# DEVELOPMENTAL FACTORS IN ADULT OBESITY: DIET, ENVIRONMENTAL CHEMICALS AND IMPORTANCE OF ANIMAL MODELS

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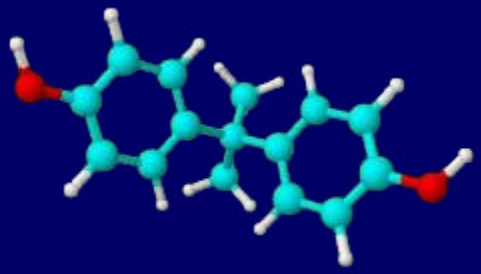
Bisphenol A

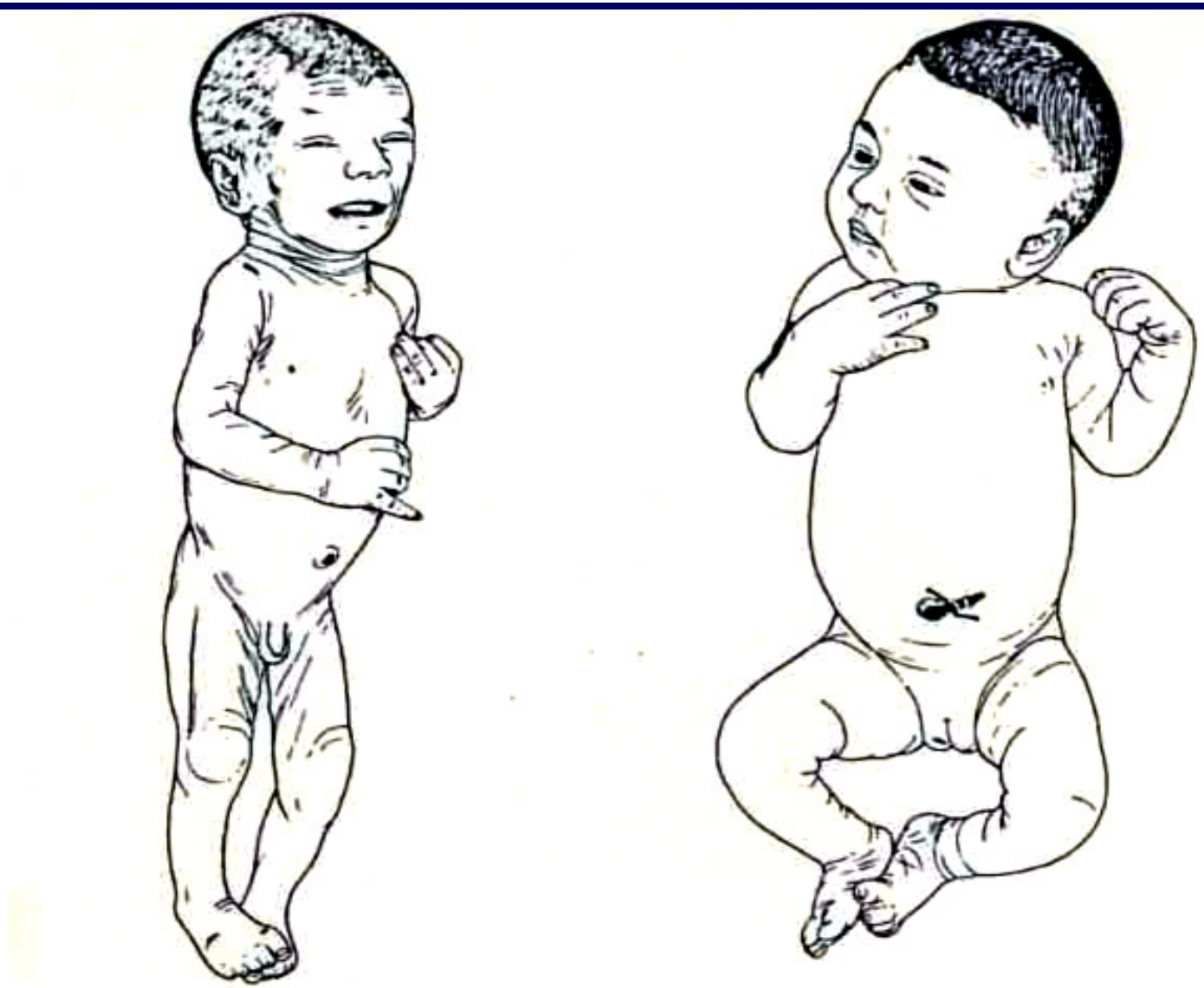


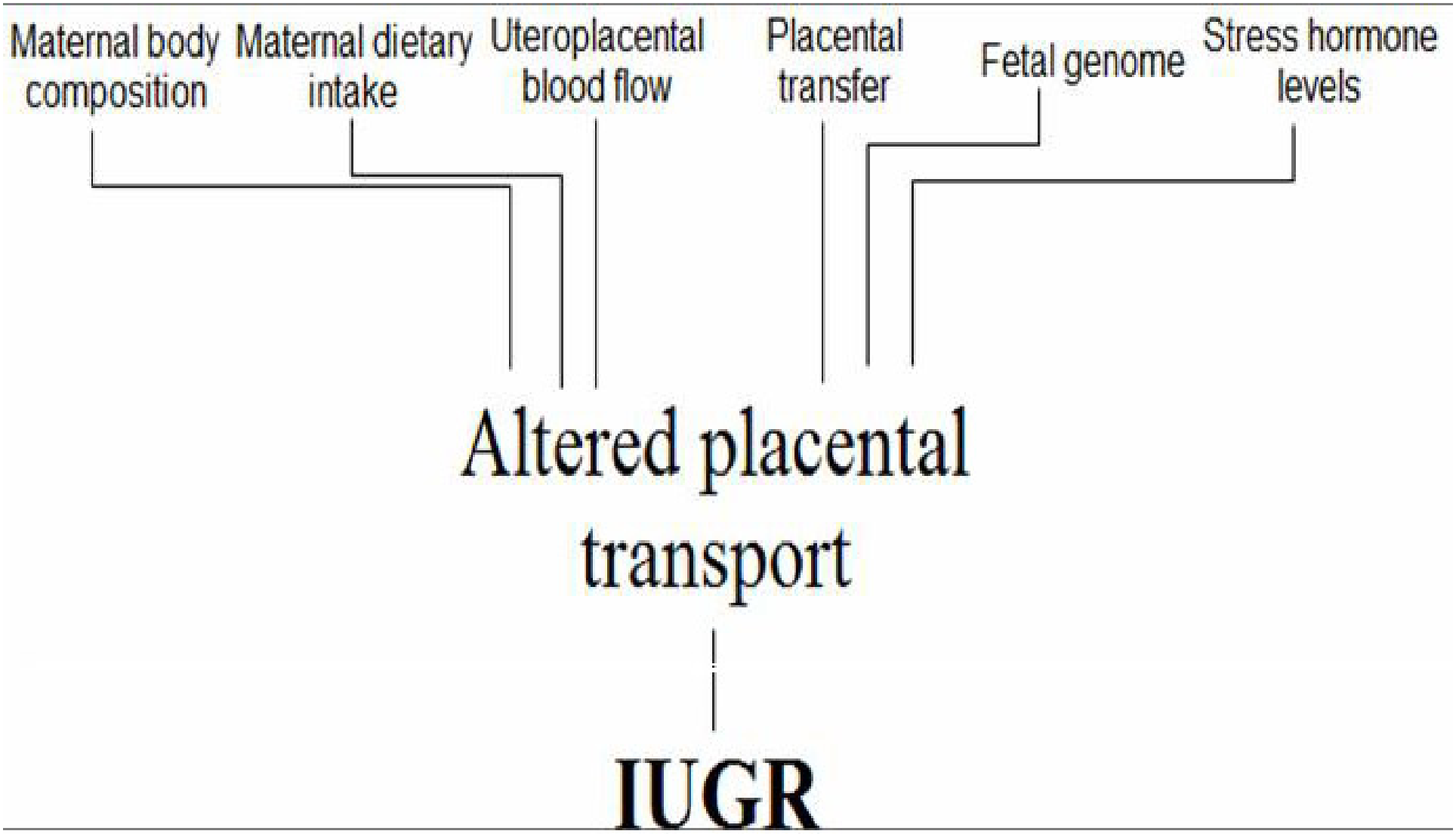
Funded by research grants from the National Institutes of Health (NIH)

**IUGR** **MACROSOMIA**

**(Premature)** **(Maternal Type II diabetes)**

**(Reduced placental blood flow)**

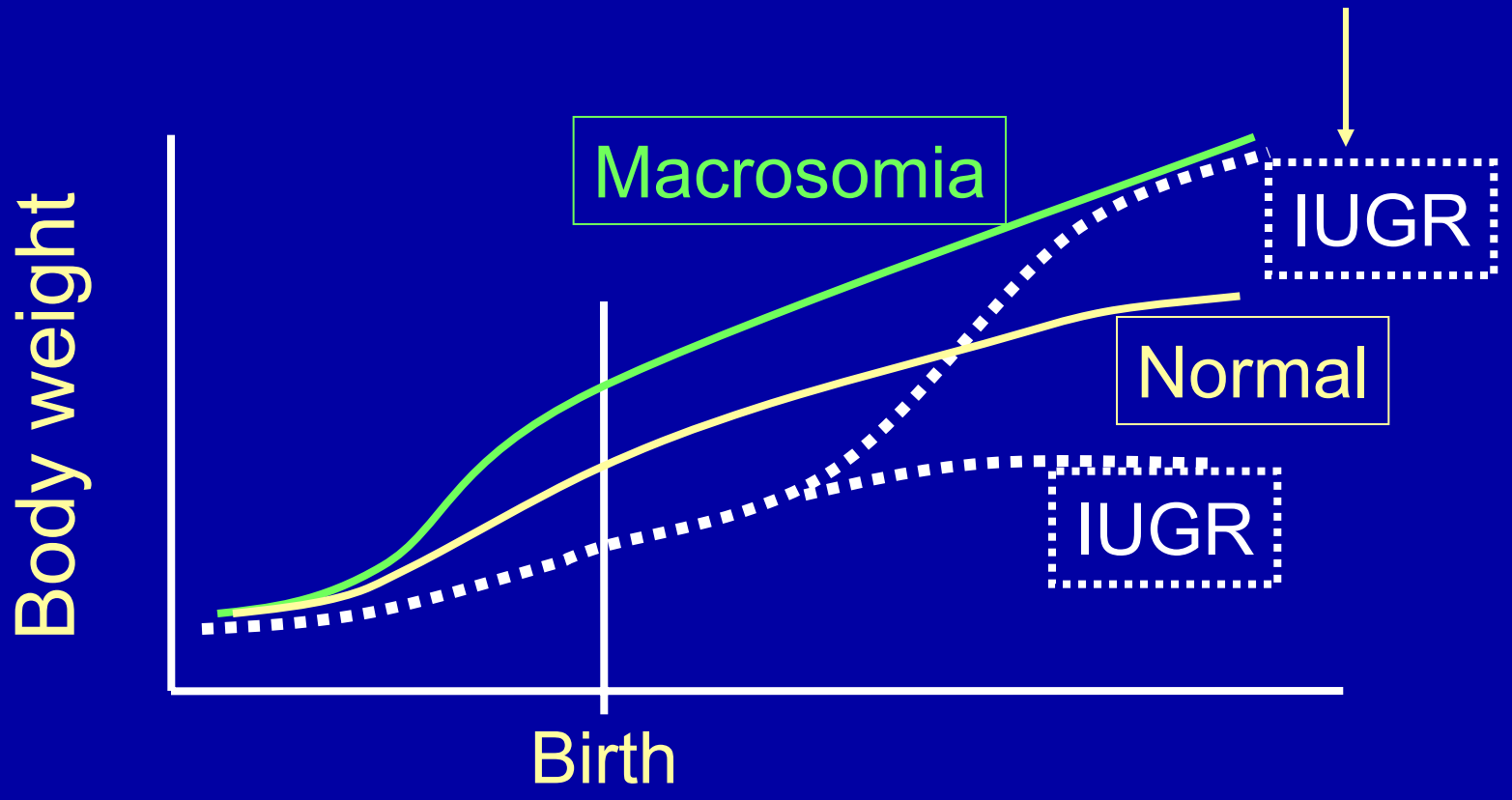





Proposed factors influencing induction of IUGR

- Babies that are overweight at birth are at risk for adult obesity and metabolic disease.
- Some babies with intrauterine growth restriction (IUGR) are at risk for a rapid period of postnatal weight gain, adult obesity and metabolic disease.

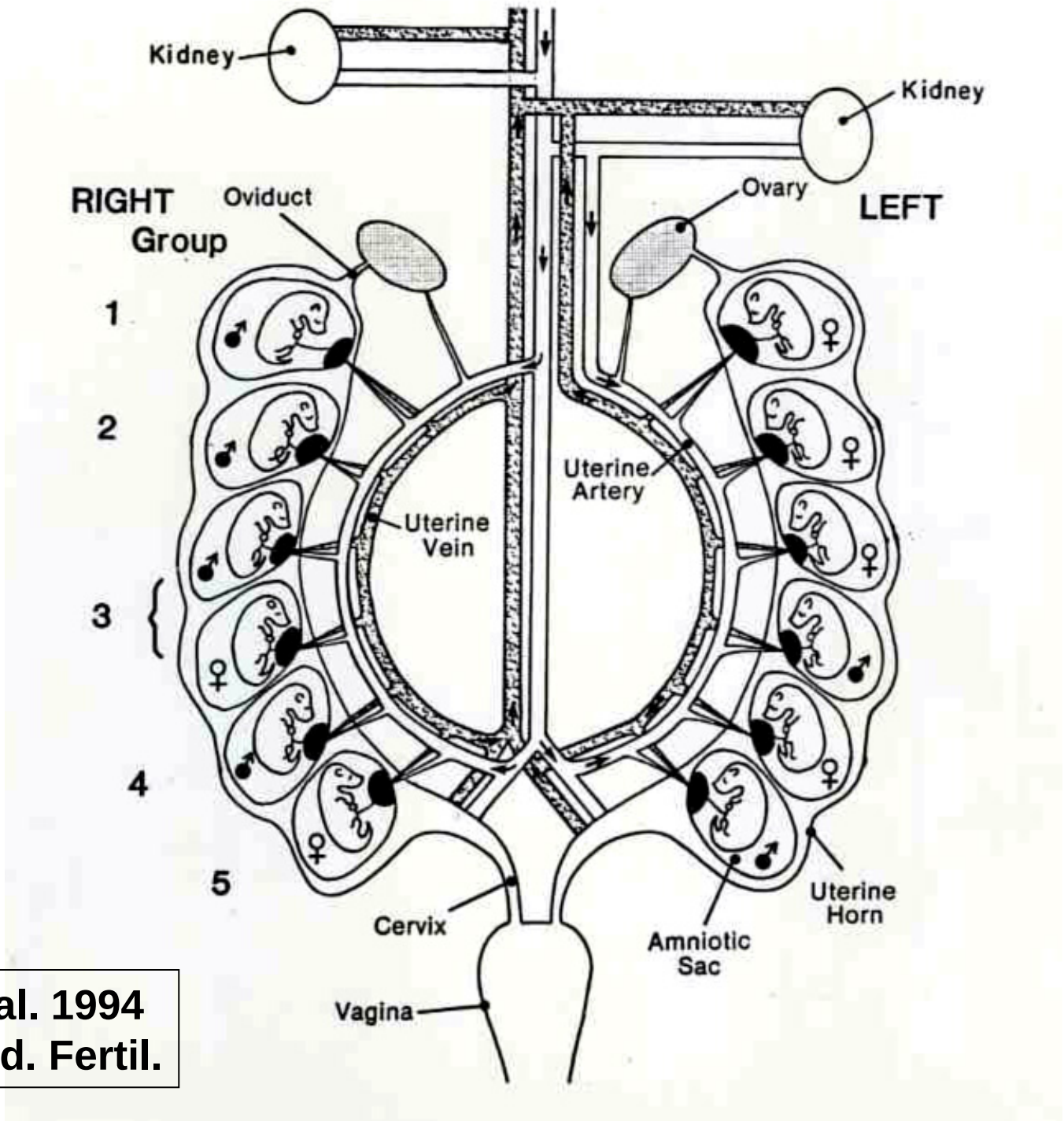
## THRIFTY PHENOTYPE HYPOTHESIS



# EXPERIMENTAL APPROACHES FOR ANIMAL RESEARCH ON THE FETAL BASIS OF METABOLIC SYNDROME

## Treatment of Pregnant Females

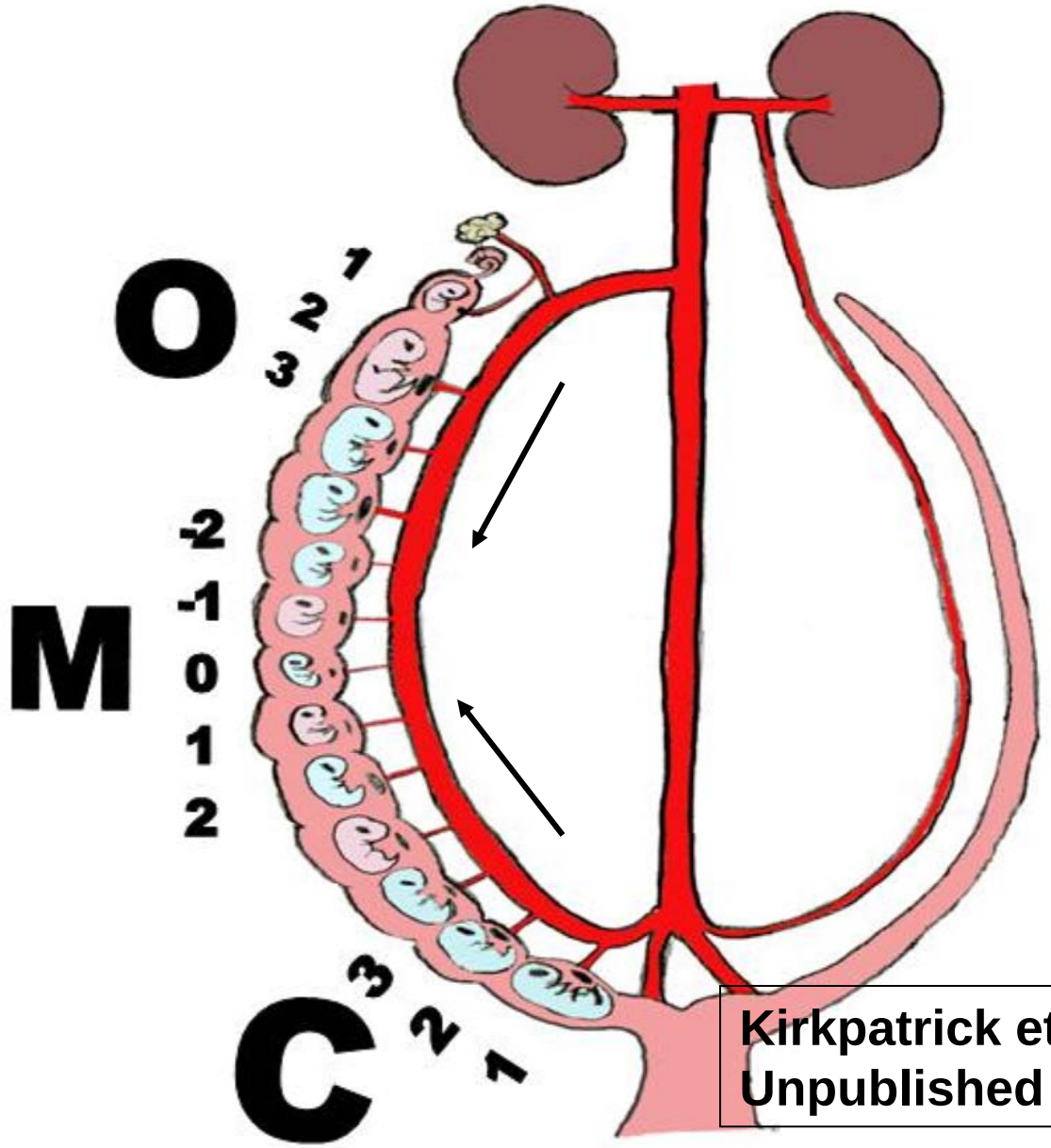
- Caloric restriction
- Protein restriction
- High fat diet
- Exercise
- Dexamethasone administration
- Knockout mice (e.g. 11ß-HSD)
- Environmental chemicals - PLASTIC




**Even et al. 1994**
**J. Reprod. Fertil.**

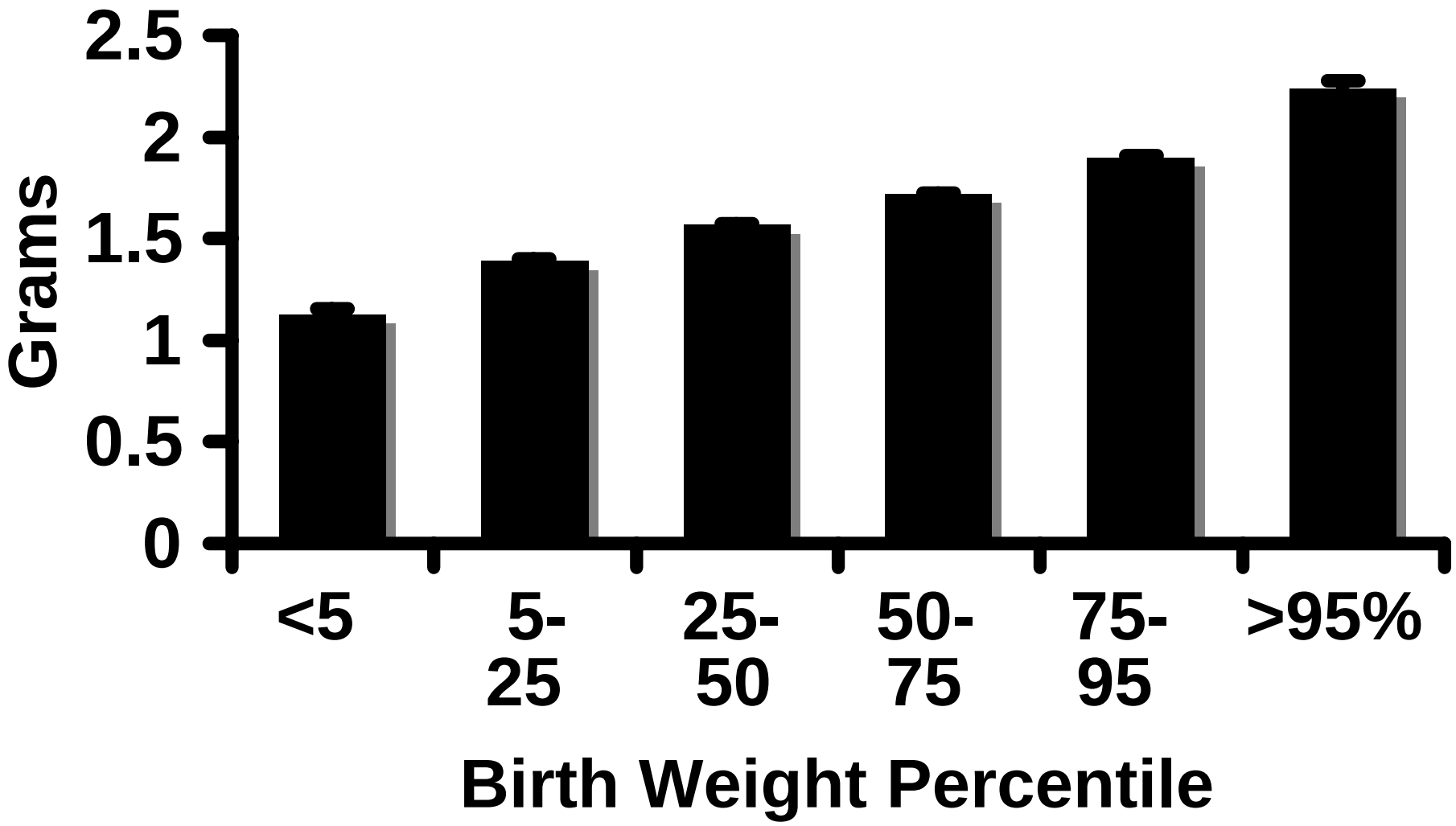
# RADIOLABELED MICROSPHERES

| Uterine Position | Placental Blood Flow |
|---|---|
| O 1 | 315 |
| O 2 | 331 |
| O 3 | 206 |
| M-2 | 208 |
| M-1 | 9.3 |
| M0 | 188 |
| M1 | 273 |
| M2 | 297 |
| C 3 | 313 |
| C 2 | 435 |
| C 1 | 366 |

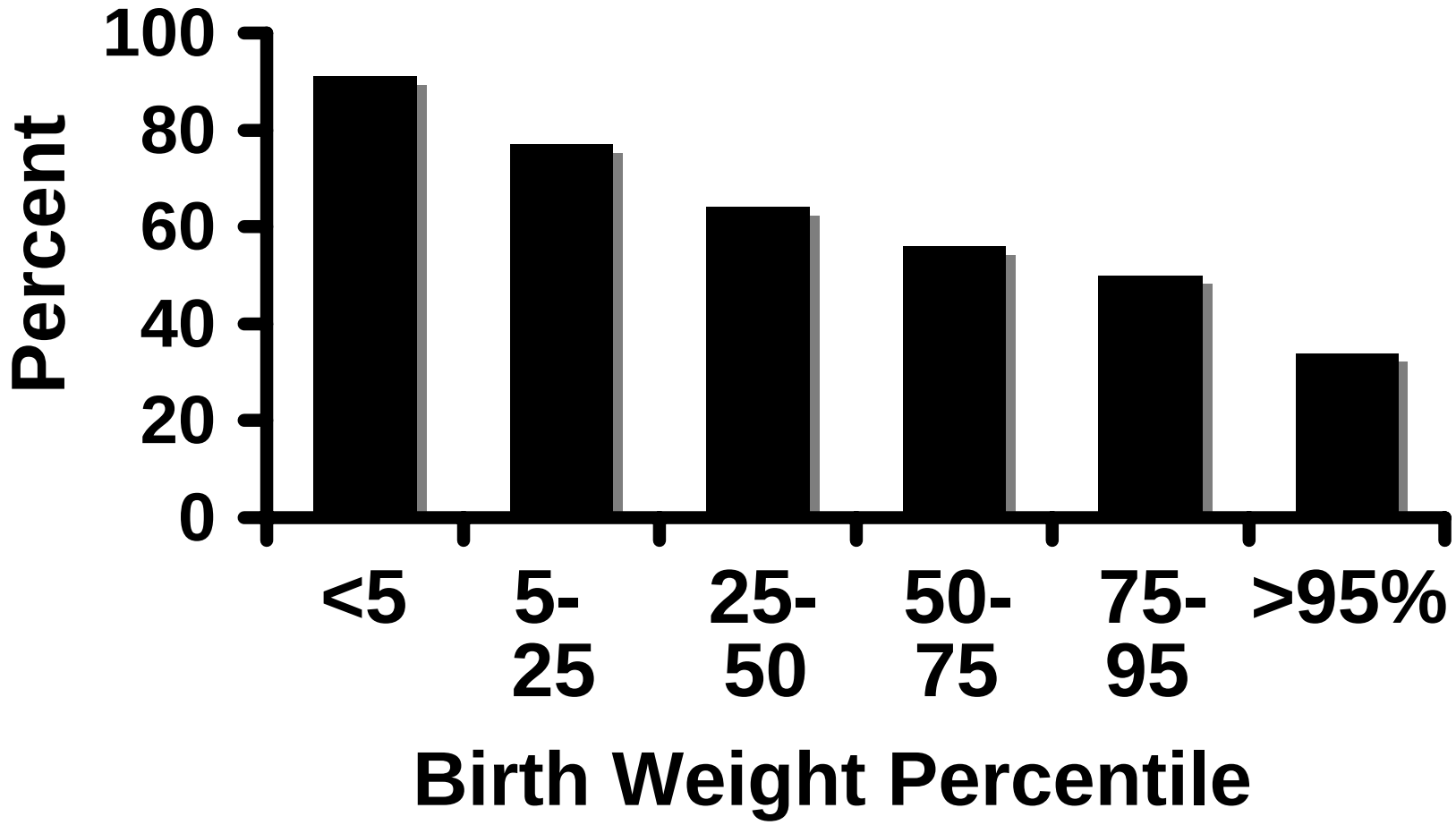


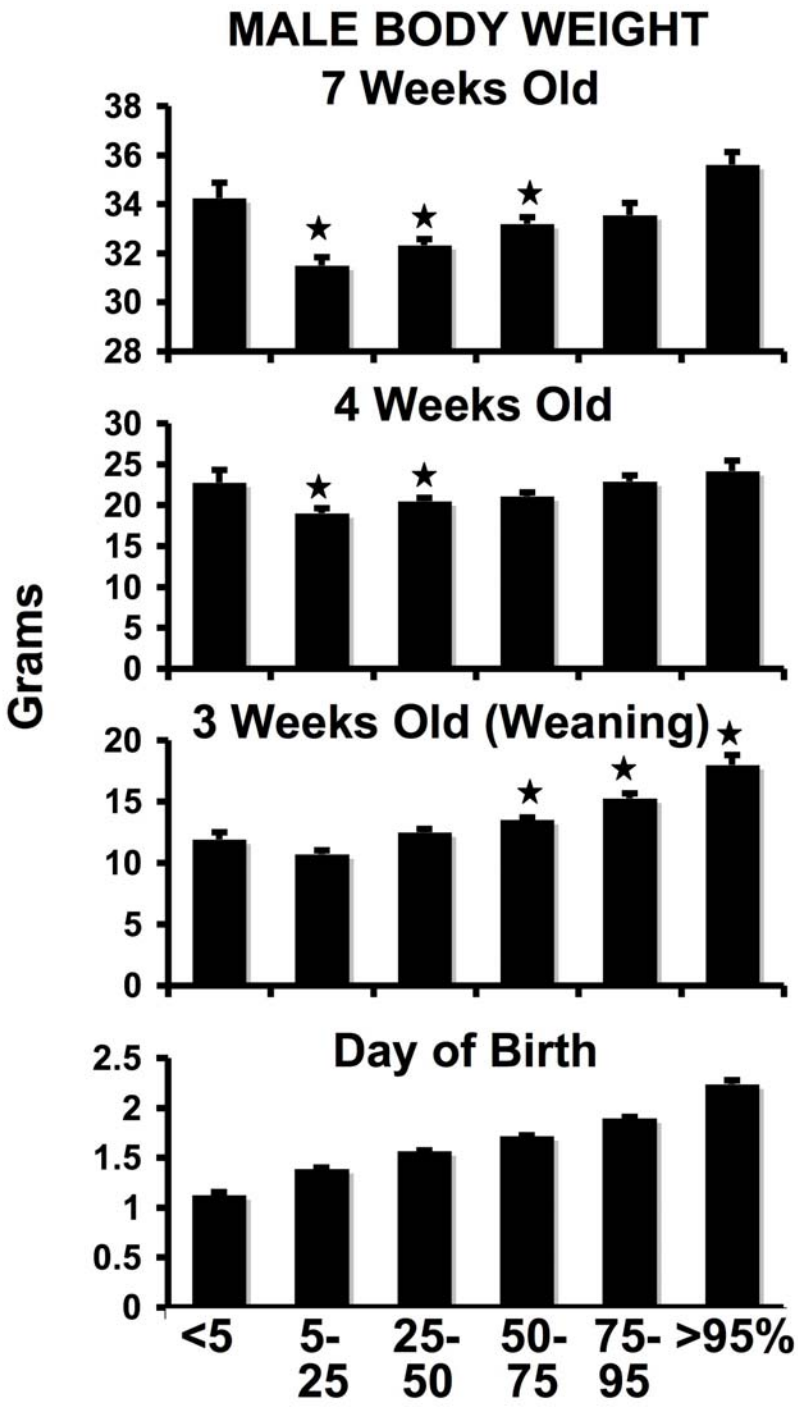

Kirkpatrick et al
Unpublished

# MALE MOUSE BODY WEIGHT AT BIRTH



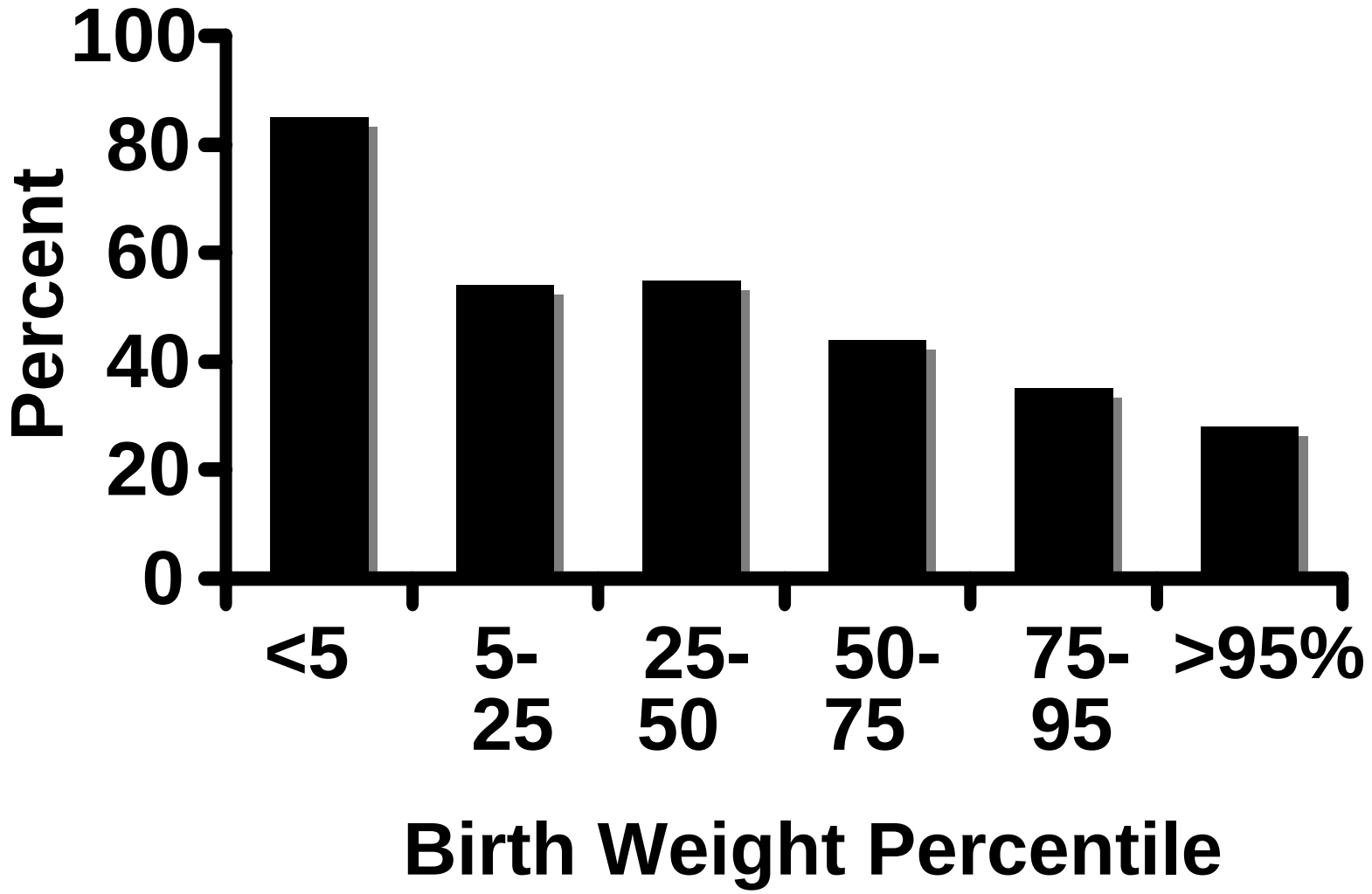
# PERCENT INCREASE IN BODY WEIGHT DURING THE 7 DAYS AFTER WEANING IN MALE MICE

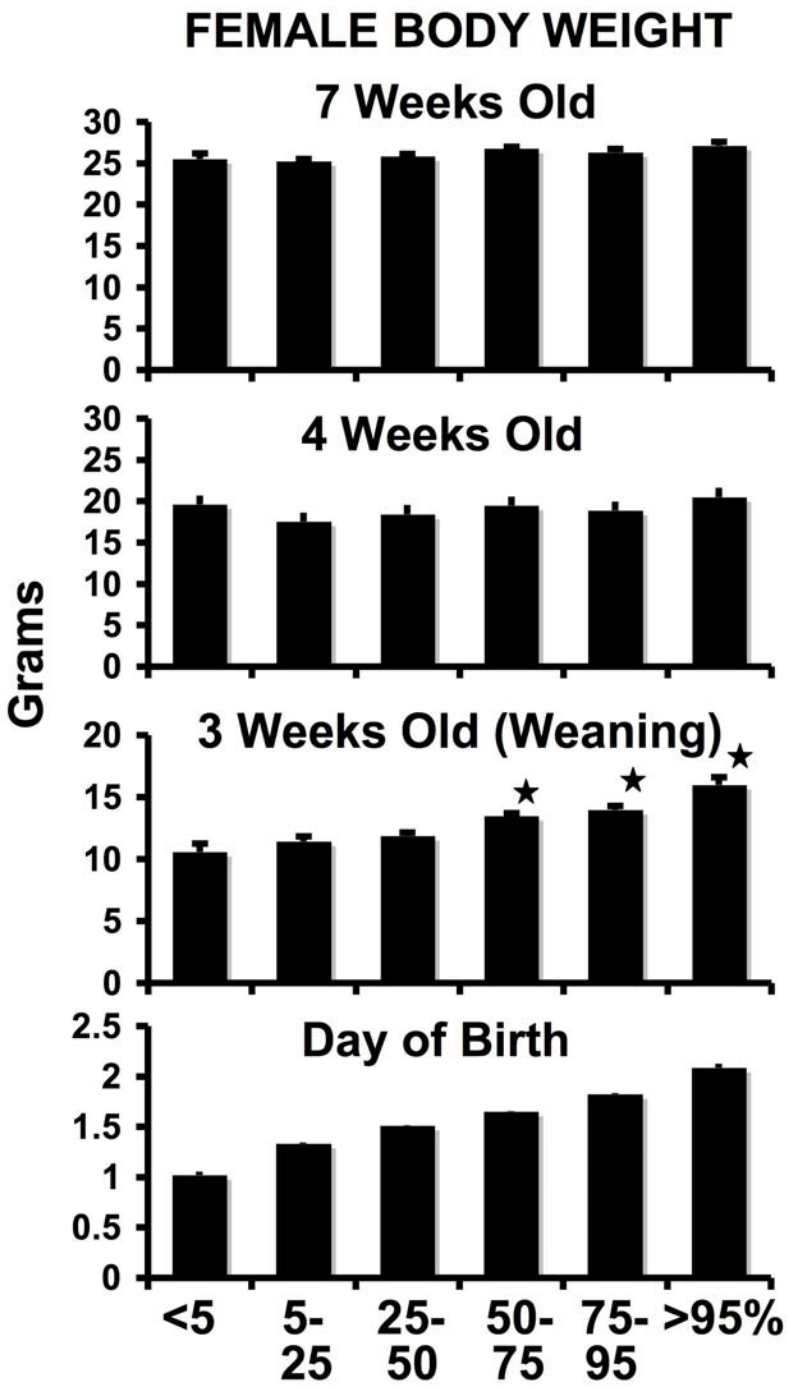



MALE BODY WEIGHT
7 Weeks Old
38
36
34
32
30
28
4 Weeks Old
30
25
20
15
10
5
0
Grams
3 Weeks Old (Weaning)
20
15
10
5
0
Day of Birth
2.5
2
1.5
1
0.5
0
<5
5-25
25-50
50-75
75-95
>95%

N = 294 pups

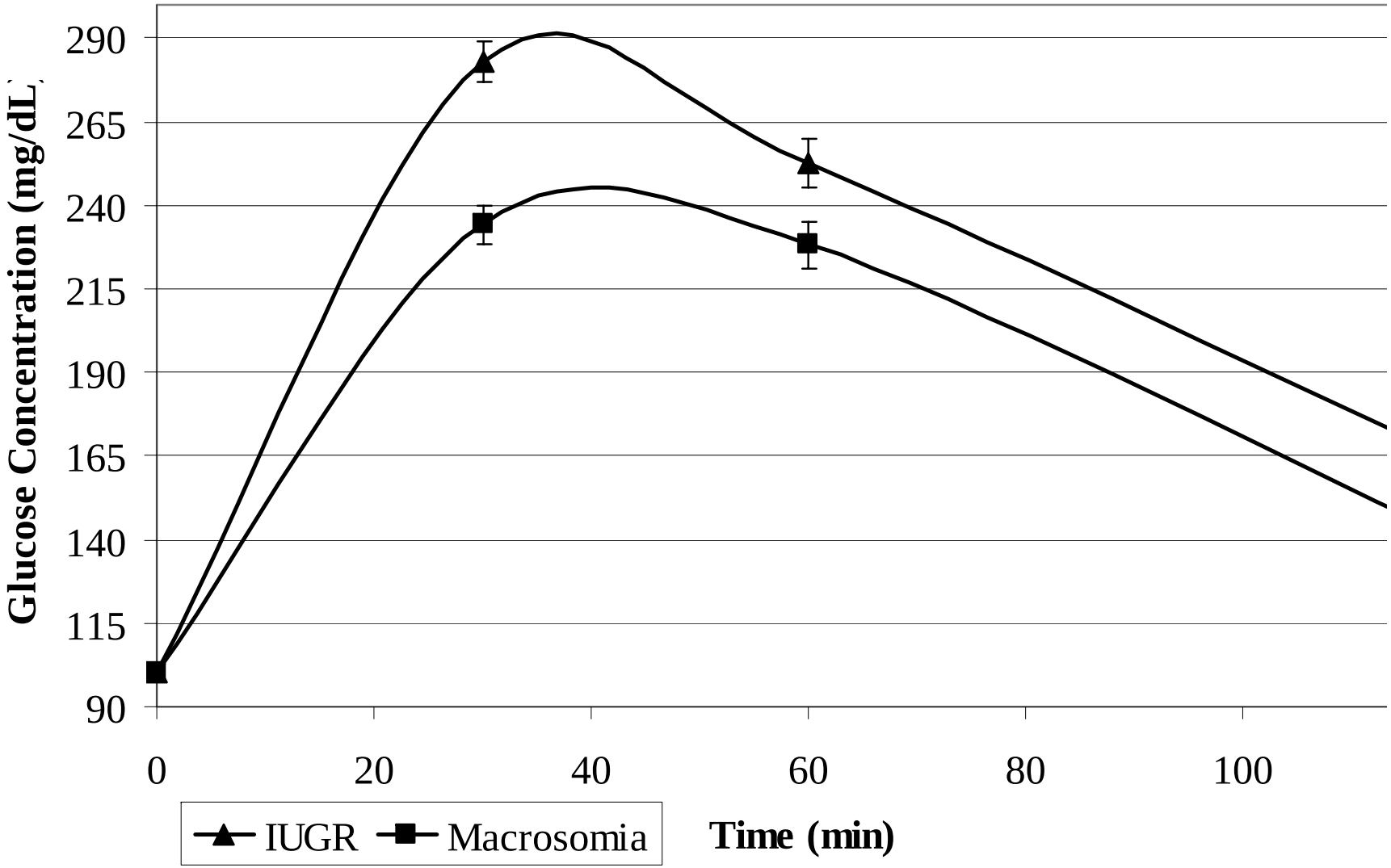
# PERCENT INCREASE IN BODY WEIGHT DURING THE 7 DAYS AFTER WEANING IN FEMALE MICE




FEMALE BODY WEIGHT
7 Weeks Old
4 Weeks Old
3 Weeks Old (Weaning)
Day of Birth
Grams
<5
5-25
25-50
50-75
75-95
>95%

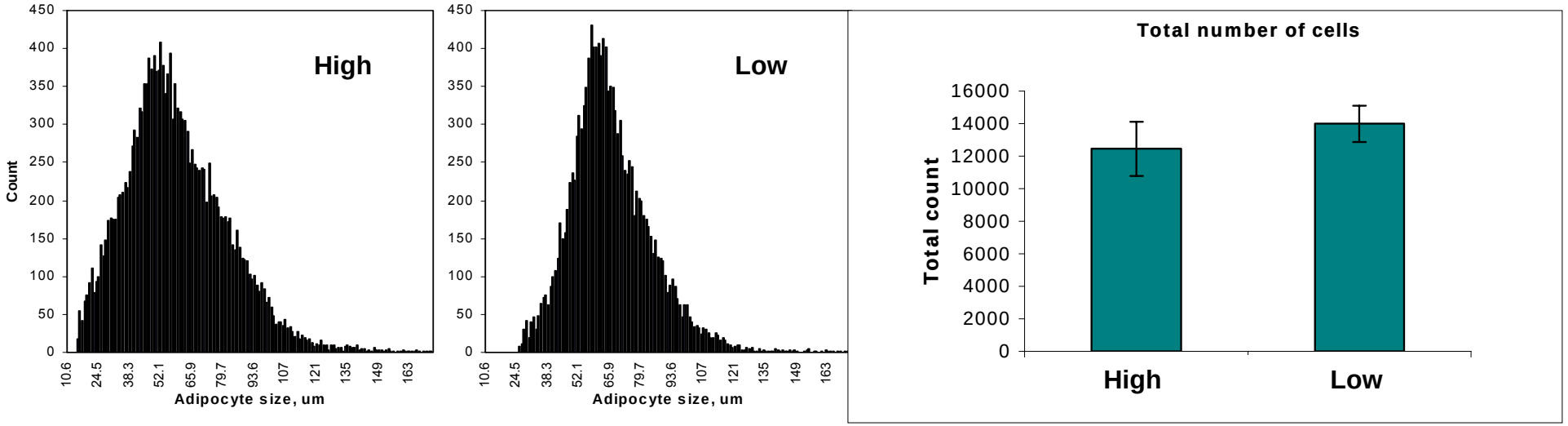
N = 287 pups

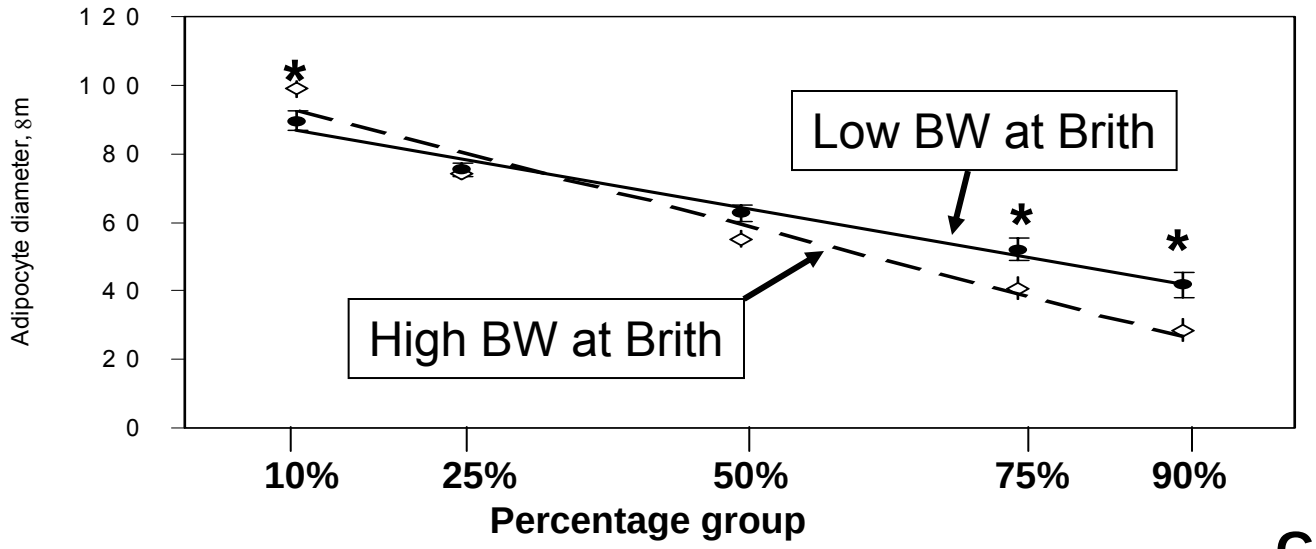
# GLUCOSE TOLERANCE IN MALE MICE




**Coe et al. unpublished**

# COULTER COUNTER ANALYSIS OF FAT CELL DIAMETER IN MALE MICE

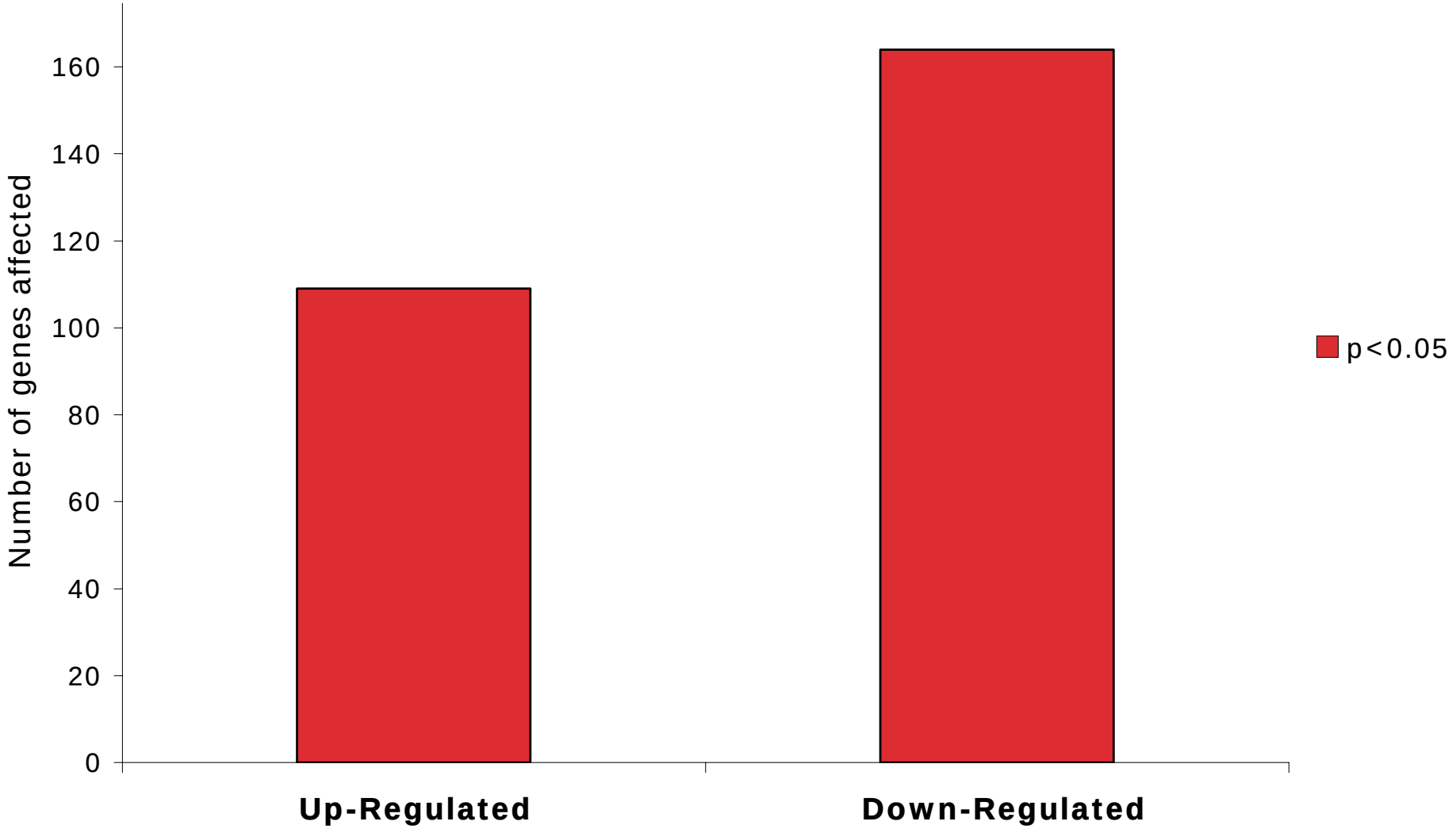



* indicates difference between High and Low birth wt groups (P<0.05)

**Coe et al. unpublished**

# ADULT EPIDIDYMIDAL ADIPOCYTE GENE EXPRESSION: COMPARISON OF MALES CATEGORIZED WITH IUGR AND MACROSOMIA AT BIRTH




**Taylor et al. unpublished**

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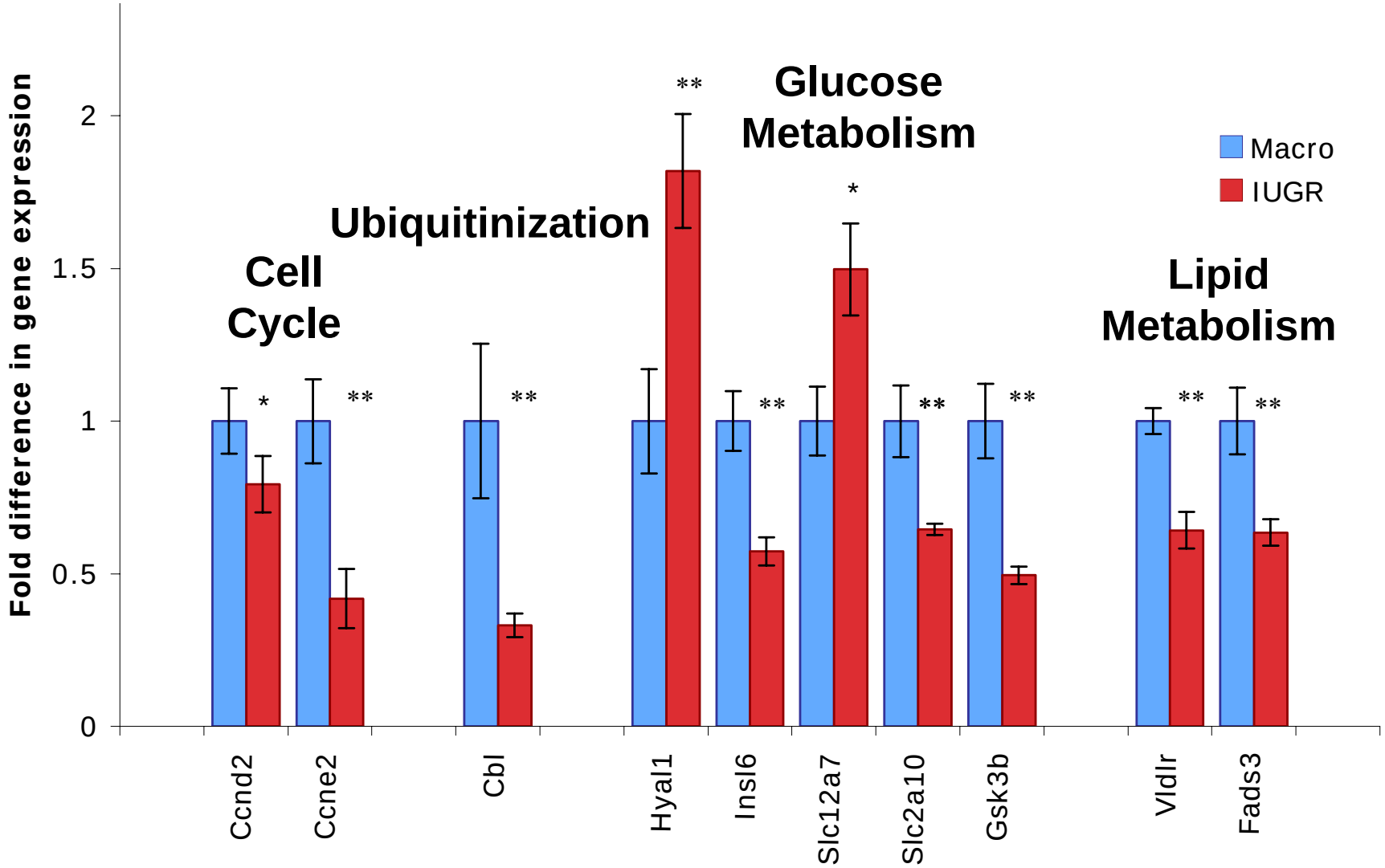
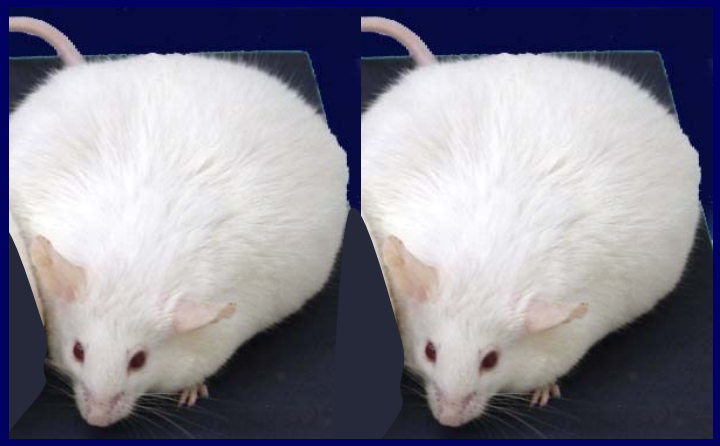



Taylor et al. unpublished

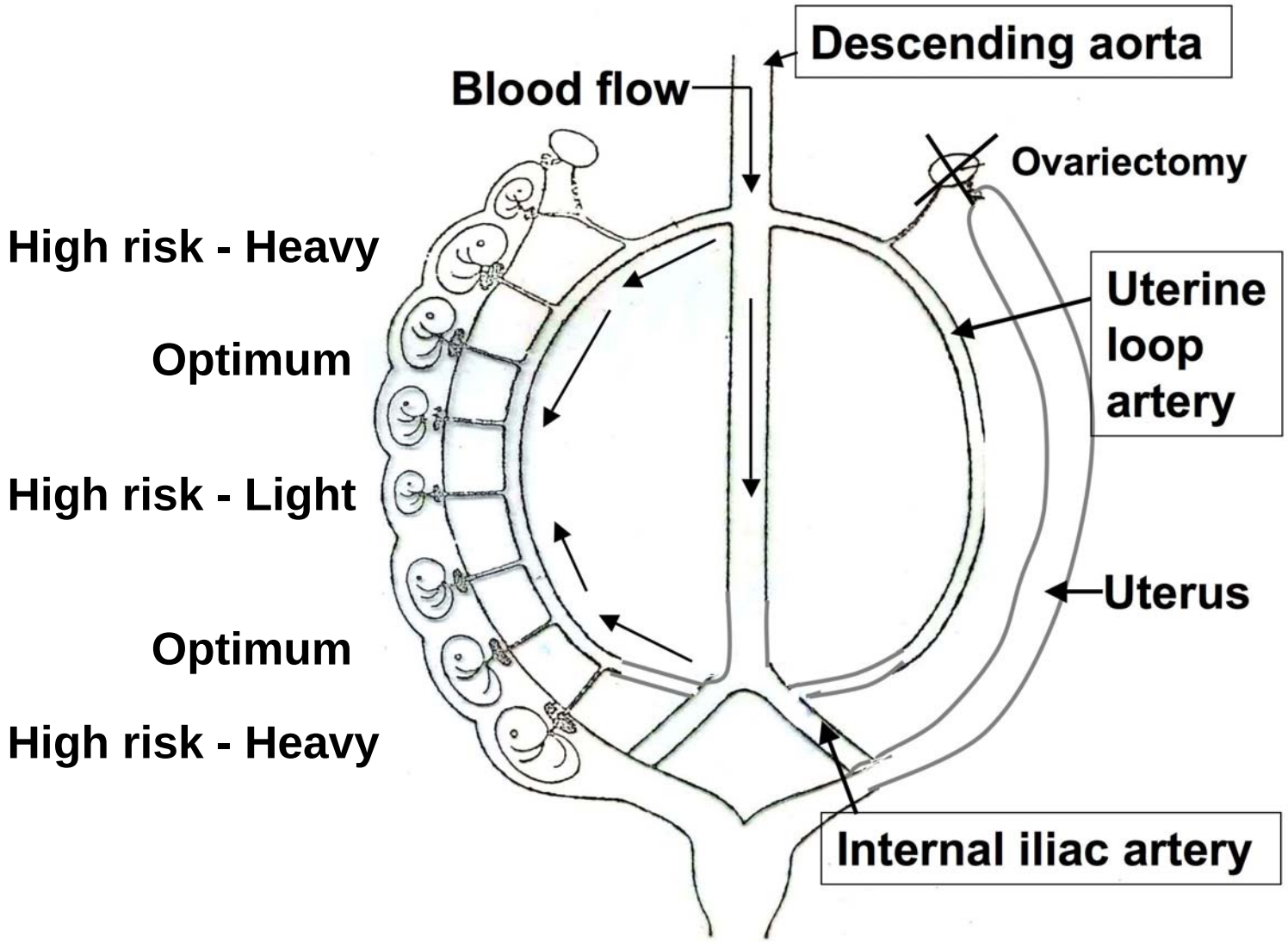
# IUGR and Macrosomia Result in Differences in Adult Obesity



Hundreds of Genes in Epididymidal Adipocytes Differ in Activity

Affymetrix Mouse Genome 430 Array

# Compensatory Ovulation Following Hemiovariectomy



# EXPERIMENTAL DESIGN

**Randomly assign adult CD-1 mice to be fed different mouse feeds**

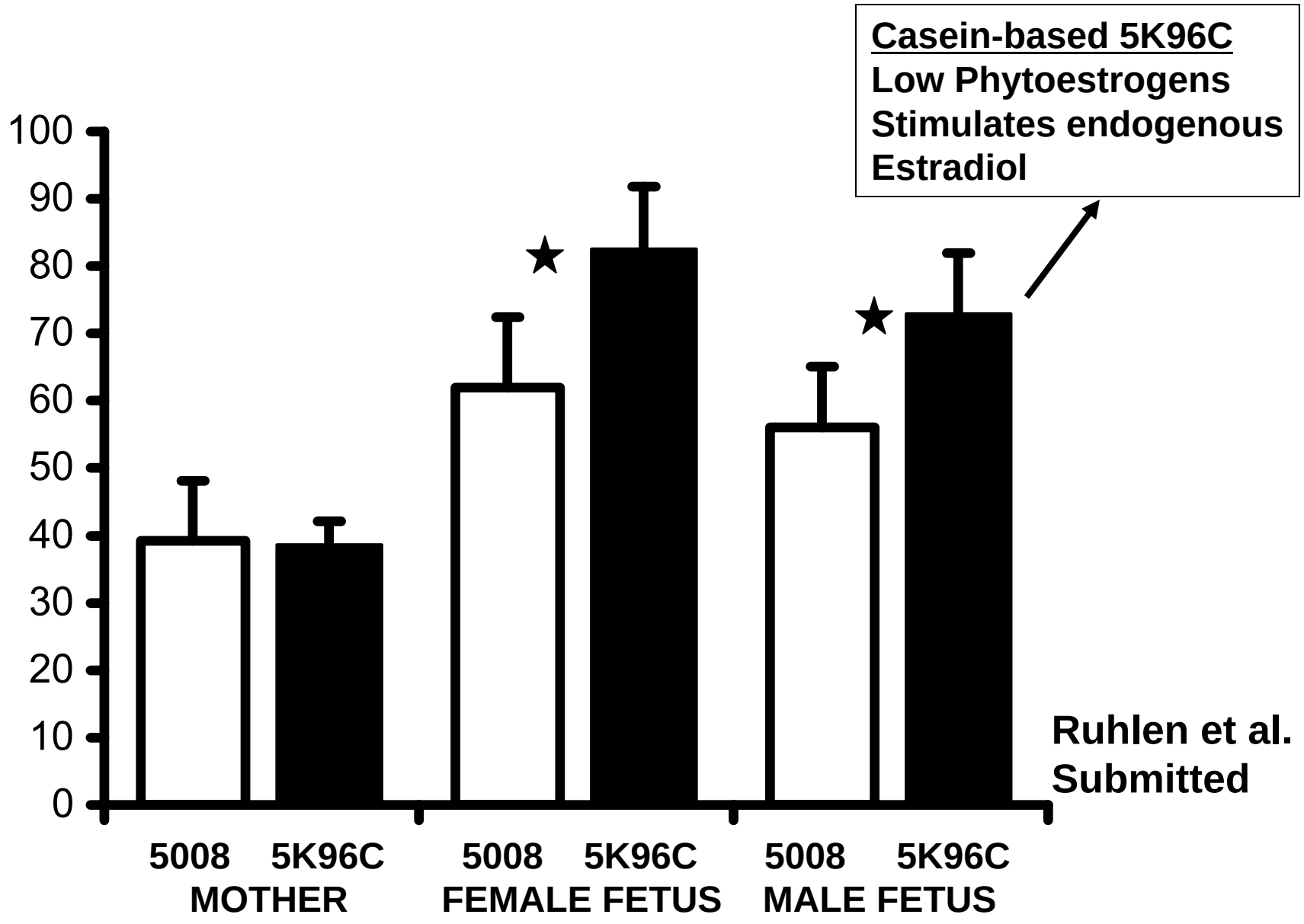
1. **Purina 5008: Pregnancy and lactation chow**

   **Purina 5001: Post-weaning chow**
   - **soy based rodent feeds**
   - **high levels of phytoestrogens: genistein and daidzein**

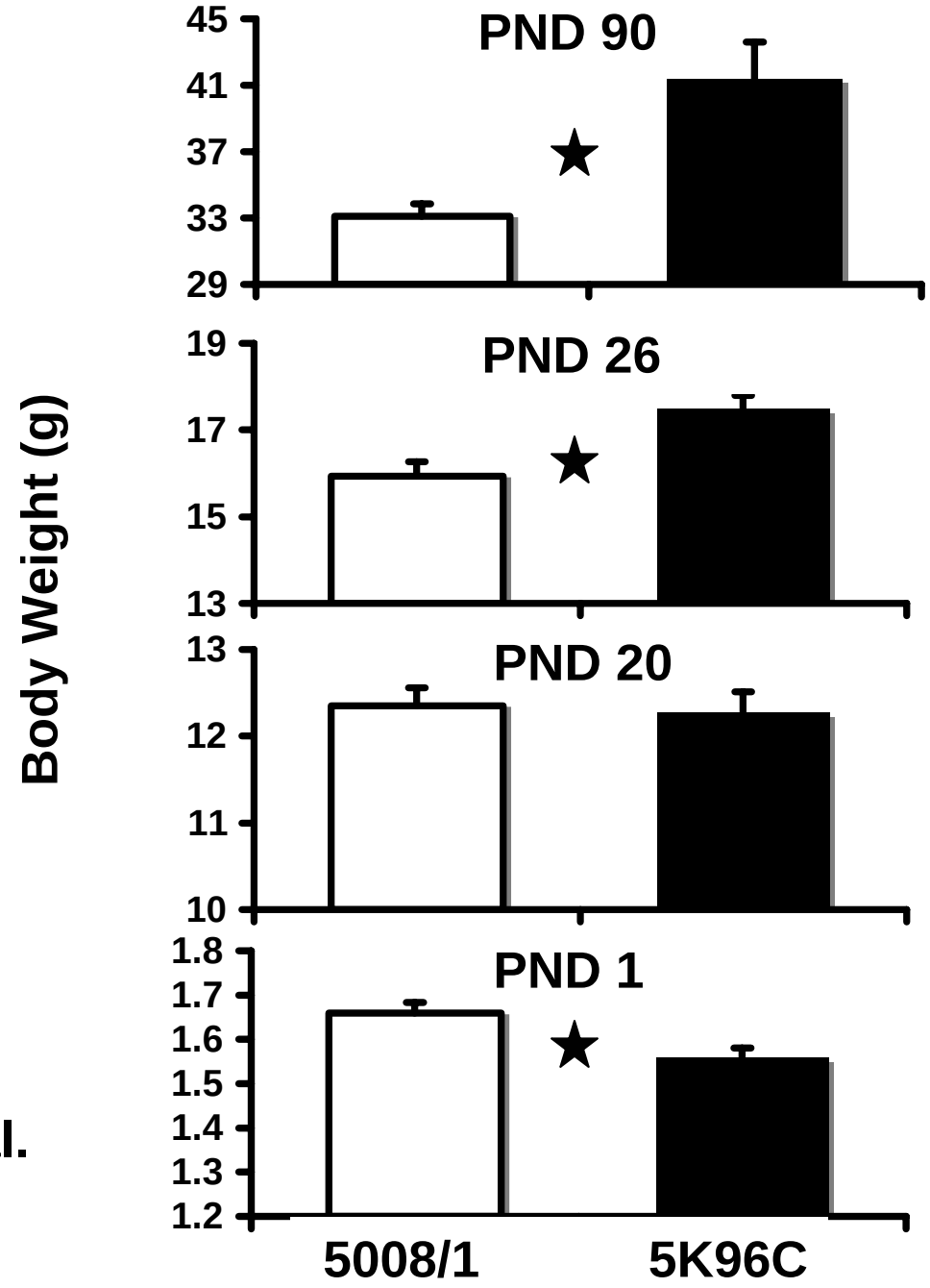
2. **Purina 5K96C**
   - **casein based feed**
   - **undetectable phytoestrogens (MCF-7 cells)**

**Examine offspring at different ages**

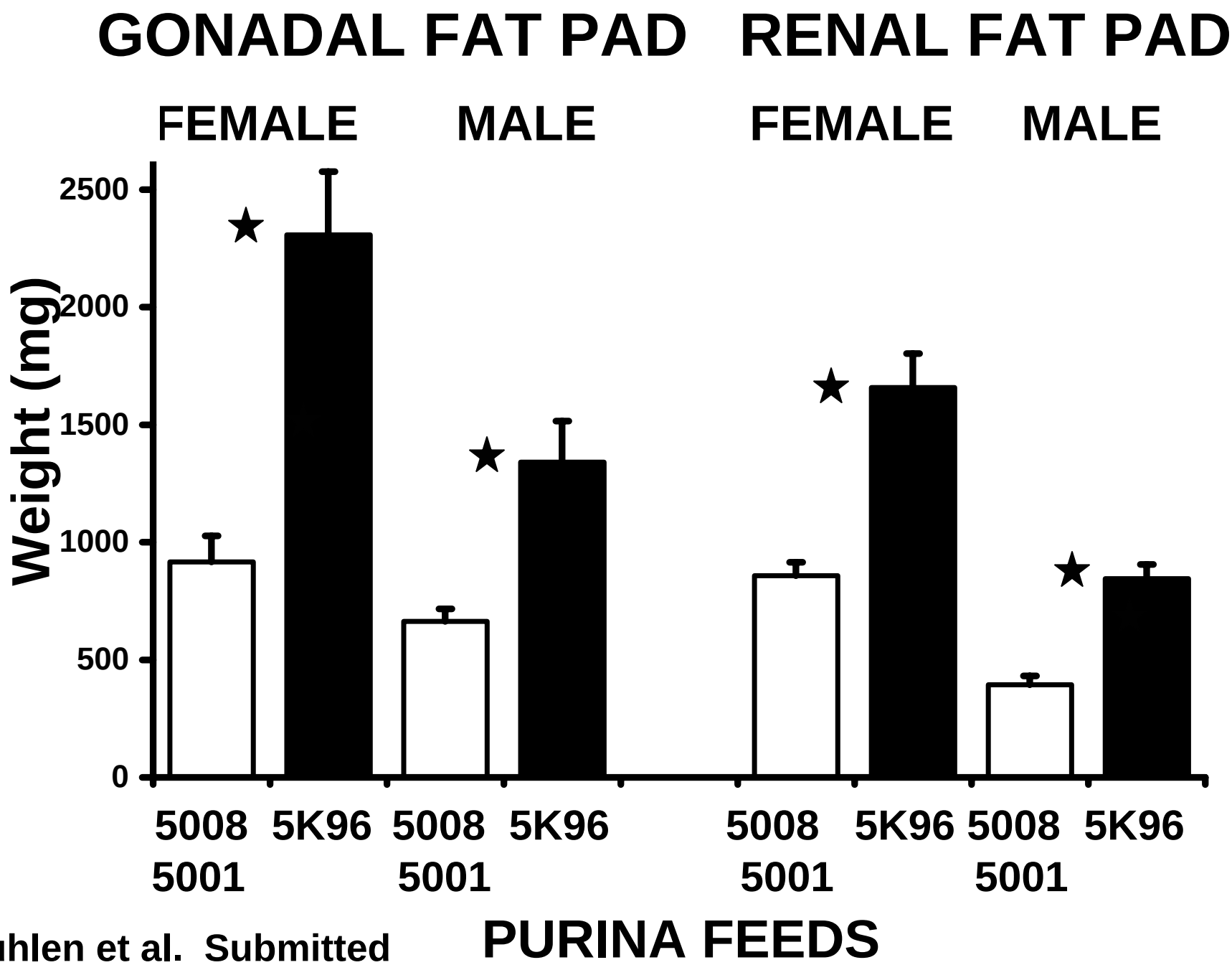
# SERUM ESTRADIOL



# EFFECT OF FEED ON BODY WEIGHT IN FEMALE MICE

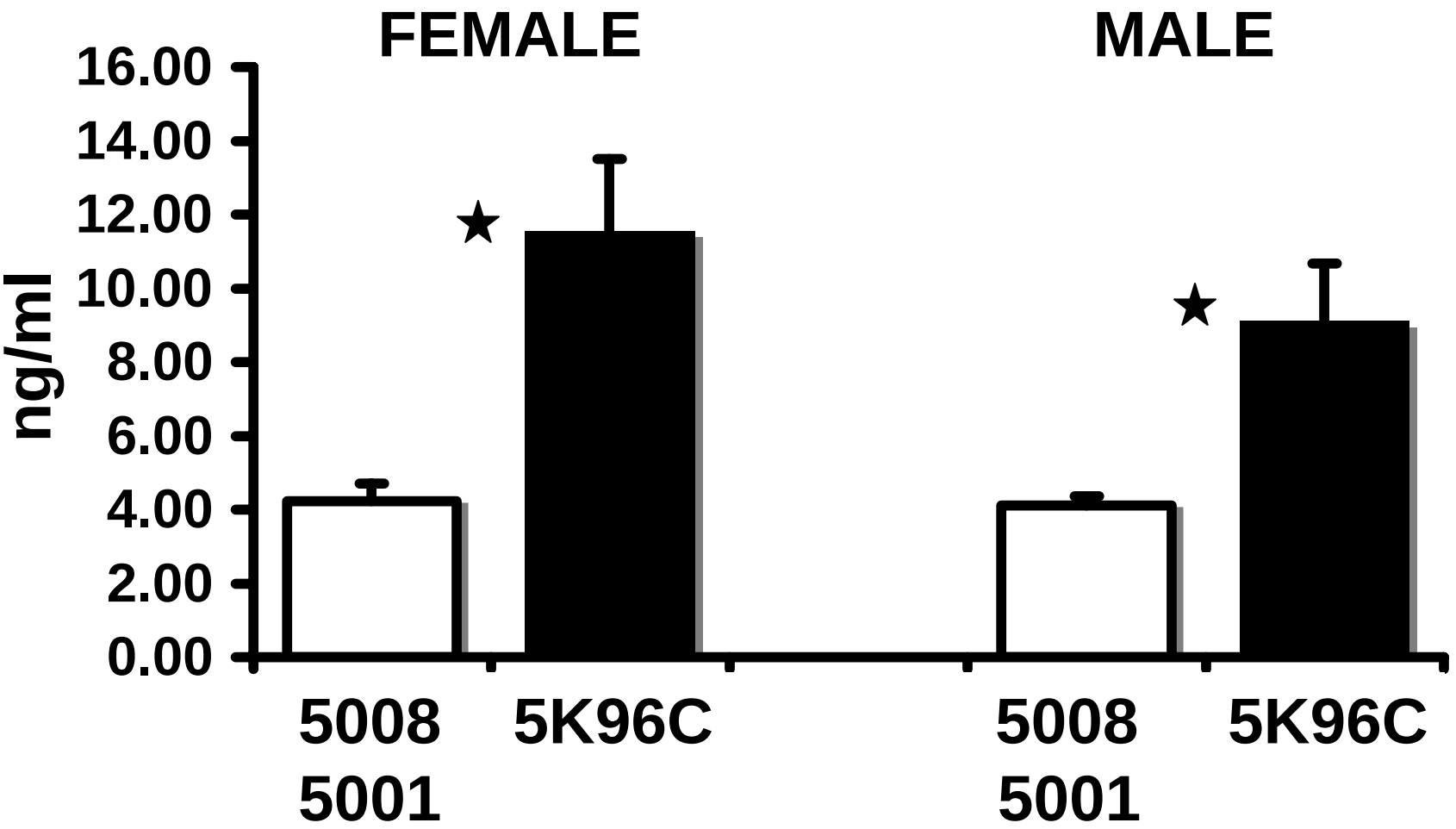



Ruhlen et al.
Submitted



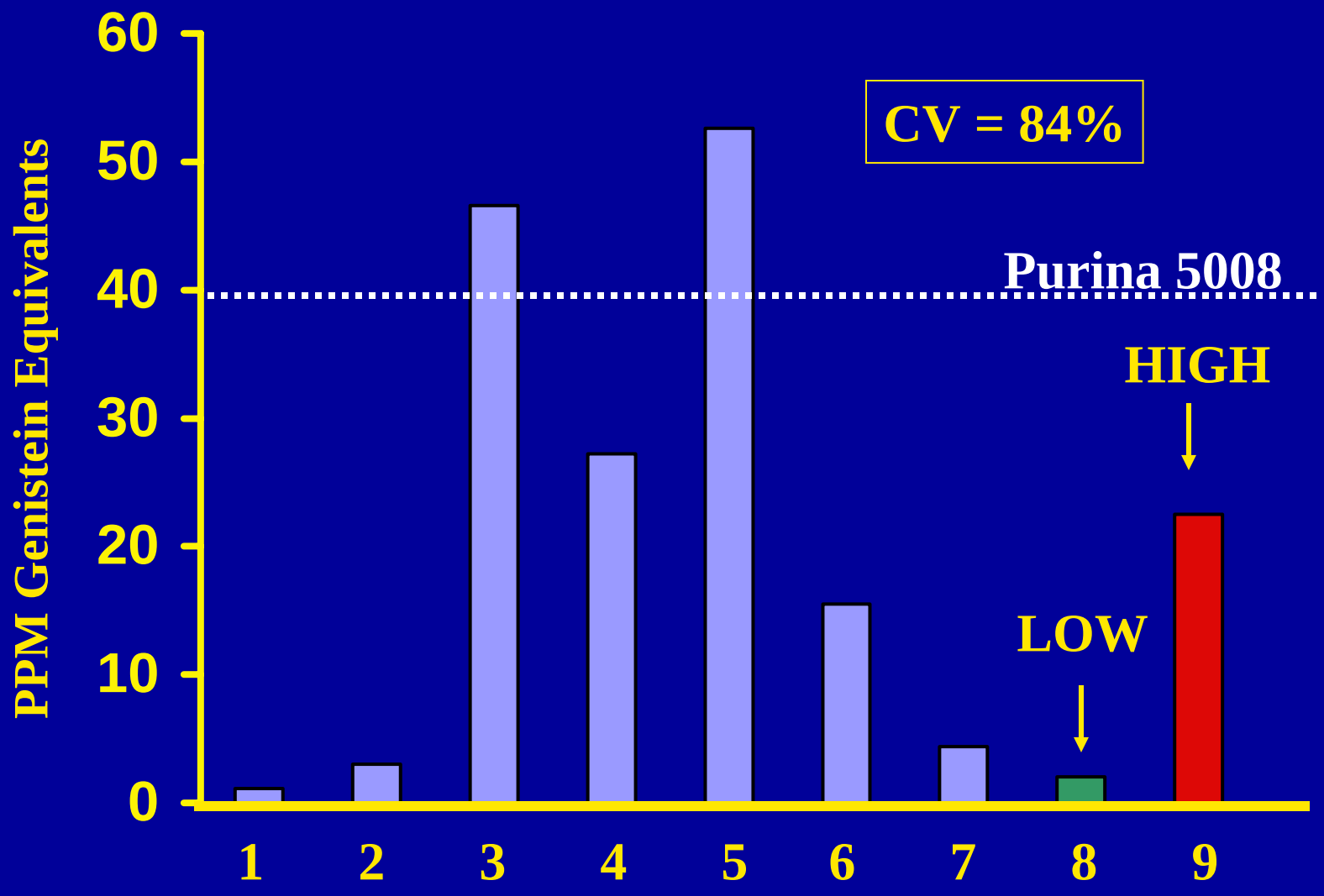

Ruhlen et al. Submitted

# SERUM LEPTIN IN ADULT MICE



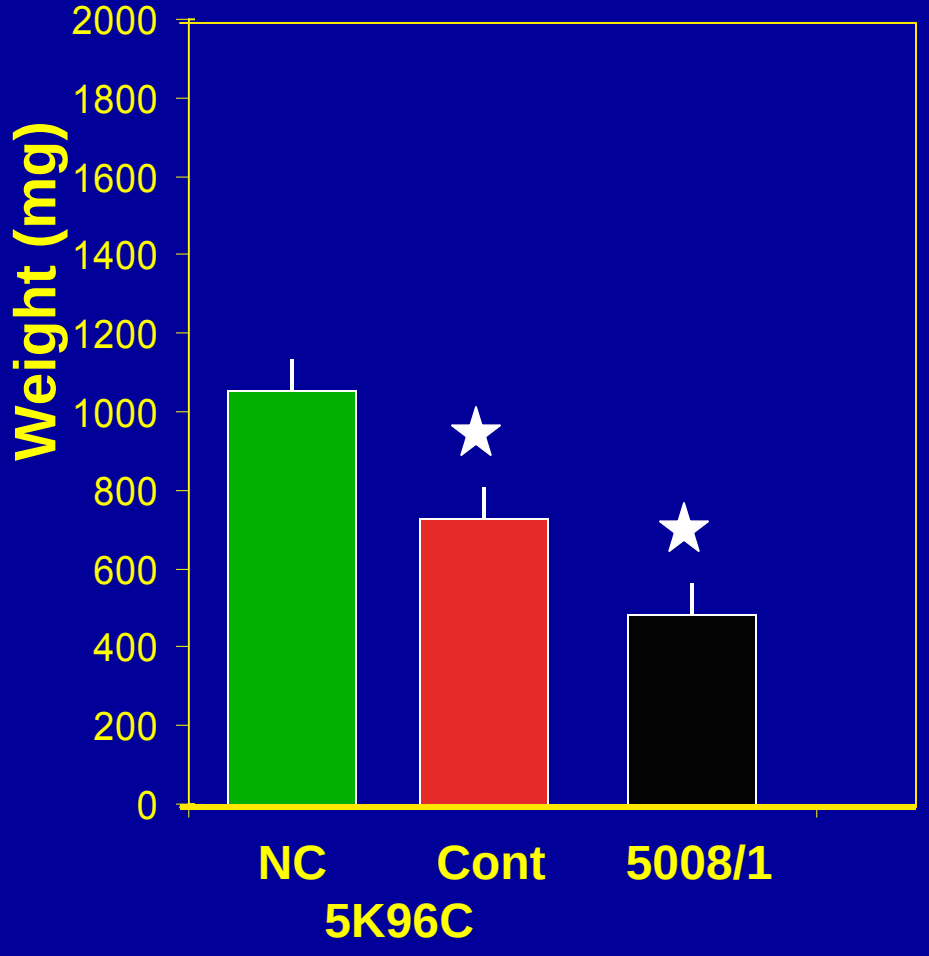

Ruhlen et al.
Submitted

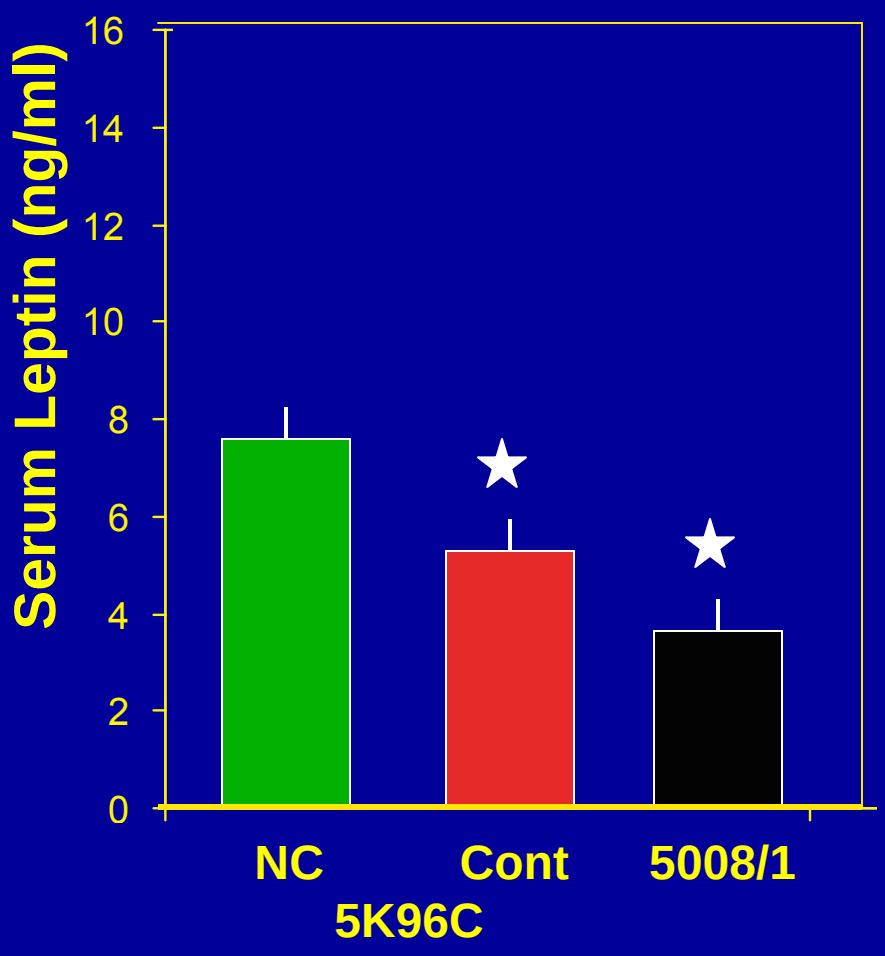
# ESTROGENIC ACTIVITY IN DIFFERENT LOTS OF CASEIN-BASED PURINA 5K96C FEEDS MCF-7 CELL BIOASSAY




Welshons and Taylor unpublished

# 2-MONTH OLD CD-1 FEMALE MICE

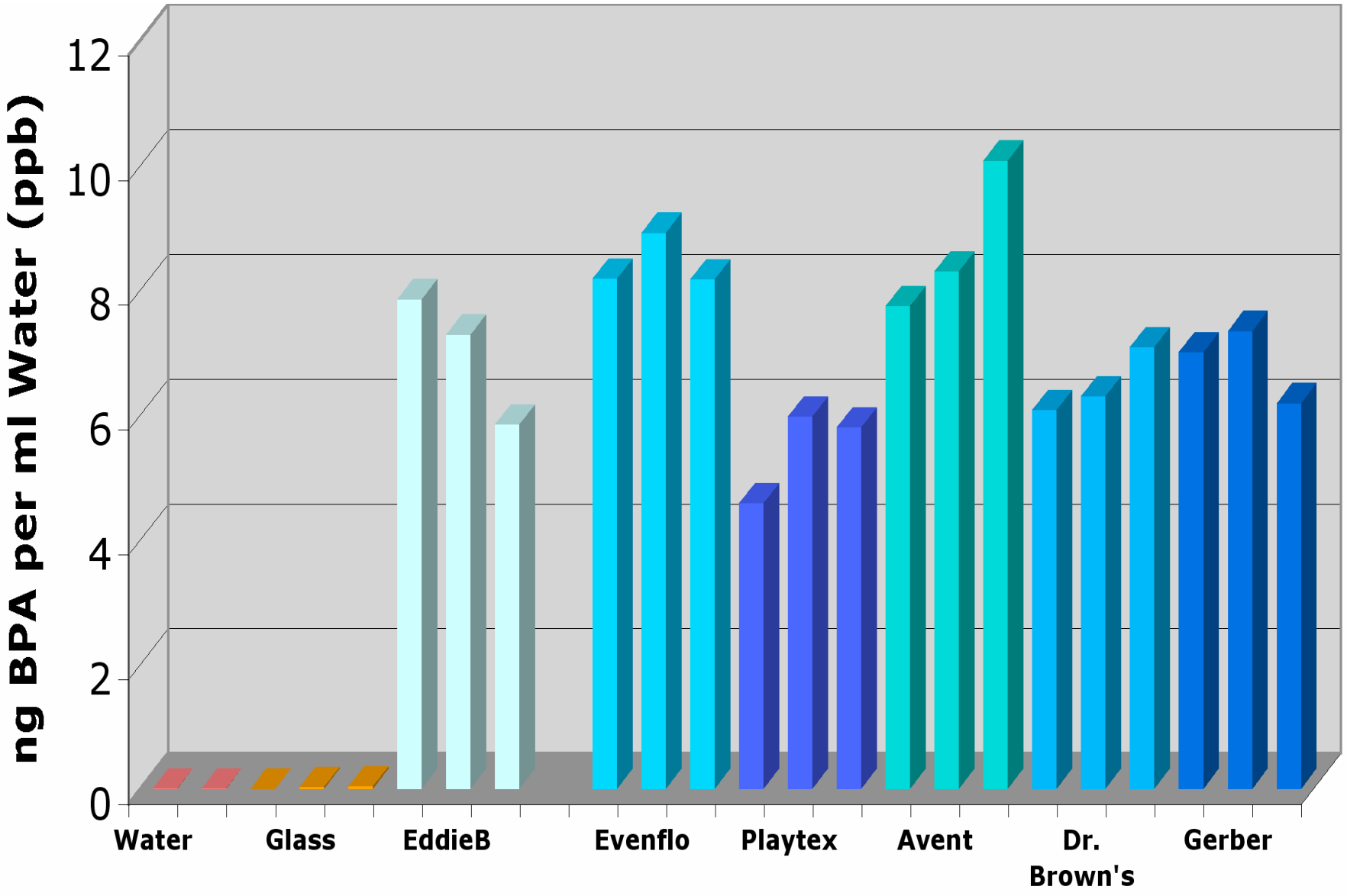


# USES OF BISPHENOL A IN PRODUCTS
## Production Capacity > 6.5 Billion Pounds / Year




# BISPHENOL A LEACHES FROM NEW POLYCARBONATE BABY BOTTLES

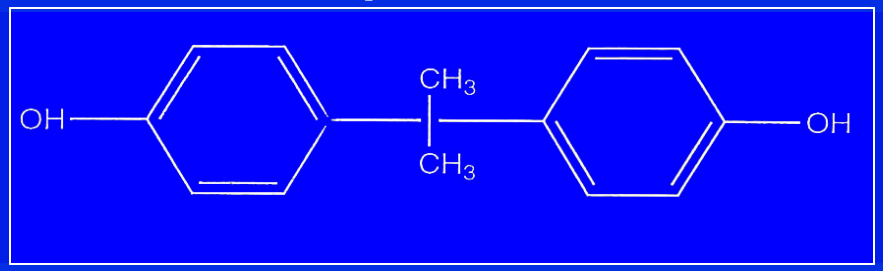



Taylor, vom Saal, Welshons and Rottinghaus (unpublished)

# NATURAL AND MANMADE ESTROGENS

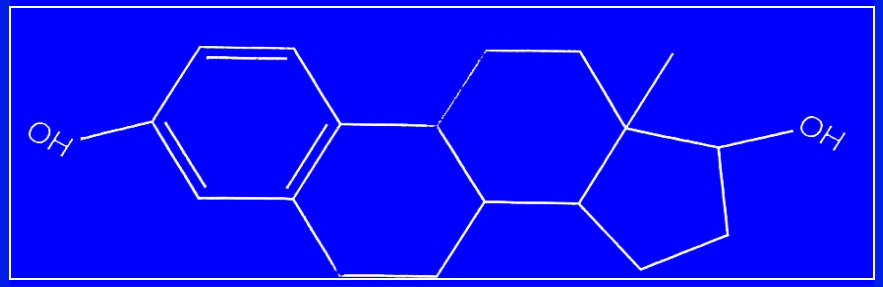
## POLYCARBONATE PLASTIC & RESIN

**Bisphenol A**



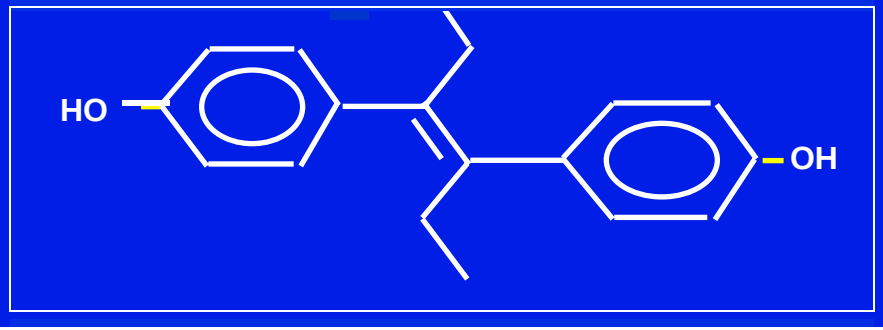

## NATURAL HORMONE

**Estradiol**




## ESTROGENIC DRUG

**Diethylstilbestrol (DES)**



# INTRAUTERINE POSITION INFLUENCES SERUM ESTRADIOL AND TESTOSTERONE IN MALE MOUSE FETUSES

**2M**

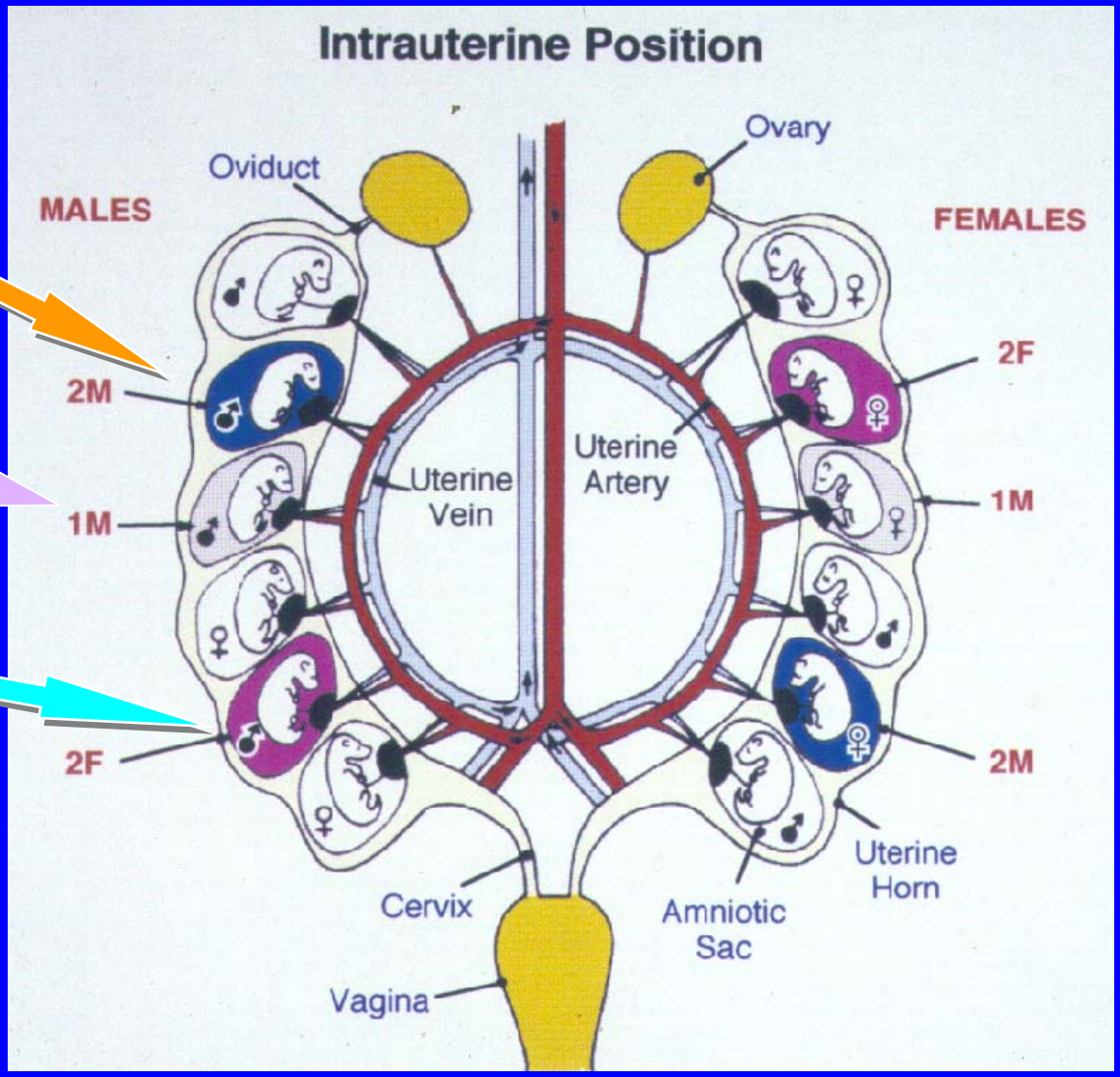
$E_2$ = 78 pg/ml
T = 5.7 ng/ml

**1M**

$E_2$ = 94 pg/ml
T = 4.6 ng/ml

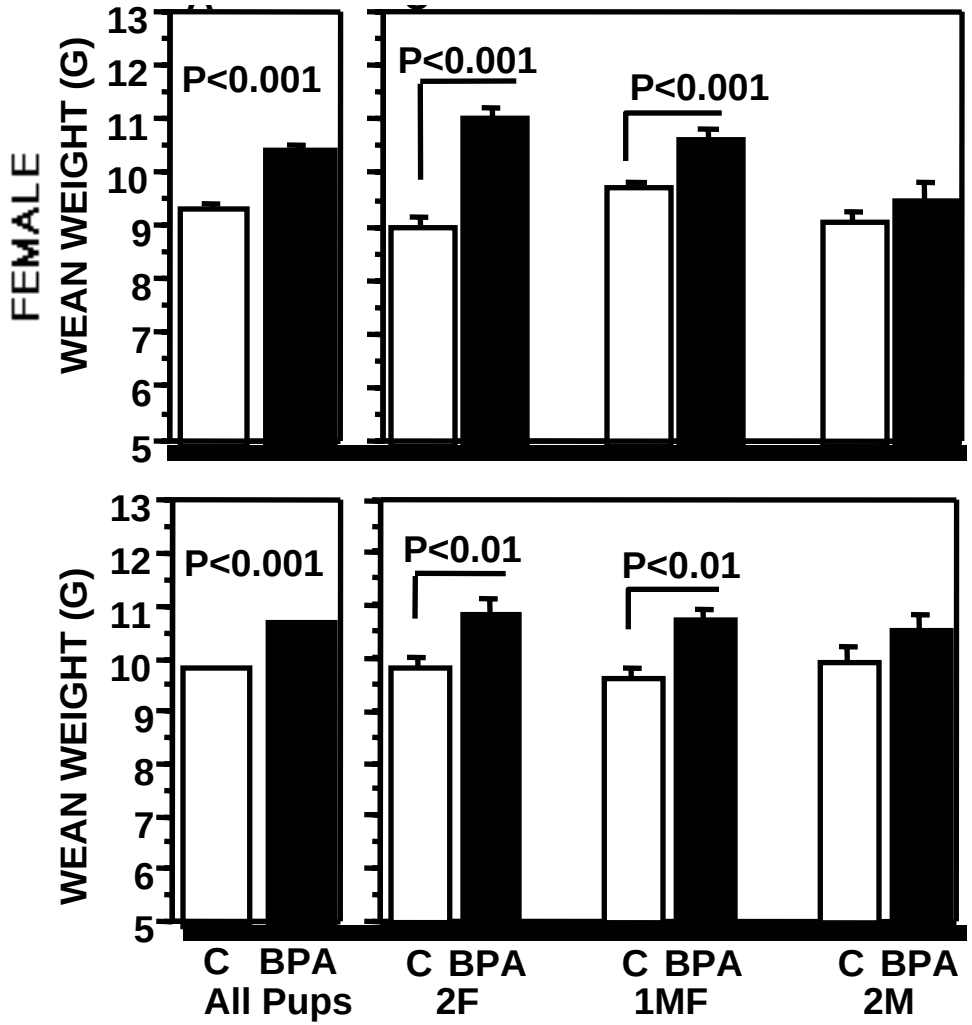
**2F**

$E_2$ = 101 pg/ml
T = 4.2 ng/ml




F. vom Saal
J. Anim. Sci.
67:1824-1840, 1989

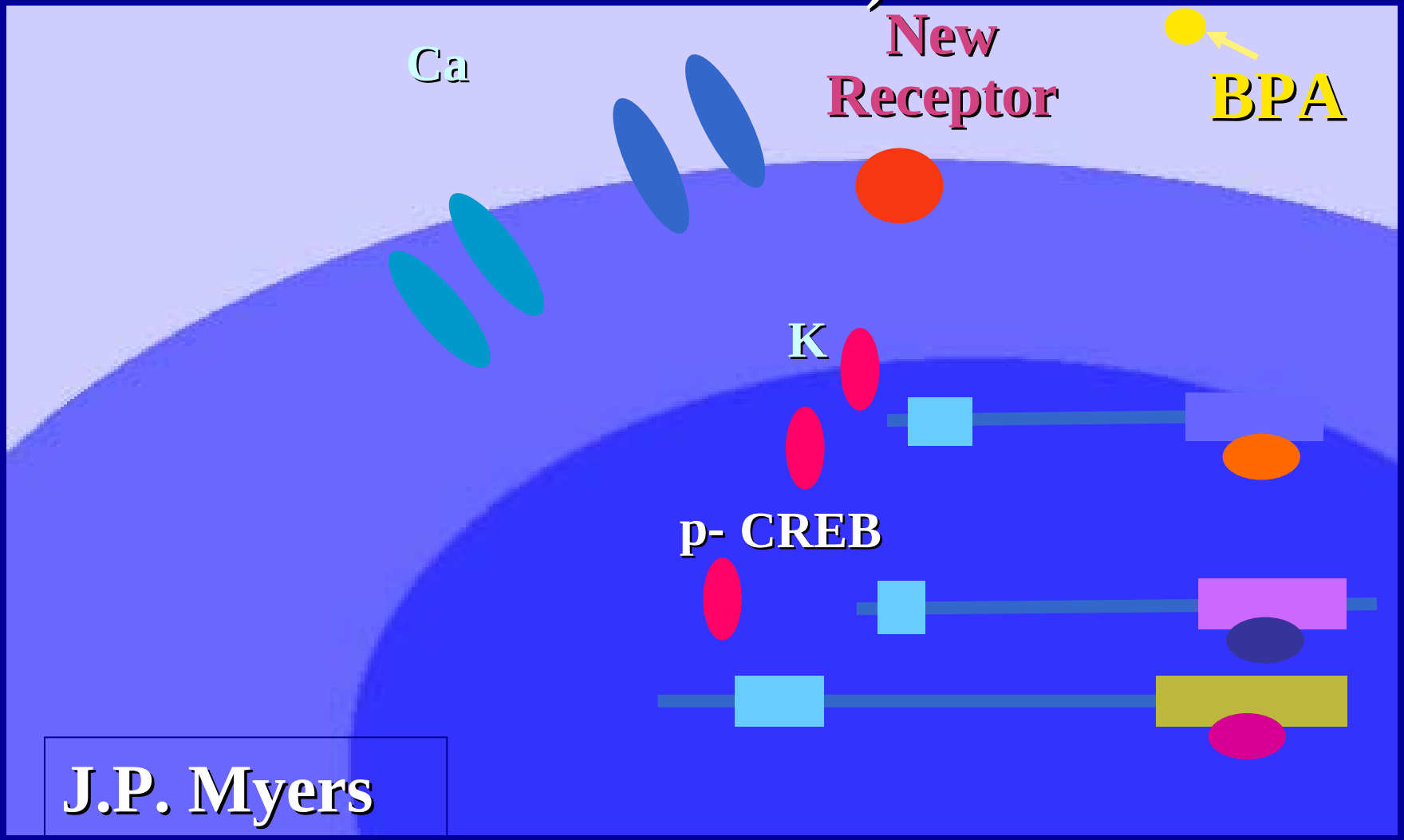
# PRENATAL BISPHENOL A EXPOSURE INCREASES BODY WEIGHT AT WEANING IN MICE WITH ELEVATED FETAL ESTROGEN LEVELS




**Maternal BPA Oral Dose:**
**2 µg/kg/day, GD 11-17**

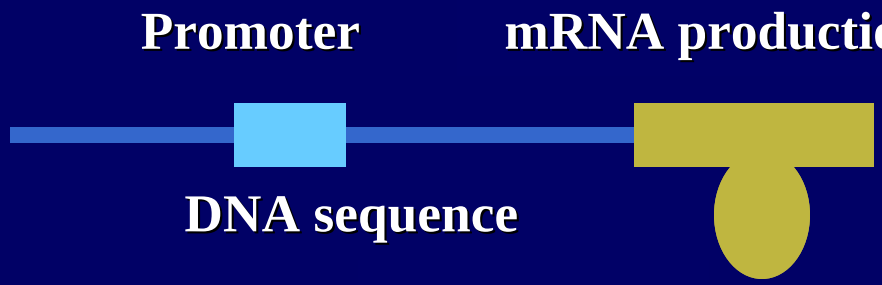
**Howdeshell et al.**
**Nature, 1999**

# Bisphenol A activates cAMP Responsive Element Binding Protein (CREB) at Human Exposure Levels (95% of Americans)



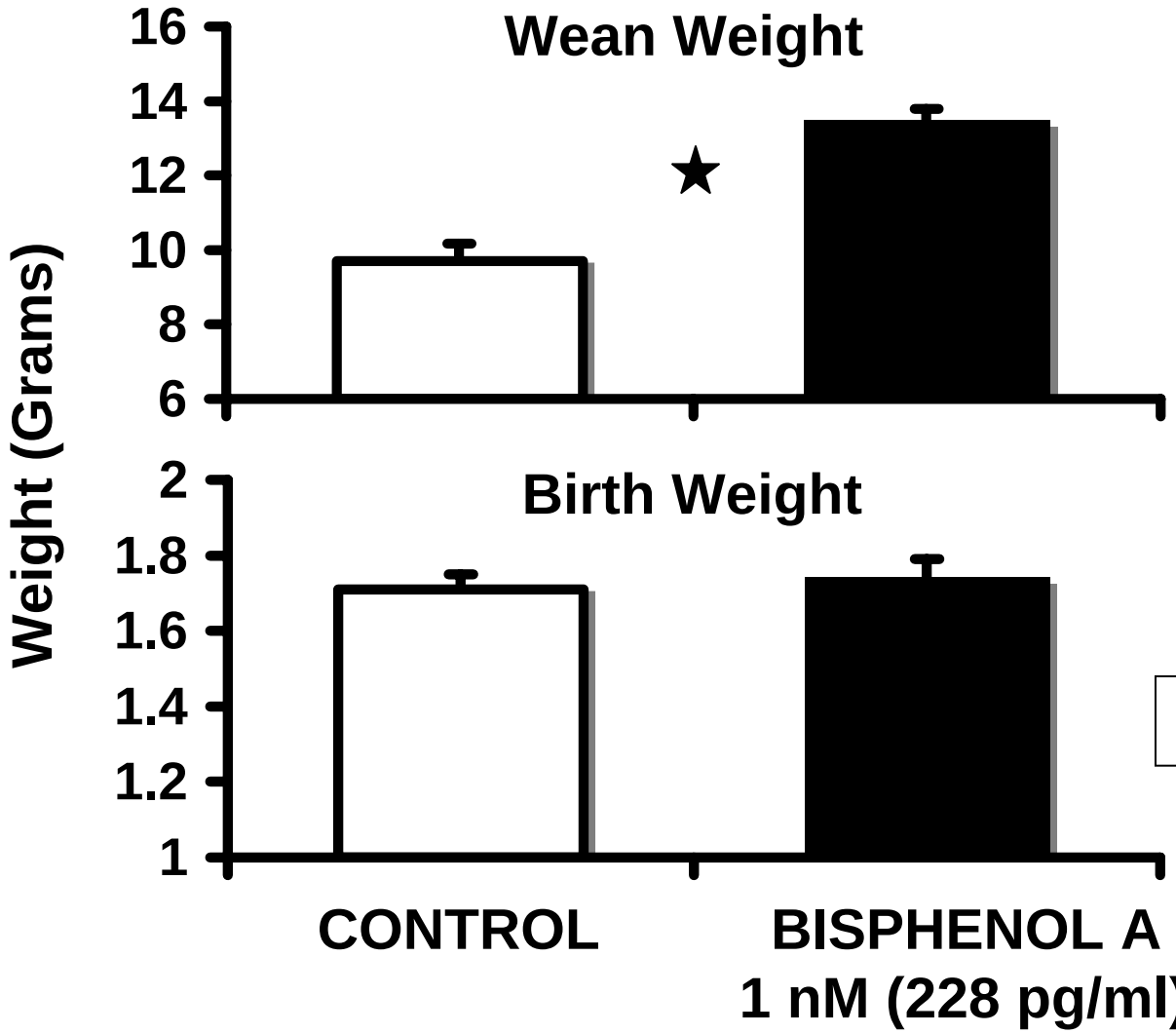

Calafat et al. 2005; Zhang et al. 2003; Quesada et al. 2003

# Gene in differentiating fat cell




P-CREB

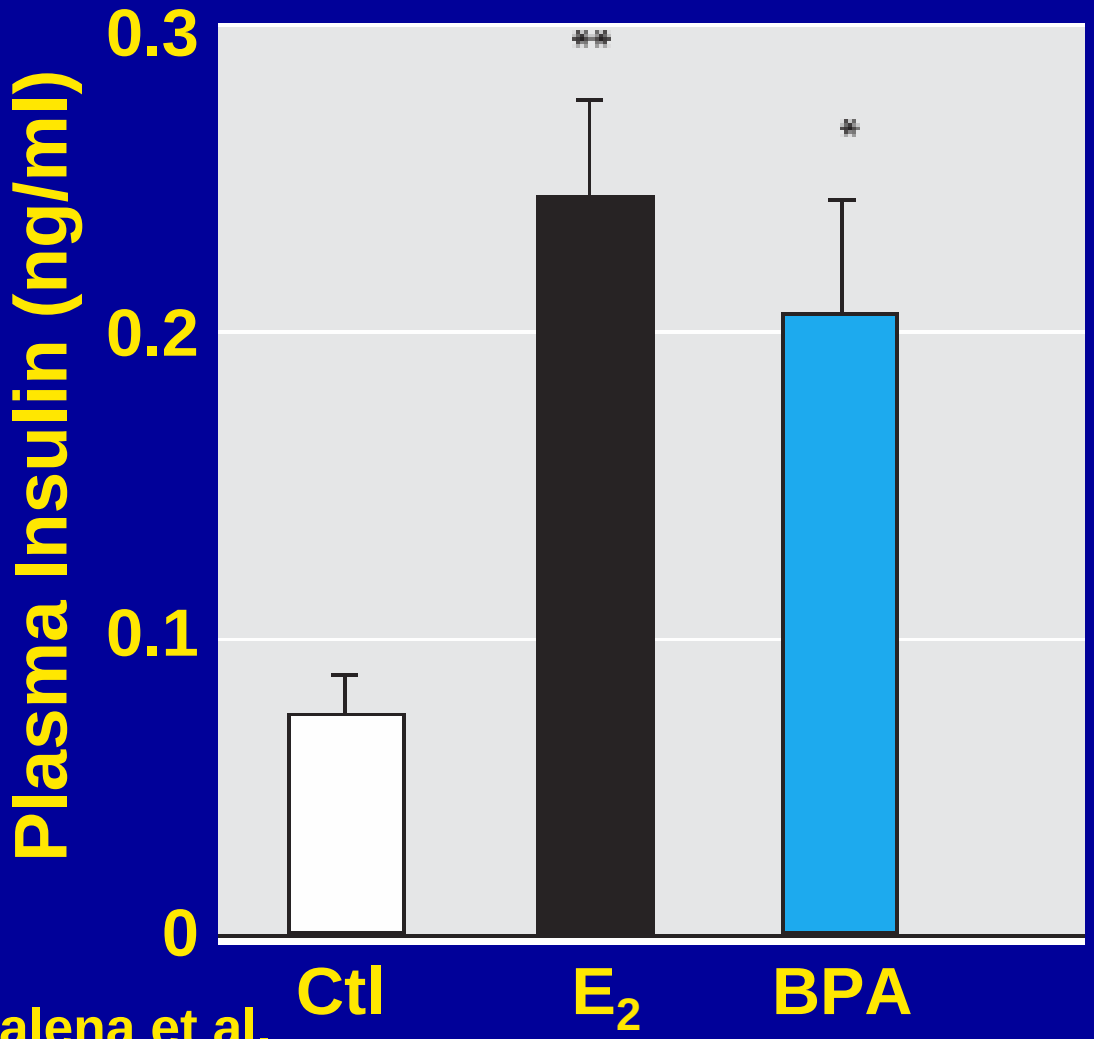
# EMBRYONIC EXPOSURE TO BISPHENOL A INCREASES POSTNATAL GROWTH RATE IN MICE




~4 pups / litter

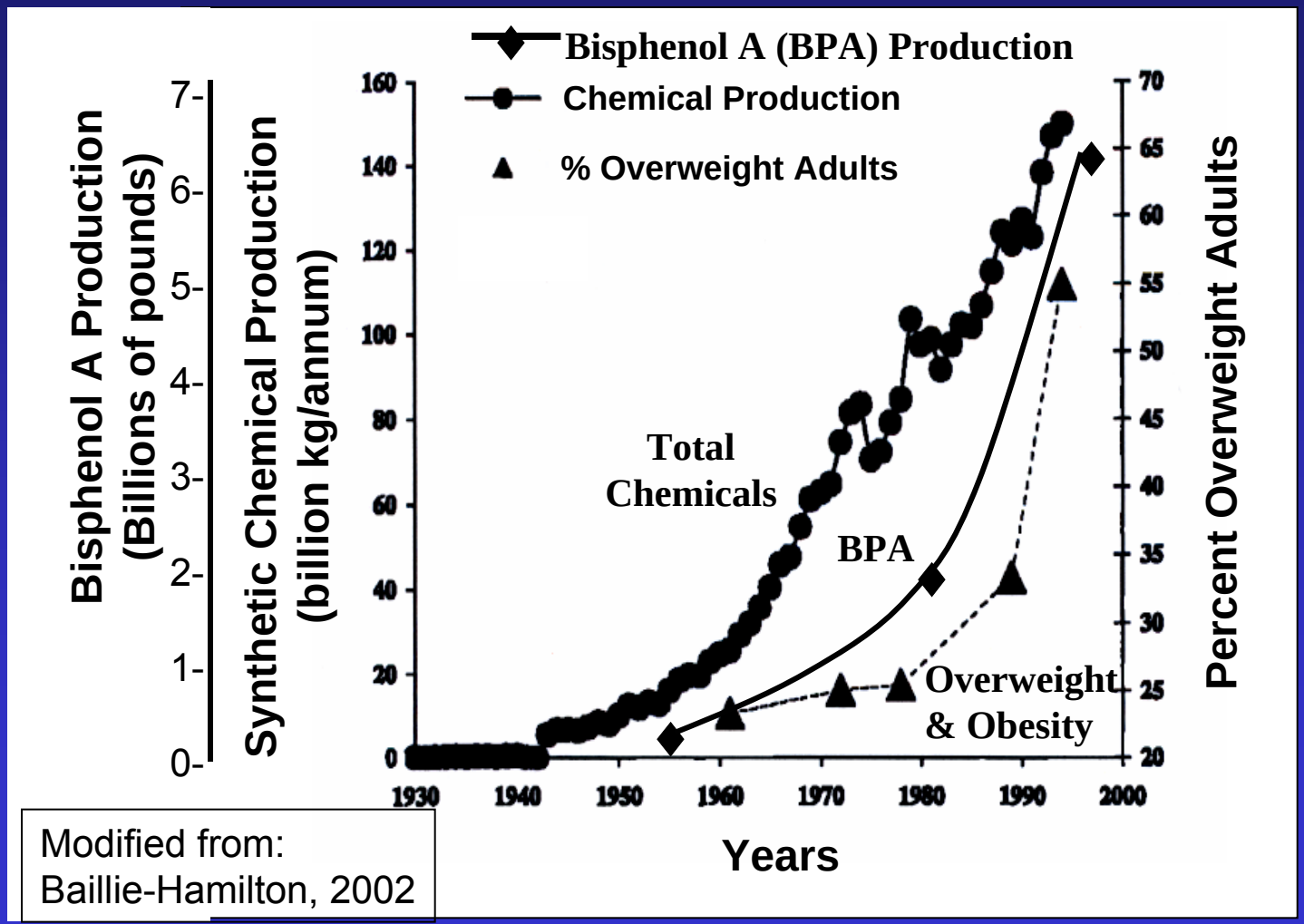
Takai et al.. 2000
Biochem. Biophys. Res. Comm.

# BISPHENOL A STIMULATES INSULIN SECRETION IN PANCREATIC ß CELLS IN MICE




Alonso-Magdalena et al.
Env.Health Pers. 2006

# All Manmade Chemicals and Bisphenol A: Production Parallels the Global Obesity Epidemic




Modified from:
Baillie-Hamilton, 2002

# BISPHENOL A
# (as of December 2007)
# EVIDENCE FOR BIAS DUE TO SOURCE OF FUNDING IN RELATION TO REPORTED OUTCOME IN RESEARCH WITH ANIMALS

| SOURCE OF FUNDING | STUDY OUTCOME: HARM | NO HARM | |
|---|---|---|---|
| Government | 153 (92%) | 14 (8%) | 167 |
| Chemical Corporations | 0 (0%) | 13 (100%) | 13 |
| | 153 | 23 | 180 |

vom Saal and Hughes, 2005 Environ. Health Perspect.

Also > 180 studies of moleculear mechanisms

# BIASED OUTCOME DUE TO SOURCE OF FUNDING IN LOW-DOSE BISPHENOL A RESEARCH (as of December 2005)

## STUDIES THAT USED THE ESTROGEN-INSENSITIVE CHARLES RIVER SPRAGUE-DAWLEY (CD-SD) RAT

| SOURCE OF FUNDING | REPORTED STUDY OUTCOME | | |
|---|---|---|---|
| | HARM | NO HARM | TOTAL |
| Government | 0 (0%) | 7 (100%) | 7 |
| Chemical Corporations | 0 (0%) | 3 (100%) | 3 |
| | 0 (0%) | 10 (100%) | 10 |

vom Saal and Hughes, 2005
Environ. Health Perspect.

DOCUMENT PROVIDED TO THE CALIFORNIA ASSEMBLY

ÑReported low-dose effects have not been replicated in repeat studies conducted in independent laboratories. The vast majority of available data shows no low dose effect whatsoever.Ó

Bisphenol A Safety Overview
American Chemistry Council
Document for California Assembly
December 2005

# Environmental Science and Technology
# February 22, 2006

## THE WEINBERG PROPOSAL

Paul D. Thacker

**A scientific consulting firm says that it aids companies in trouble, but critics say that it manufactures uncertainty and undermines science.**

**“We will harness, focus and involve the scientific and intellectual capital of our company with one goal in mind — creating the outcome our client desires.”**

# Letter from the FDA to the California Assembly, April, 2005

## The FDA sees no reason to ban bisphenol A.

The FDA approved bisphenol A for use in food and beverage containers in 1963. The standard was that bisphenol A was Generally Regarded As Safe (GRAS), since it had been in use for a few years and there was no evidence of harm.

George Pauli, Ph.D.
Associate Director for Science and Policy
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

# PUBLISHED STUDIES SINCE 1997 REPORTING LOW-DOSES EFFECTS OF BISPHENOL A IN MICE AND RATS DURING DEVELOPMENT

- 17=Altered brain structure & chemistry
  21=Altered behavior
- 5=Increased prostate size and cancer
  9=Lowered sperm production
- 6=Altered adult hormone levels
- 7=Abnormal mammary glands
  3=Early puberty in females
- 7=Increased subsequent body weight
- 2=Altered immune system

# SHOULD BISPHENOL A (BPA ) BE BANNED IN BABY PRODUCTS AND FOOD AND BEVERAGE CONTAINERS?

**Hundreds of published scientific studies show:**

1) High exposure is occurring: fetuses - adults.
2) Developing fetuses and babies are more sensitive to BPA than adults.
3) BPA is an endocrine disruptor that causes a wide range of abnormalities in animals.
4) Alternative plastics that are much more stable and safer than BPA are available.

# STUDENTS AND COLLABORATORS

## STUDENTS

- Brittany Angle
- Benjamin Coe
- James Kirkpatrick
- Maren Bell
- Davide Ponzi

## COLLEAGUES

- Wade Welshon
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- Paola Palanza
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- Huidong Shi
- Steve Yang

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- Jiude Mao
- Julia Taylor