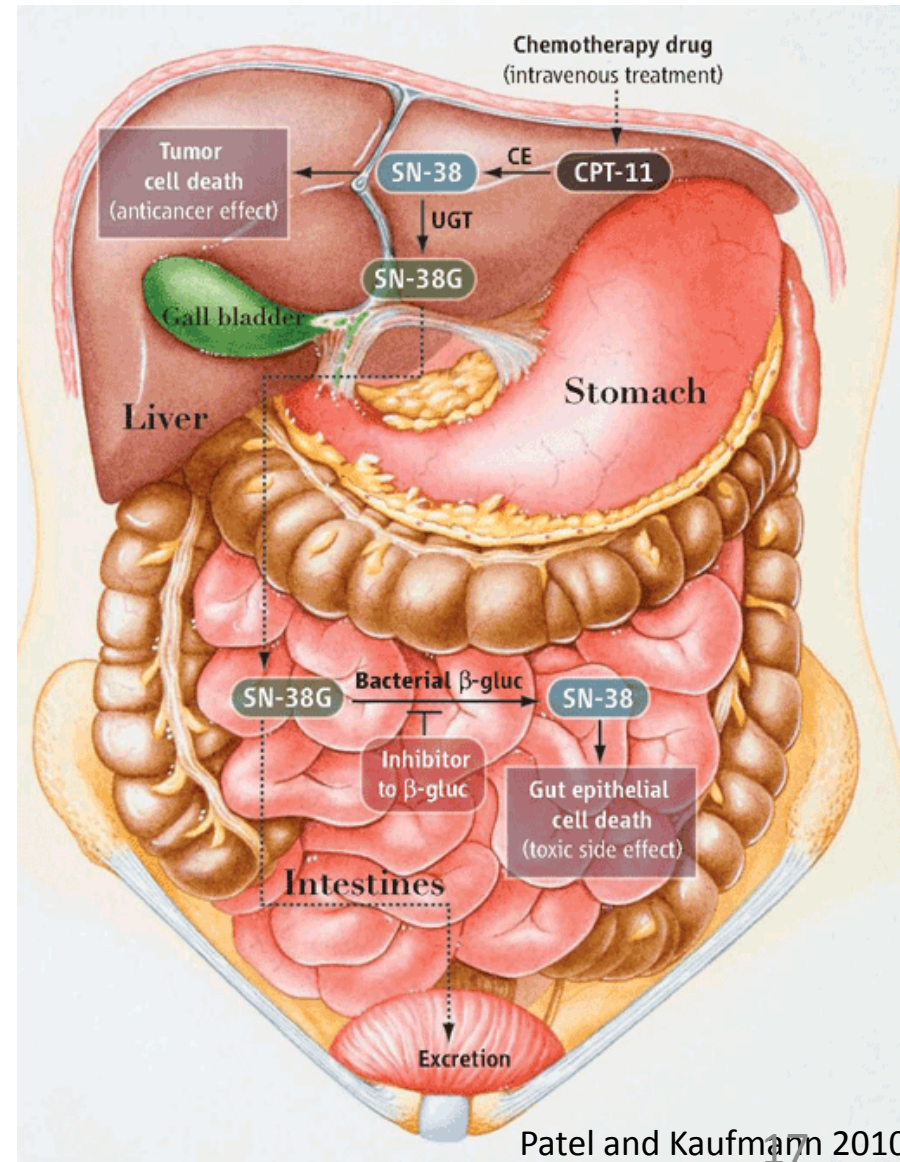


Altered Enterohepatic Cycling

- Ingestion followed by absorption in the small intestine
- 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





Disposition of Environmental Chemicals

Interindividual variability in glucuronidase activity

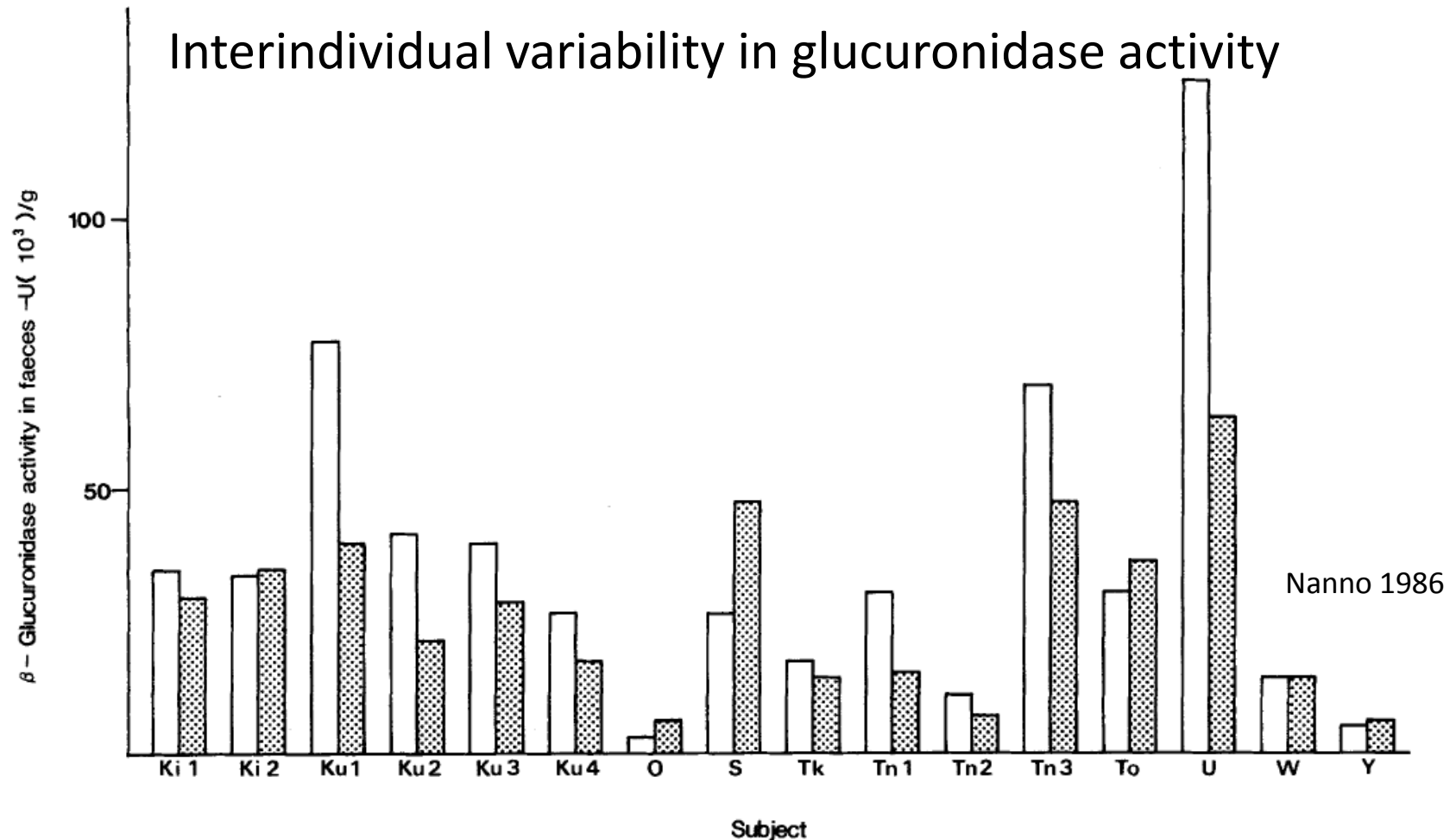
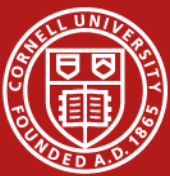


Figure. β -Glucuronidase activity in fresh human faeces. Each sample of faeces was diluted with the anaerobic diluent and its activity was assayed with p-nitrophenyl glucuronide (□) and phenolphthalein glucuronide (▨). Numbers against subjects indicate that 18 samples were collected from the same subjects 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 interindividual 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?

Published Oct. 31, 2011, in *Environmental Health Perspectives*
<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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