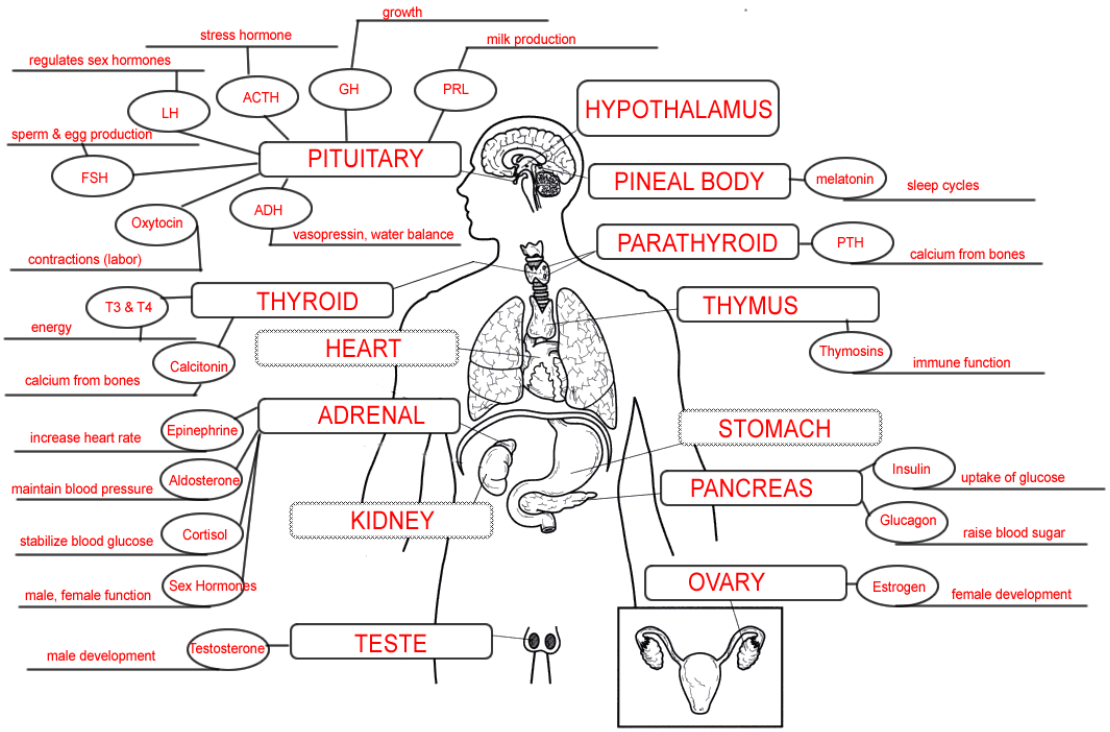
Pregnancy is critical window for endocrine disrupting chemical effects on maternal endocrine and metabolic health

Alyssa K. Merrill

Email: alyssa_merrill@urmc.rochester.edu

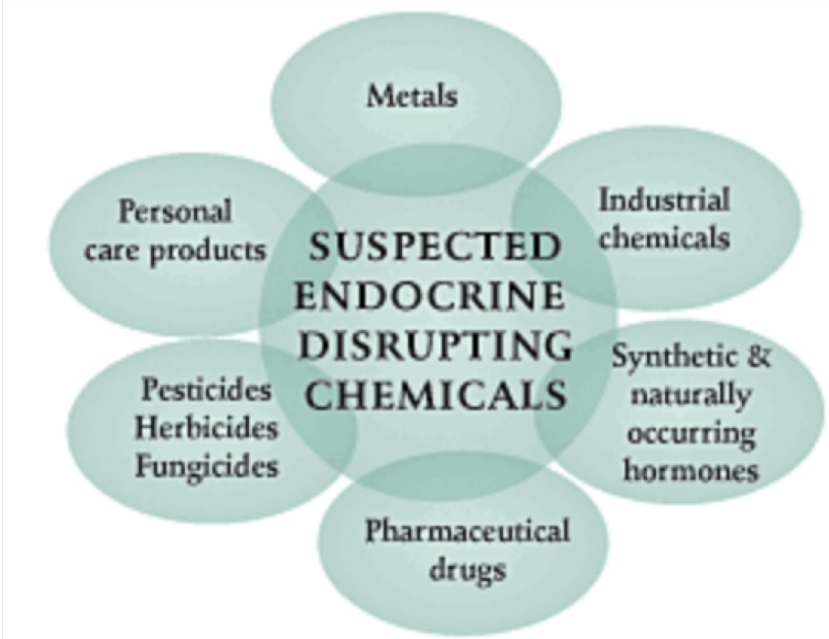
Endocrine Disrupting Chemical (EDC)

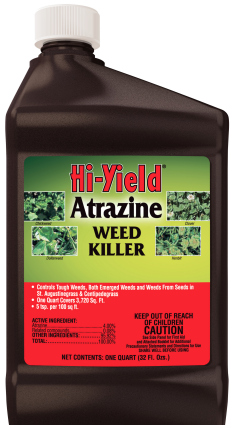
EDC is any chemical that interferes with the hormone activity, including the production, secretion, transportation, metabolism, binding action, and/or excretion of endogenous hormones.

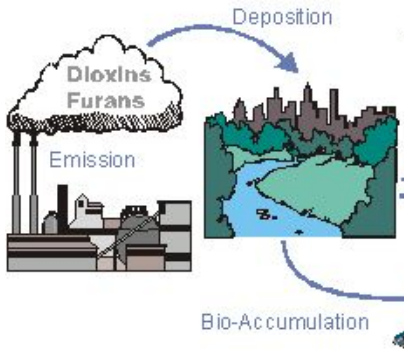


Endocrine Disrupting Chemical

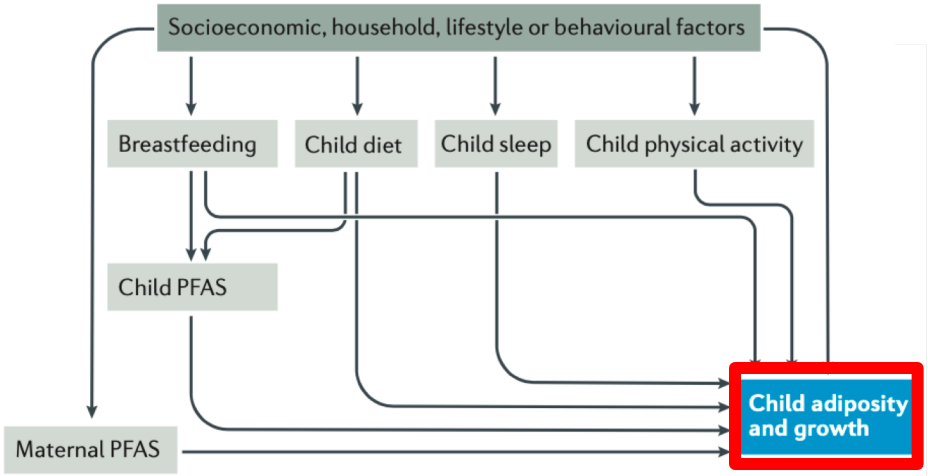
Over a 1,000 xenobiotics have been recognized to have endocrine active properties.



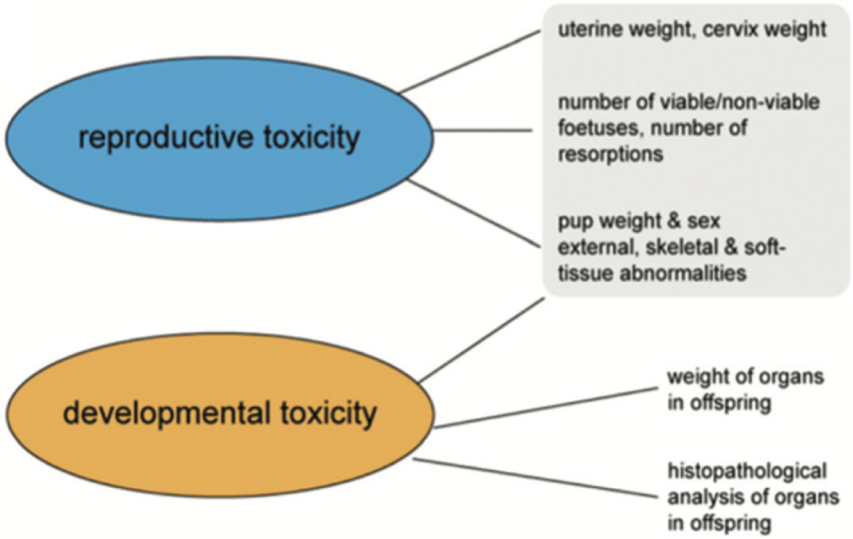




Maternal EDC Exposures Classically Focuses on Fetal Health or Reproductive Capacity

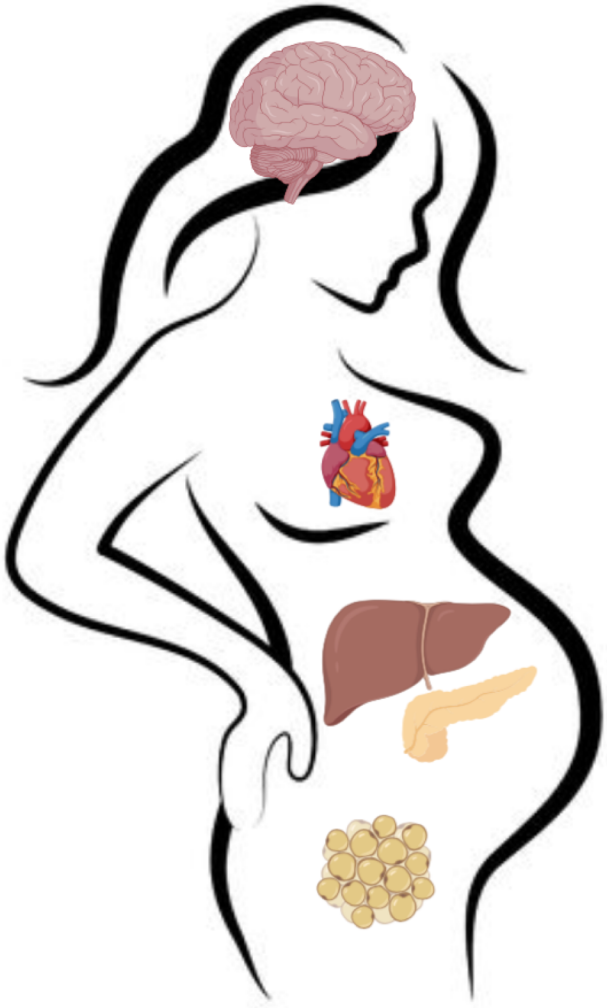


Braun 2017



Catanese et al. 2015

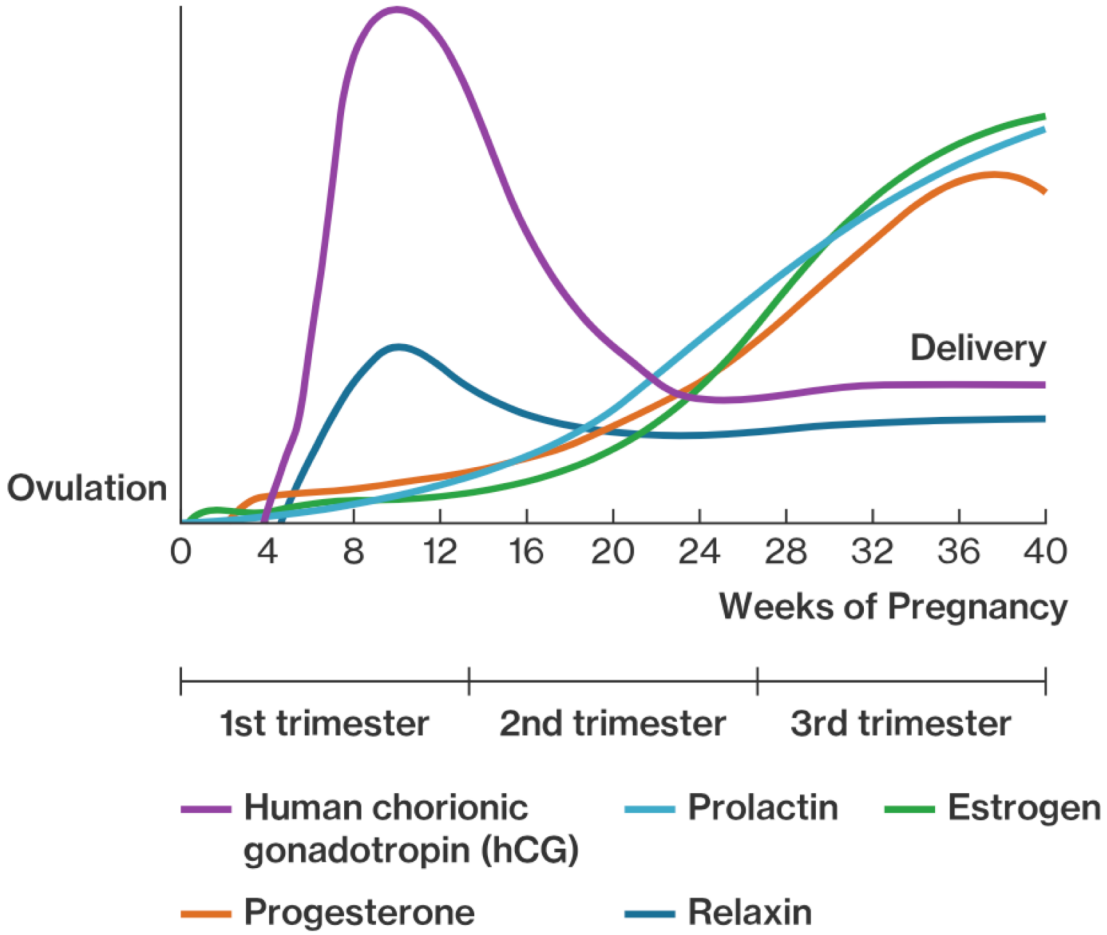
Pregnancy is a Critical Window for Long-term Maternal Health



Disease during pregnancy	Long-term maternal health outcomes
Hypertensive disorders	• Chronic hypertension • Ischemic heart disease
Gestational diabetes and weight gain	• Diabetes • Metabolic syndrome • Insulin resistance • Obesity
Intrahepatic cholestasis	• Cholangiopathy • Cirrhosis • Liver transplantation
Mental Health: Anxiety and Depression	• Postpartum depression

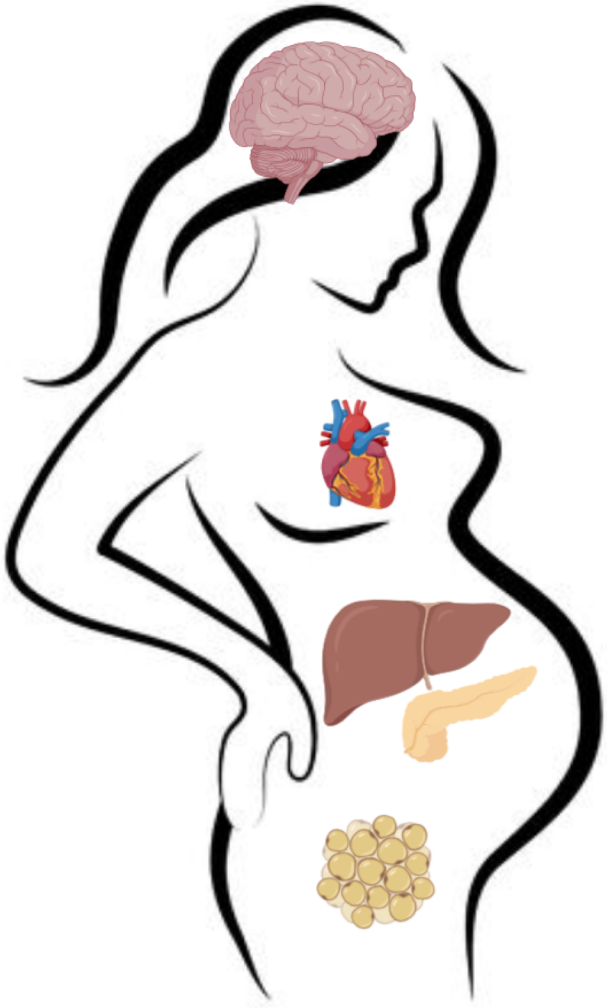
Adapted from Rahim et al. 2020 and Yim et al. 2015

Pregnancy is Coordinated by Predictable Shifts in Hormones



https://www.coursehero.com/sg/anatomy-and-physiology/pregnancy/

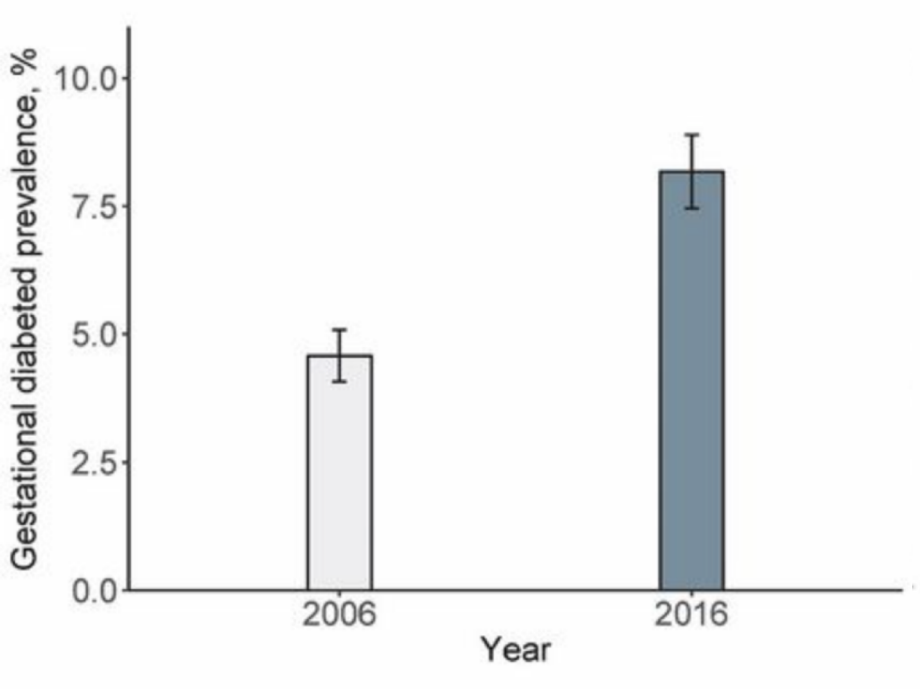
Pregnancy EDC Exposure and Long-term Maternal Health

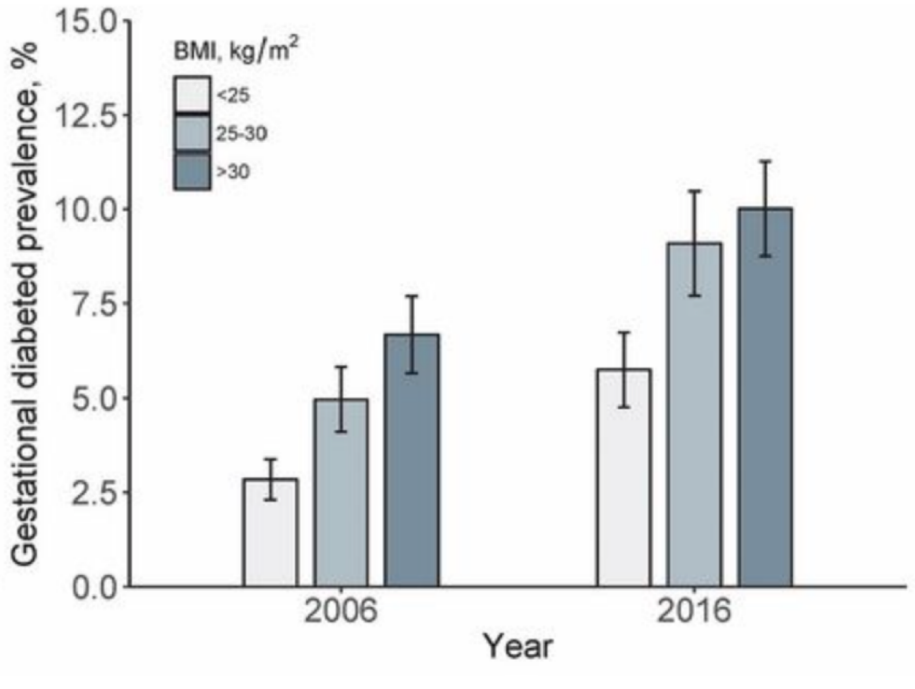


EDC Exposure	Disease during pregnancy	Long-term maternal health outcomes
Altered reproductive hormone levels	**Gestational diabetes and weight gain**	• Diabetes • Metabolic syndrome • Insulin resistance • Obesity
	Hypertensive disorders	• Chronic hypertension • Ischemic heart disease
	Intrahepatic cholestasis	• Cholangiopathy • Cirrhosis • Liver transplantation
	Mental Health: Anxiety and Depression	• Postpartum depression

Adapted from Rahim et al. 2020 and Yim et al. 2015

The Prevalence of Gestational Diabetes is Rising





Zhou et al. 2018

EDCs Alter Metabolic Health During Pregnancy

Trimester-Specific Urinary Bisphenol A Concentrations and Blood Glucose Levels Among Pregnant Women From a Fertility Clinic

Yu-Han Chiu,[1,2] Lidia Mínguez-Alarcón,[3] Jennifer B. Ford,[3] Myra Kell
Ellen W. Seely,[6] Carmen Messerlian,[3] John Petrozza,[5] Paige L. Williar
Xiaoyun Ye,[7] Antonia M. Calafat,[7] Russ Hauser,[2,3,5] and Tamarra Jar
for EARTH Study Team

Exposure to Bisphenol a Substitutes and Gestational Diabetes Mellitus: A Prospective Cohort Study in China

Wenyin Zhang[1], Wei Xia[1], Wenyu Liu[1], Xinping Li[1], Jie Hu[1], Bin Zhang[2], Shunqing Xu[1], Zongwei Cai[3] and Yuanyuan Li[1]**

Health (HUST), Ministry of Education and Ministry of Environmental Protection, State

Pesticide Exposure and Self-Reported Gestational Diabetes Mellitus in the Agricultural Health Study

Tina M. Saldana, PHD1, Olga Basso, PHD1, Jane A. Hoppin, SCD1,
Knott, MPA2, Aaron Blair, PHD3, Michael C.R. Alavanja, DRPH3 an

Pregnancy urinary phthalate metabolite concentrations and gestational diabetes risk factors

D. Meeker [c], Tianyi Huang [b, d], Russ Hauser [a], Kelly K. Ferguson [c, e],
cElrath [f], Ellen W. Seely [g]

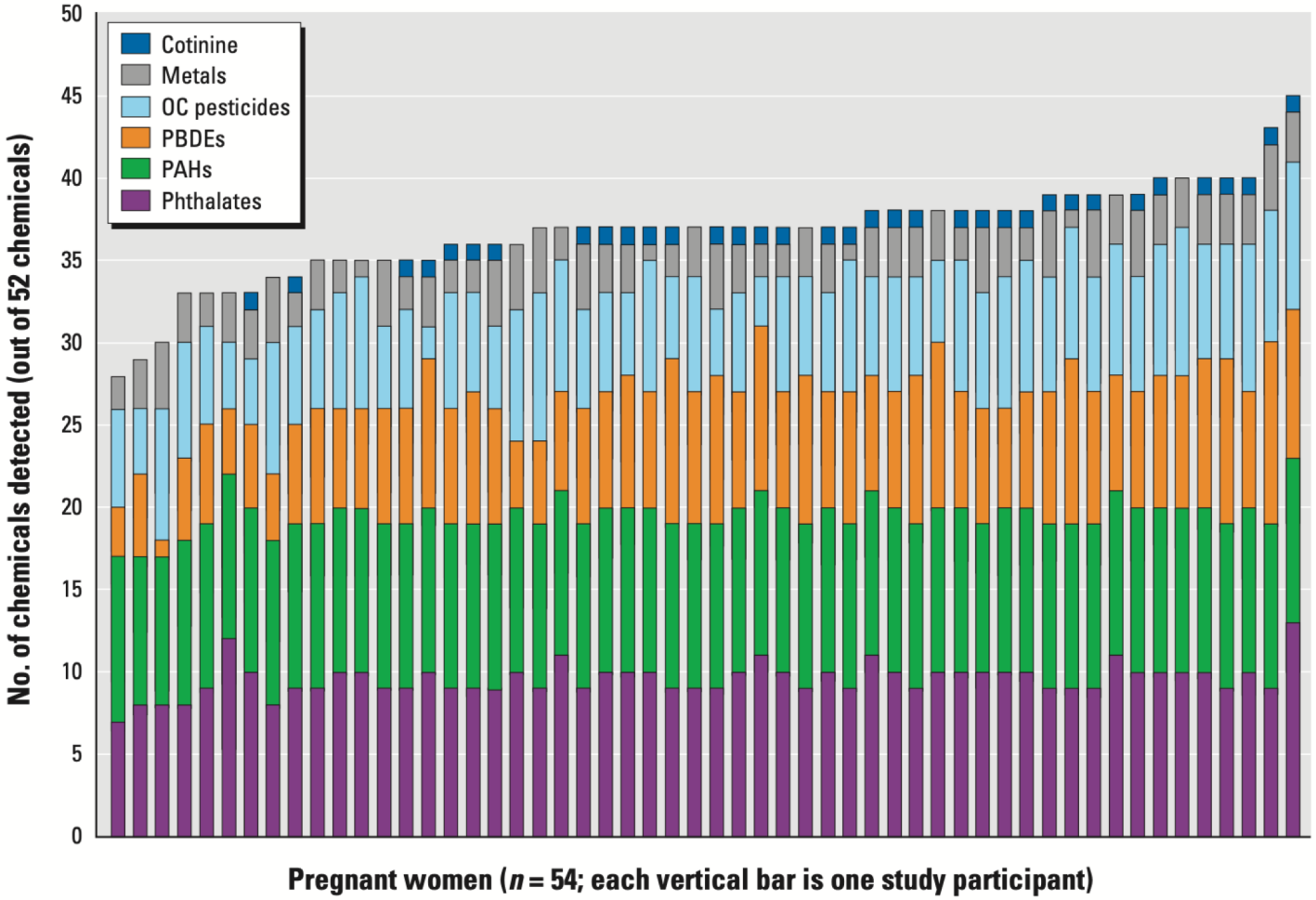
Maternal urinary phthalate metabolites in relation to gestational diabetes and glucose intolerance during pregnancy

Rachel M. Shaffer [a], Kelly K. Ferguson [b], Lianne Sheppard [a, c],
Suchitra Chandrasekaran [g], Shanna H. Swan [h], Emily S. Barrett [i], Ru
McElrath [l], Sheela Sathyanarayana [a, m], the TIDES Study team

Urinary concentrations of parabens mixture and pregnancy glucose levels among women from a fertility clinic

Andrea Bellavia [a, b], Yu-Han Chiu [c], Florence M. Brown [d], Lidia Mínguez-Alarcón [a], Jennifer B. Ford [a], Myra Keller [a], John Petrozza [e], Paige L. Williams [b, f], Xiaoyun Ye [g], Antonia M. Calafat [g], Russ Hauser [a, e, f], Tamarra James-Todd [a, f], for the EARTH Study Team

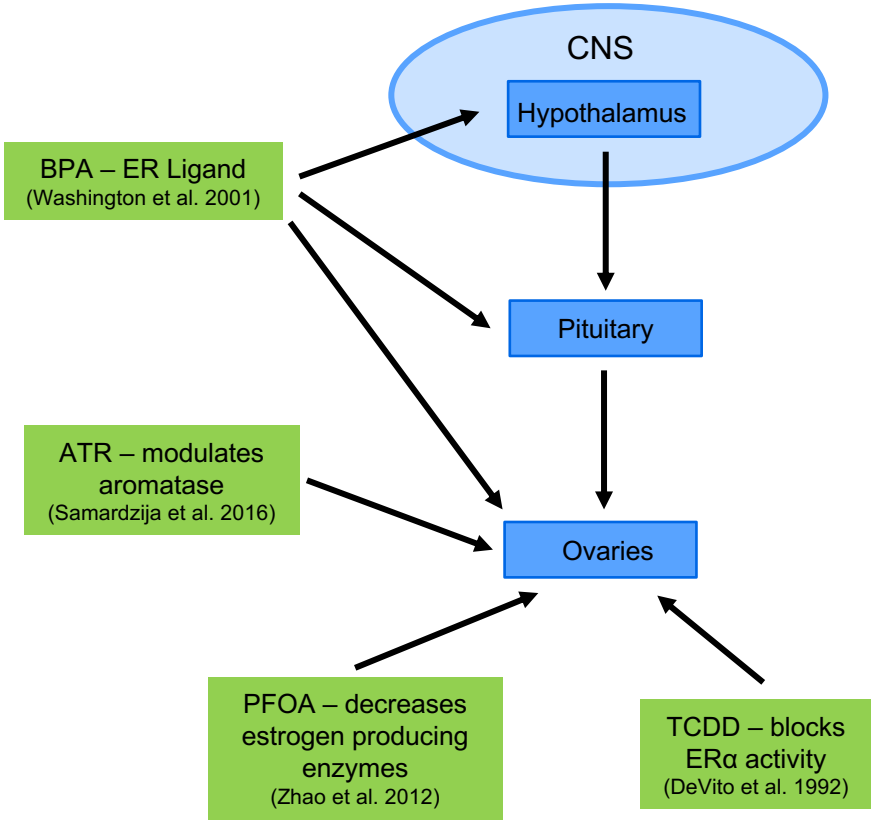
Pregnant Women are Exposed to Numerous EDCs

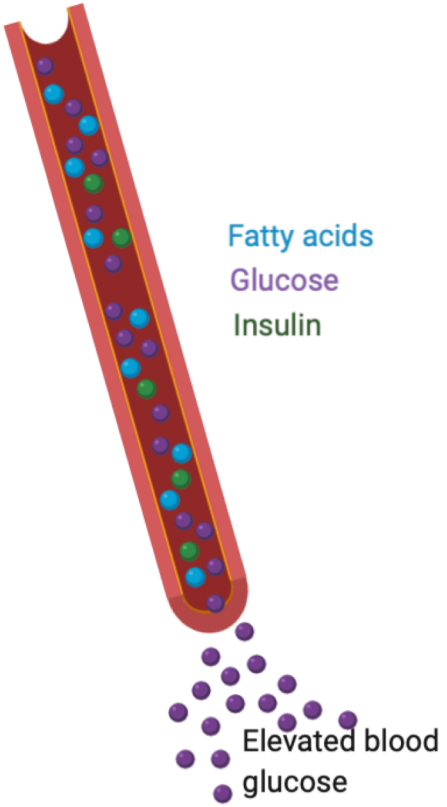


Woodruff et al. 2011

Multiple Estrogenic Hits

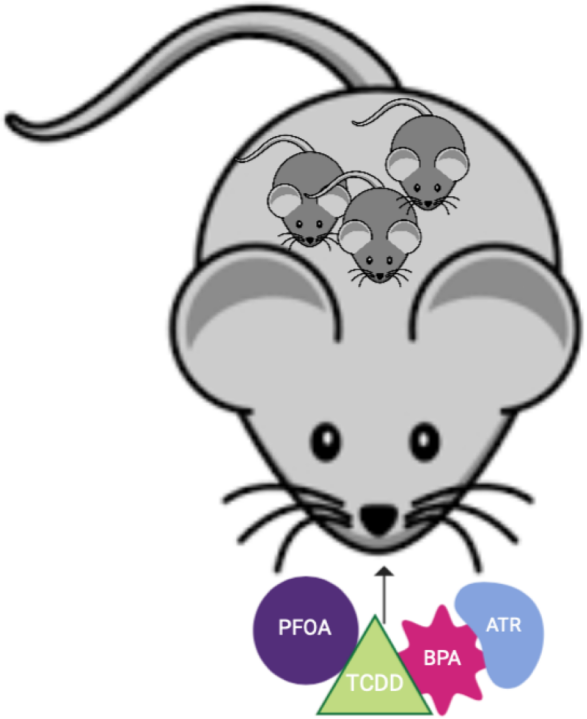
Hypothesis: Multiple EDC hits during pregnancy will disrupt the hypothalamic-pituitary-gonadal axis and increases blood glucose.

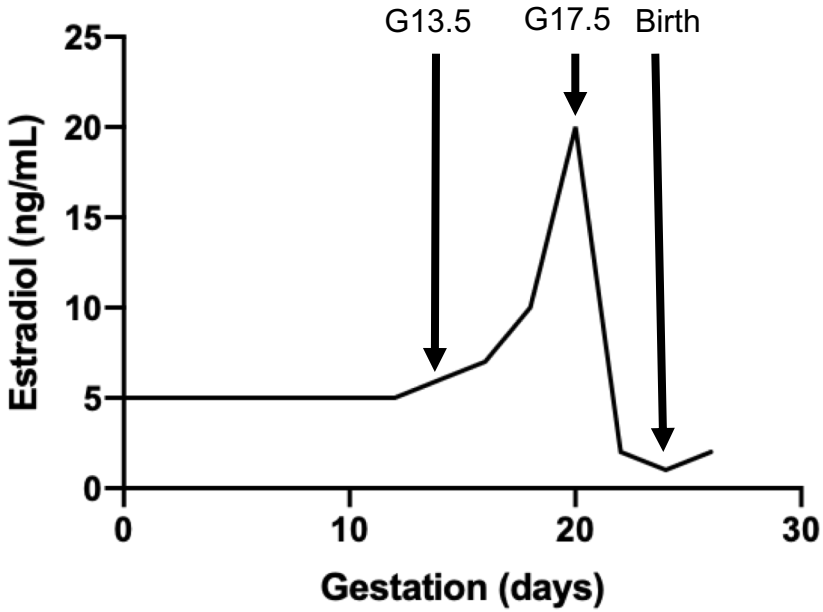




Brummelte and Galea 2016; Miller and Takahashi 2013; Cory-Slechta 2005

Does MIX exposure decrease estradiol during pregnancy?

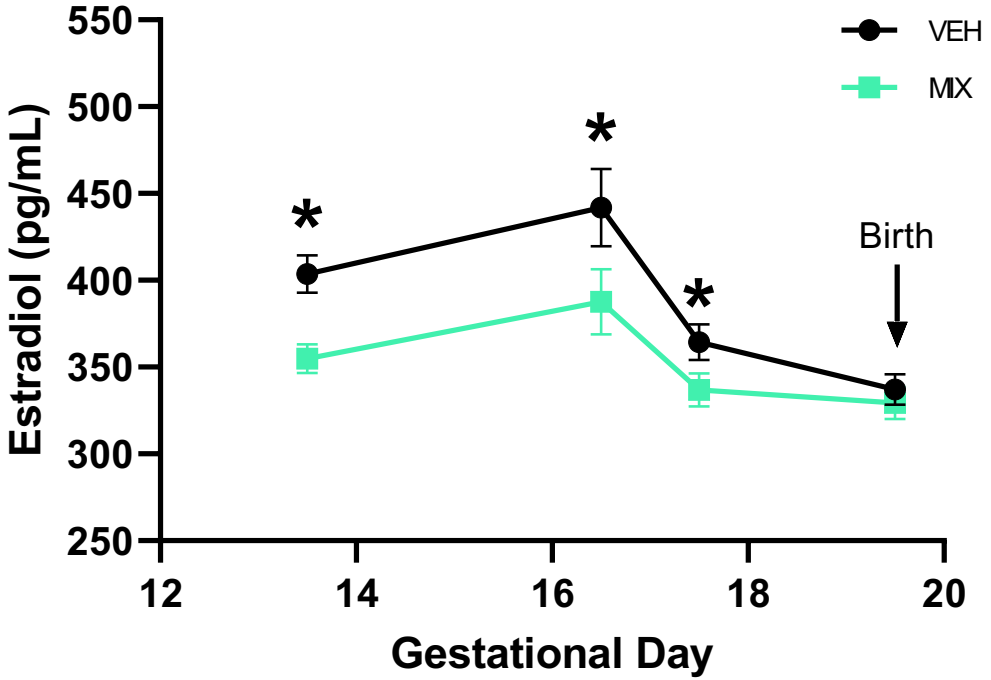




Atrazine (ATR): 10 mg/kg
Bisphenol-A (BPA): 50 μg/kg
Perfluorooctanoic acid (PFOA): 0.1 mg/kg
2,3,7,8-tetrachlorodibenzodioxin (TCDD): 0.036 μg/kg

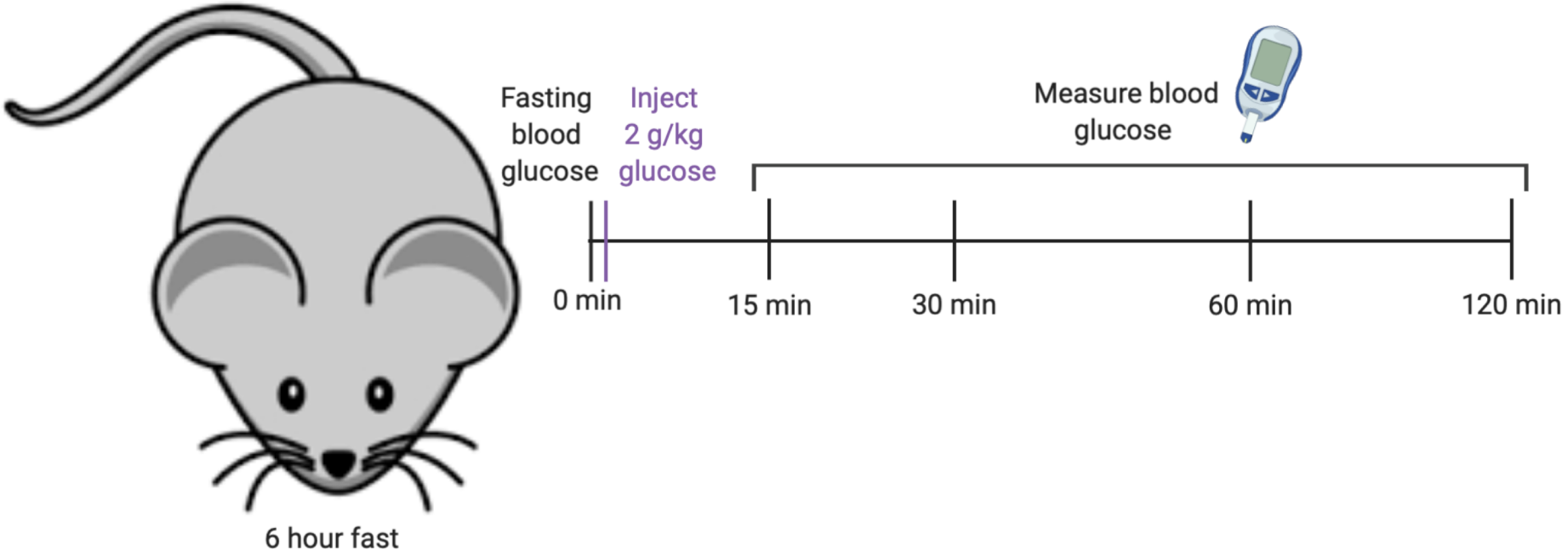
Adapted from Brummelte and Galea 2016

Pregnant MIX dams had lower serum estradiol

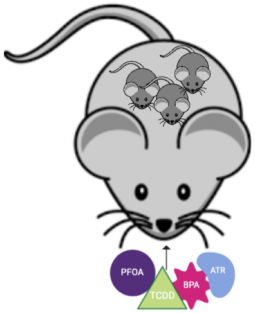


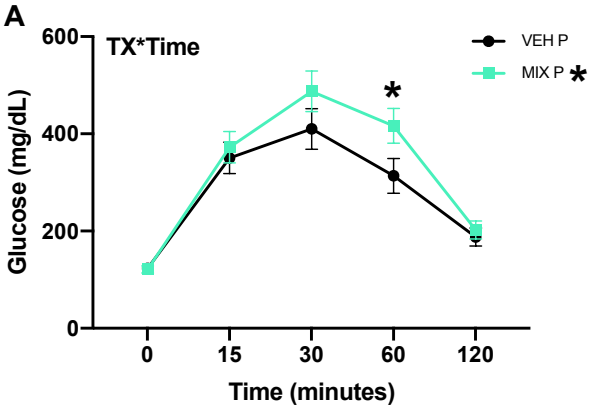
One-sided Student's t test
Data mean ± standard error
n = 4-9/treatment group, * indicated $p \leq 0.05$

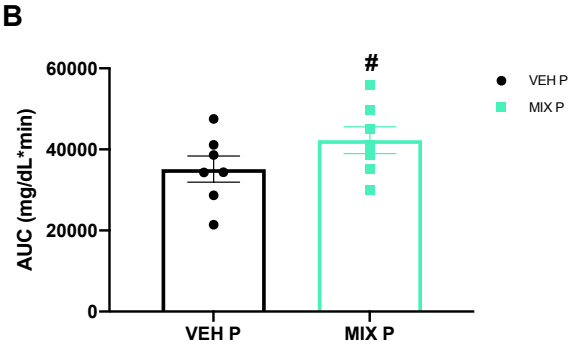
Glucose Tolerance Test

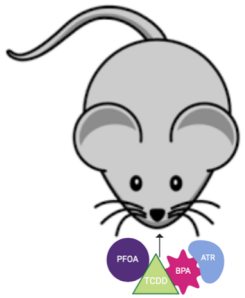


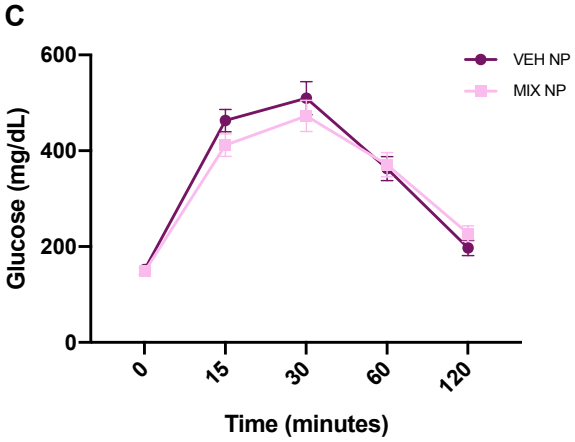
Acute MIX exposure induces metabolic dyshomeostasis only in pregnant females

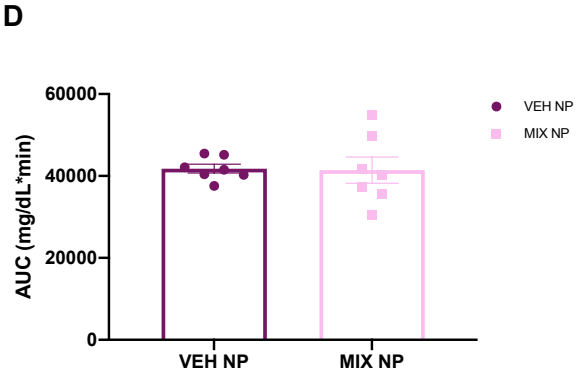






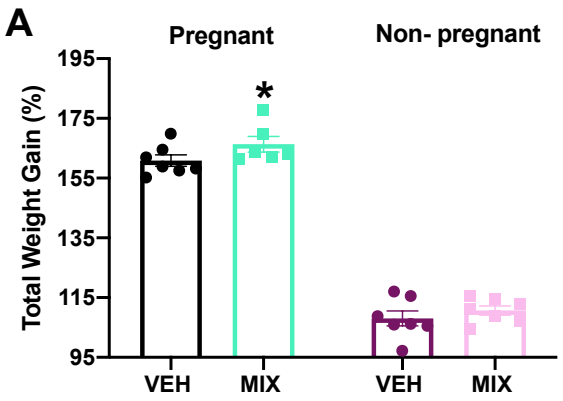


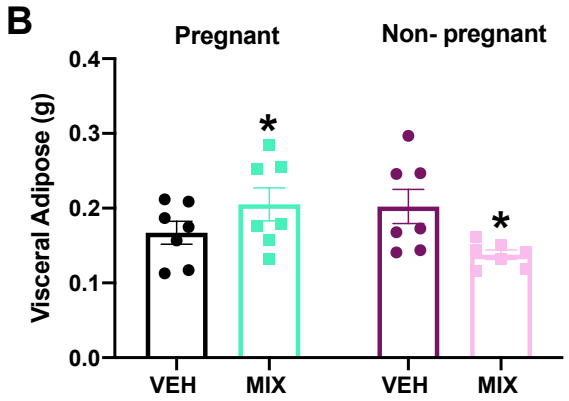


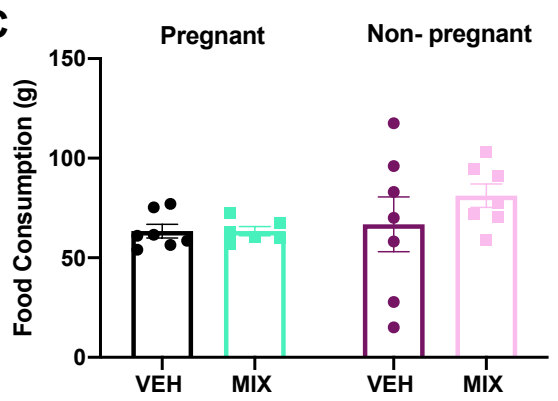


A) and B) Repeated measures ANOVAs
C) and D) Student's t test
Data mean ± standard error
n = 7/treatment group, * indicated $p \leq 0.05$, # indicated $p = 0.07$
P = Pregnant and NP =Non-pregnant

Elevated weight gain and visceral adipose in only MIX pregnant females

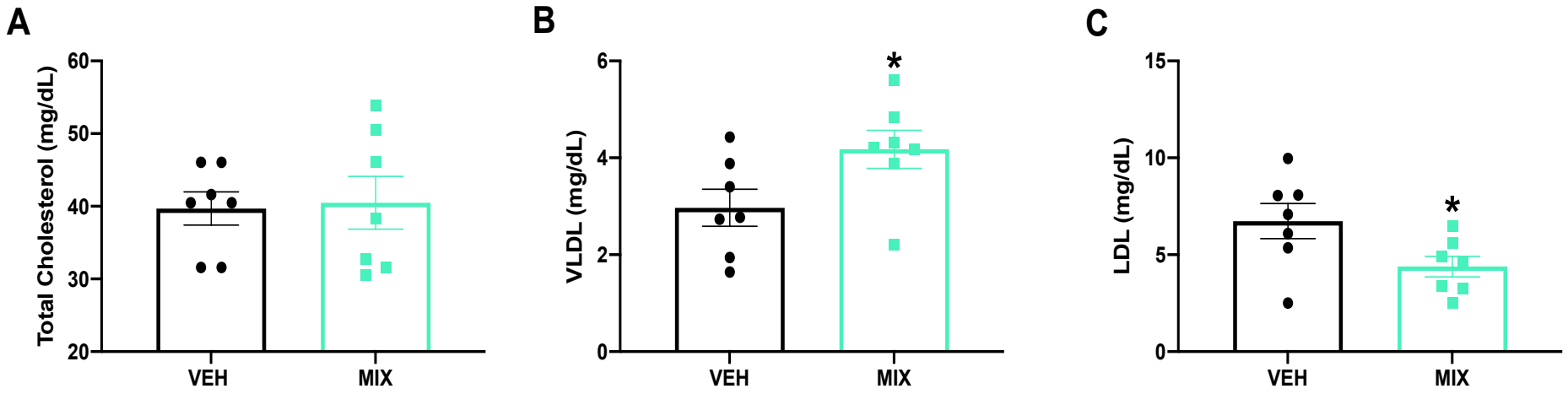






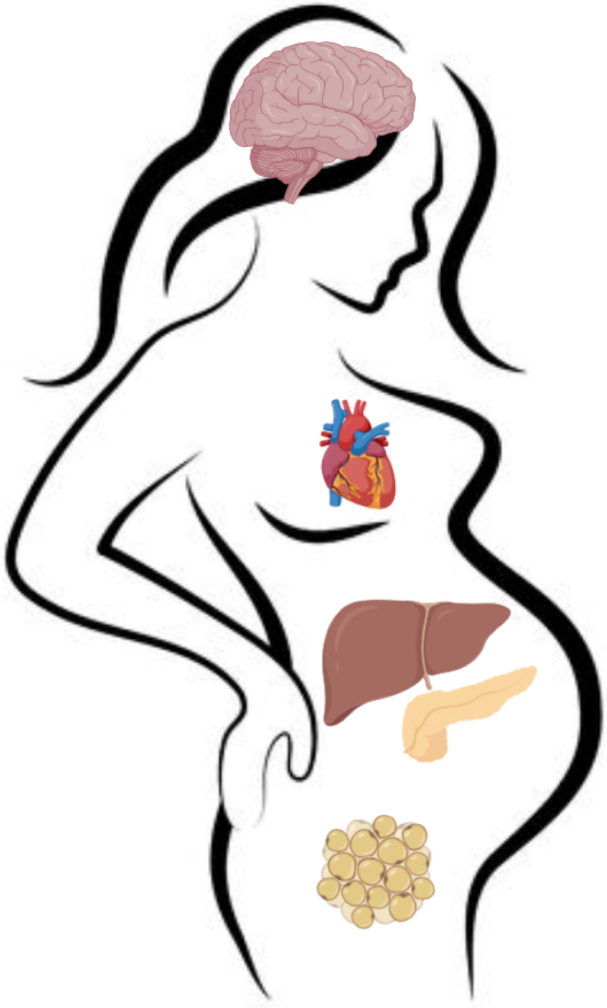
Student's t test
Data mean ± standard error
n = 6-7/treatment group, * indicated $p \leq 0.05$
P = Pregnant and NP =Non-pregnant

Acute MIX exposure altered lipids in pregnant females



Student's t test
Data mean ± standard error
n = 7/treatment group, * indicated $p \leq 0.05$

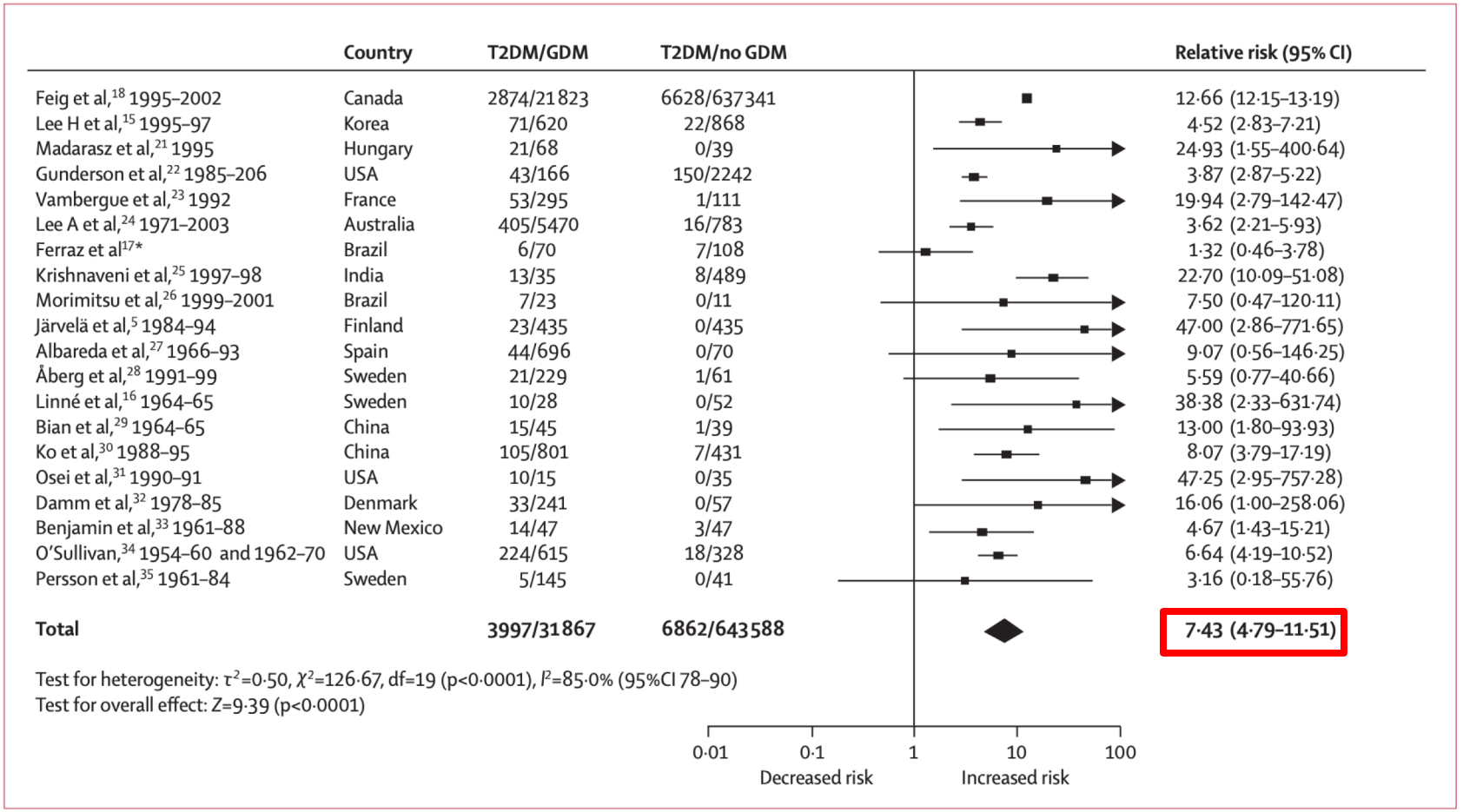
Pregnancy EDC Exposure and Long-term Maternal Health



EDC Exposure	Disease during pregnancy	Long-term maternal health outcomes
Altered reproductive hormone levels	Gestational diabetes and weight gain	• Diabetes • Metabolic syndrome • Insulin resistance • Obesity
	Hypertensive disorders	• Chronic hypertension • Ischemic heart disease
	Intrahepatic cholestasis	• Cholangiopathy • Cirrhosis • Liver transplantation
	Mental Health: Anxiety and Depression	• Postpartum depression

Adapted from Rahim et al. 2020 and Yim et al. 2015

Gestational Diabetes, a Predictor of Type 2 Diabetes



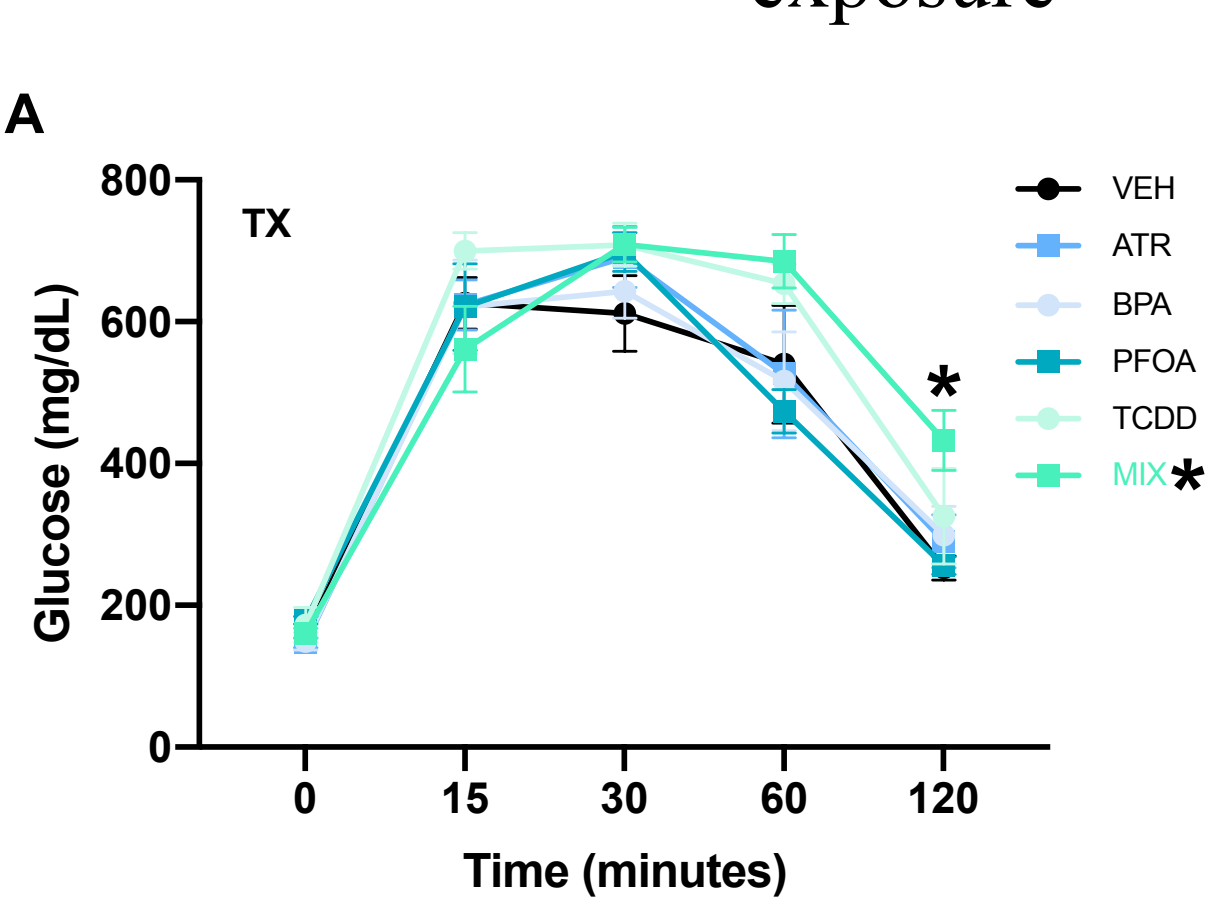
	Country	T2DM/GDM	T2DM/no GDM	Relative risk (95% CI)
Feig et al,[18] 1995–2002	Canada	2874/21823	6628/637341	12·66 (12·15–13·19)
Lee H et al,[15] 1995–97	Korea	71/620	22/868	4·52 (2·83–7·21)
Madarasz et al,[21] 1995	Hungary	21/68	0/39	24·93 (1·55–400·64)
Gunderson et al,[22] 1985–206	USA	43/166	150/2242	3·87 (2·87–5·22)
Vambergue et al,[23] 1992	France	53/295	1/111	19·94 (2·79–142·47)
Lee A et al,[24] 1971–2003	Australia	405/5470	16/783	3·62 (2·21–5·93)
Ferraz et al[17]*	Brazil	6/70	7/108	1·32 (0·46–3·78)
Krishnaveni et al,[25] 1997–98	India	13/35	8/489	22·70 (10·09–51·08)
Morimitsu et al,[26] 1999–2001	Brazil	7/23	0/11	7·50 (0·47–120·11)
Järvelä et al,[5] 1984–94	Finland	23/435	0/435	47·00 (2·86–771·65)
Albareda et al,[27] 1966–93	Spain	44/696	0/70	9·07 (0·56–146·25)
Åberg et al,[28] 1991–99	Sweden	21/229	1/61	5·59 (0·77–40·66)
Linné et al,[16] 1964–65	Sweden	10/28	0/52	38·38 (2·33–631·74)
Bian et al,[29] 1964–65	China	15/45	1/39	13·00 (1·80–93·93)
Ko et al,[30] 1988–95	China	105/801	7/431	8·07 (3·79–17·19)
Osei et al,[31] 1990–91	USA	10/15	0/35	47·25 (2·95–757·28)
Damm et al,[32] 1978–85	Denmark	33/241	0/57	16·06 (1·00–258·06)
Benjamin et al,[33] 1961–88	New Mexico	14/47	3/47	4·67 (1·43–15·21)
O'Sullivan,[34] 1954–60 and 1962–70	USA	224/615	18/328	6·64 (4·19–10·52)
Persson et al,[35] 1961–84	Sweden	5/145	0/41	3·16 (0·18–55·76)
Total		**3997/31867**	**6862/643588**	**7·43 (4·79–11·51)**

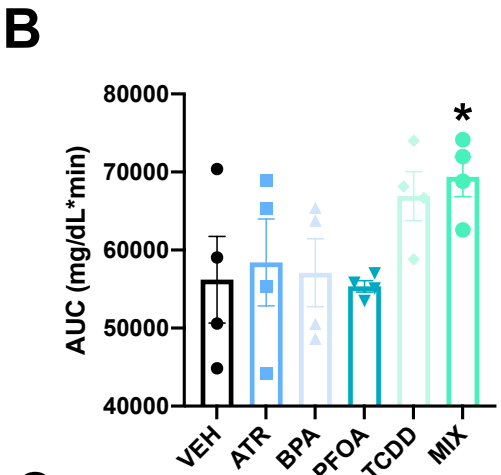
Test for heterogeneity: τ^2=0·50, χ^2=126·67, df=19 (p<0·0001), I^2=85·0% (95%CI 78–90)
Test for overall effect: Z=9·39 (p<0·0001)

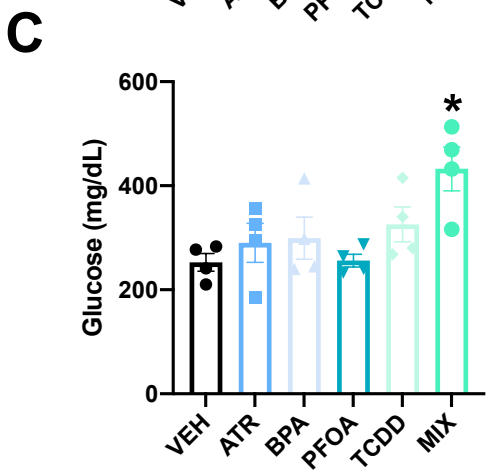
0·01 0·1 1 10 100
Decreased risk Increased risk

Bellamy et al. 2009

MIX induces elevated glucose following exposure

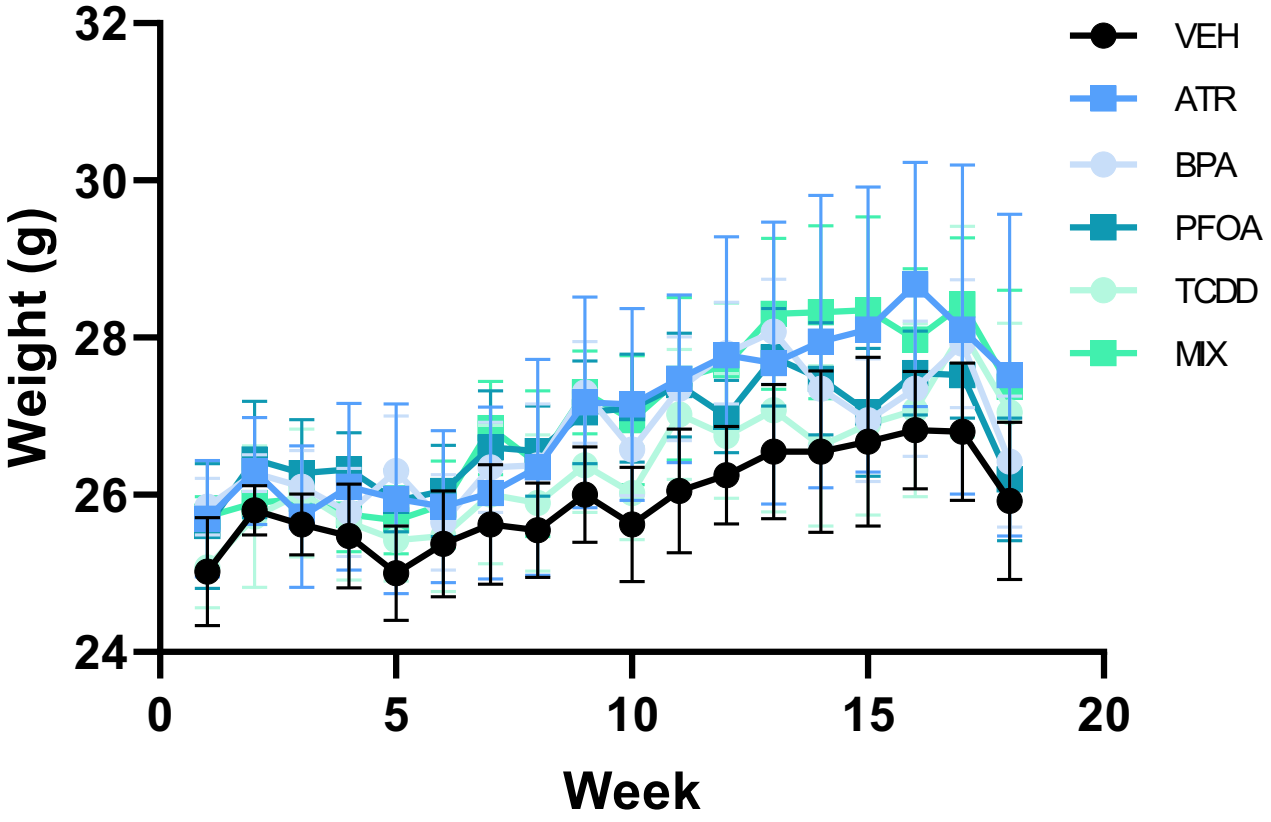






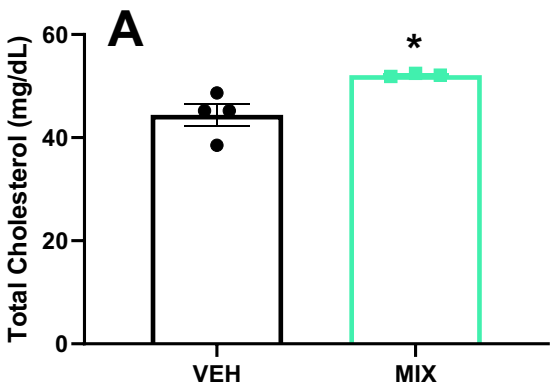
A) Repeated measures ANOVAs
B and C) One-way ANOVA followed by student's t test
Data mean ± standard error
n = 4/treatment group, * indicated $p \leq 0.05$

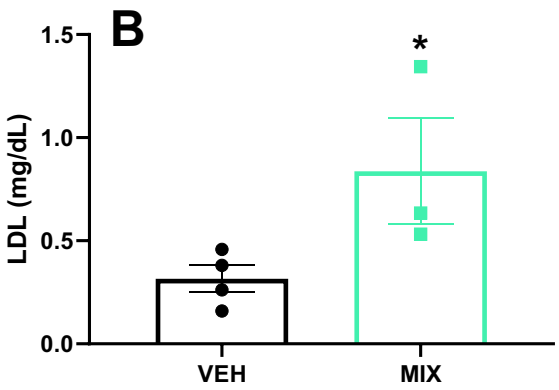
Weight was unaltered by 6 months

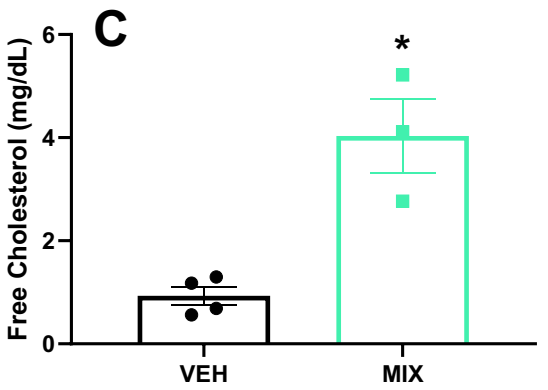


Repeated measures ANOVAs
Data mean ± standard error
n =4/treatment group

MIX elevated serum total cholesterol, LDL, and free cholesterol







Student's t test
Data mean ± standard error
n = 3-4/treatment group, * indicated $p \leq 0.05$

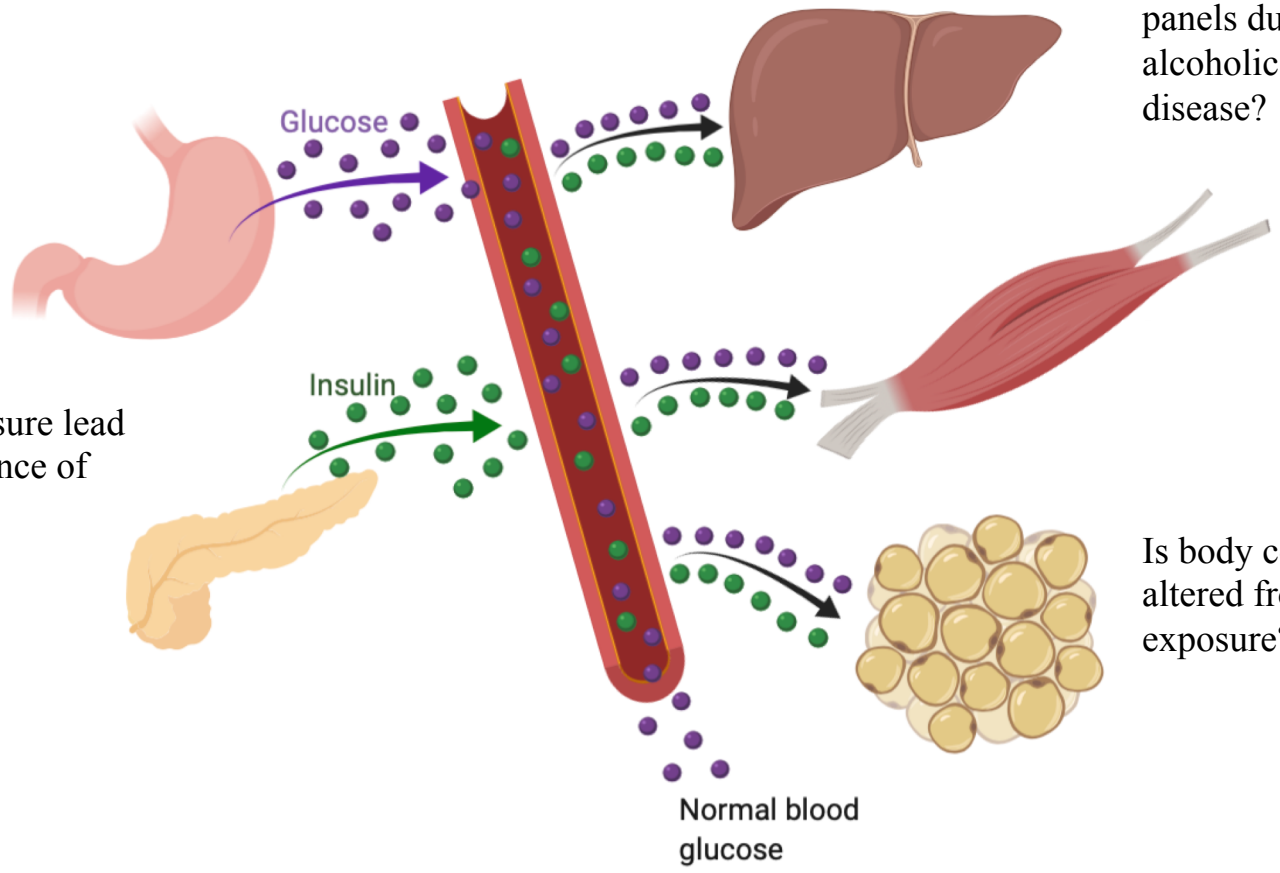
Metabolic Health Conclusions

- Metabolic Health During Pregnancy
  - MIX reduces estradiol during pregnancy.
  - Glucose processing is only altered in MIX exposed pregnant dams.
  - MIX increases gestational weight gain and visceral adipose weight.
  - MIX dams had increased VLDL and decreased LDL.
  - Pregnancy is a critical window for MIX exposure.

- Long-term Maternal Metabolic Health
  - MIX alters long-term glucose processing following a glucose tolerance test.
  - Total cholesterol, LDL, and free cholesterol are only elevated in MIX exposed dams cholesterol panels.
  - Weight gain was unaltered in MIX dams.

Future Directions

Are altered lipid panels due to non-alcoholic fatty liver disease?



Does MIX exposure lead to insulin resistance of organs?

Is body composition altered from MIX exposure?

Acknowledgements

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- Matthew Eckard, Ph.D.
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Susiarjo Lab

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- Ashley Fields, M.S.

Sobolewski Lab

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- Elena Marvin

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- Elizabeth Williams-Velasquez, M.S.
- Toxicology Students

Questions