Tris(1,3-dichloro-2-propyl) phosphate is a metabolism disrupting chemical in male mice

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EHSCC ESI Webinar Series

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University of Kentucky
Center for Appalachian Research in Environmental Sciences
HealthCare
BARNSTABLE BROWN DIABETES CENTER

Overview

- What is TDCPP and why should you care?
- Health consequences associated with exposure
- Data from my mouse model
- Potential mechanism

Why Flame Retardants?

NATIONAL FIRE PROTECTION ASSOCIATION

The leading information and knowledge resource on fire, electrical and related hazards

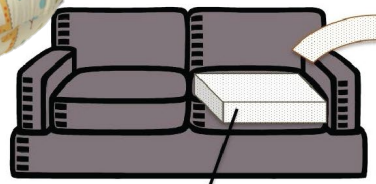
A U.S. fire department responds to a fire.

The time occupants have to escape a fire.

A home fire injury occurs in the U.S.

Organophosphate Flame Retardants

- Sprayed onto polyurethane foam



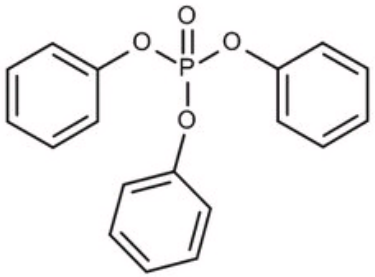
1 Flame retardants are not bound to foam.

2 They off-gas from foam and settle into dust

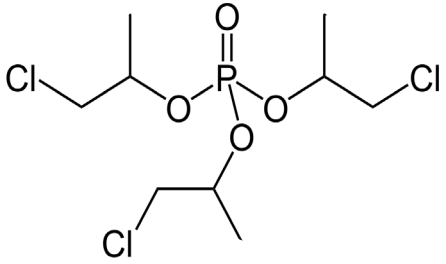
3 Dust is ingested through hand-to-mouth contact

https://www.eopugetsound.org/articles/flame-retardants

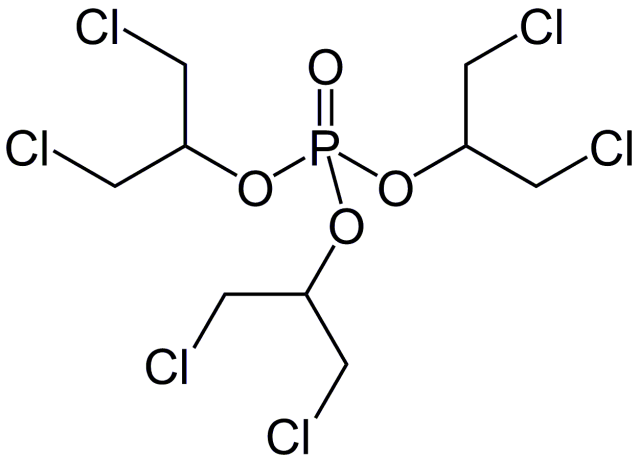
Organophosphate Flame Retardants



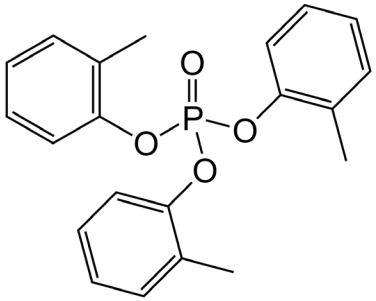
Triphenyl phosphate
TPhP



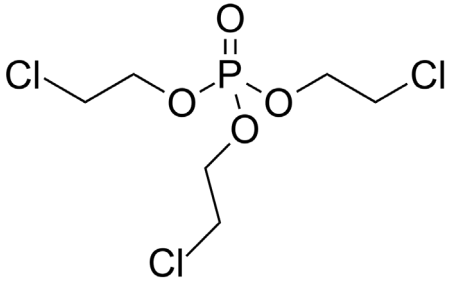
Tris(1-dichloro-2-propyl)phosphate
TCPP



Tris(1,3-dichloro-2-propyl)phosphate
TDCPP



Tricresyl phosphate
TCP



Tris(2-chloroethyl) phosphate
TCEP

TDCPP Background

Associations between urinary organophosphate ester metabolites and measures of adiposity among U.S. children and adults: NHANES 2013–2014

M. Boyle[a,1], J.P. Buckley[b], L. Quirós-Alcalá[a,*,1]

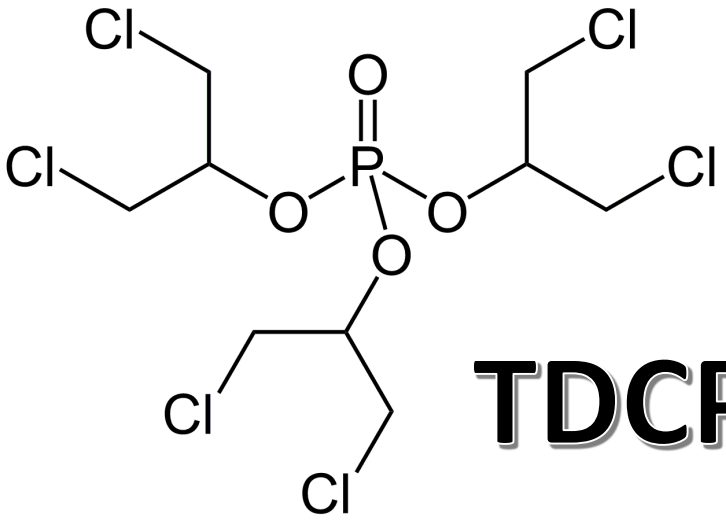
[a] Maryland Institute of Applied Environmental Health, School of Public Health, University of Maryland, College Park, MD, USA
[b] Johns Hopkins University, Department of Environmental Health & Engineering, Department of Epidemiology, Baltimore, MD, USA

	Children (N = 784)						Adults (N = 1672)					
OPE metabolite	DF%	LOD (μg/L)	GM[b]	p25	p50	p75	Max	DF%	GM[b]	p25	p50	p75	Max
DPHP	96.4	0.16	1.51 (1.57)	0.73 (0.77)	1.43 (1.41)	2.97 (2.66)	193 (235.4)	90	0.72 (0.79)	0.32 (0.40)	0.72 (0.68)	1.44 (1.28)	102 (112.1)
BDCPP	98.7	0.11	1.71 (1.78)	0.72 (0.76)	1.57 (1.60)	3.50 (3.26)	169 (75.8)	90.6	0.72 (0.78)	0.27 (0.35)	0.69 (0.70)	1.74 (1.41)	88.9 (67.9)
BCEP	94.8	0.08	0.63 (0.65)	0.26 (0.28)	0.57 (0.59)	1.34 (1.26)	97.4 (44.2)	87.3	0.37 (0.40)	0.15 (0.19)	0.36 (0.35)	0.85 (0.73)	110 (60.4)
DBUP	83.7	0.05	0.23 (0.24)	0.11 (0.13)	0.29 (0.24)	0.45 (0.43)	70.3 (42.3)	79.7	0.18 (0.19)	0.07 (0.11)	0.23 (0.20)	0.35 (0.33)	7.33 (15.9)
BCPP	67.2	0.10	0.22 (0.23)	<LOD	0.20 (0.21)	0.43 (0.41)	46.7 (50.8)	58.4	0.18 (0.20)	<LOD	0.14 (0.18)	0.33 (0.32)	14.6 (18.5)

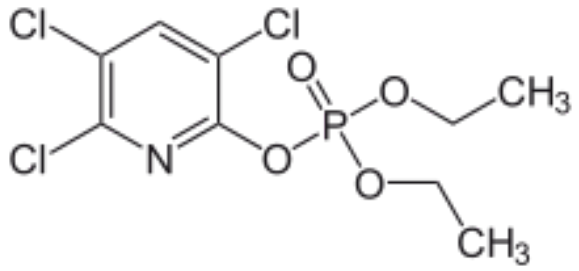
PMID: 25306433

TDCPP Background

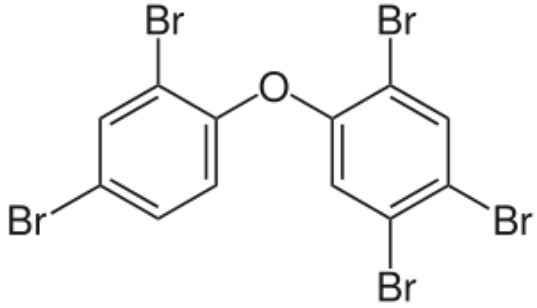
- TDCPP does not affect acetylcholinesterase activity
- TDCPP does not bioaccumulate



TDCPP



Organophosphate Pesticide: Chlorpyrifos



Flame Retardant : Pentabromodiphenyl ether (PBDE)

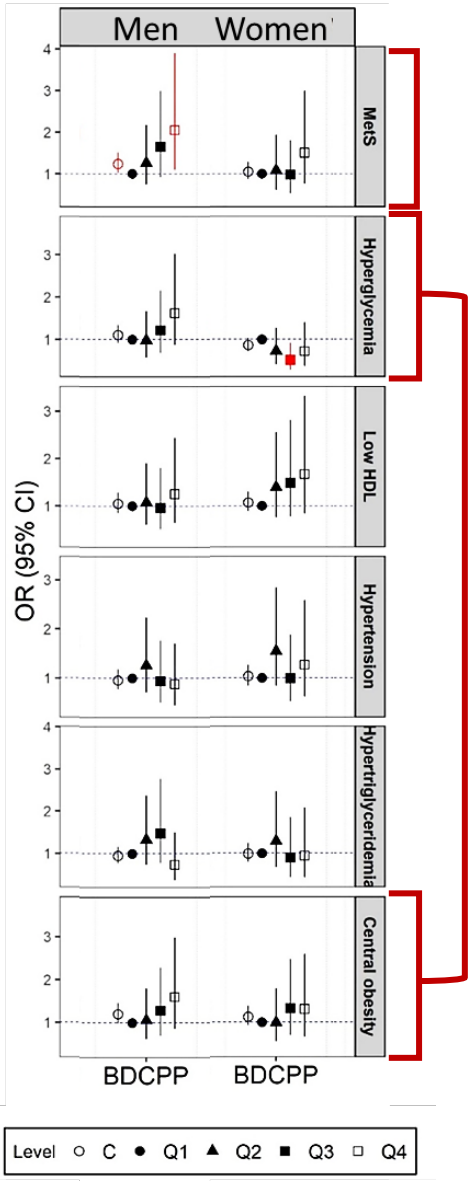
Metabolic Heath Consequences of TDCPP Exposure

Exposure to Organophosphate esters and metabolic syndrome in adults

Kai Luo [1], Rongrong Zhang [2], Ruxianguli Aimuzi [1], Yuqing Wang [3], Min Nian [1], Jun Zhang [4]

Affiliations + expand

PMID: 32679393 DOI: 10.1016/j.envint.2020.105941



Insulin resistance
Type 2 diabetes

PMID: 32679393.

TDCPP Exposure Model

- 6-week-old C57BL/6J mice
- *Ad libitum* dietary TDCPP exposure for 5 weeks
  - DMSO Vehicle control
  - 0.02 mg TDCPP/kg bw/day
  - 1 mg TDCPP/kg bw/day
  - 100 mg TDCPP/kg bw/day
- Body composition analysis
- Evaluate glucose homeostasis

Selected Nutrient Information[1]			
		% by weight	% kcal from
Protein		17.7	18.9
Carbohydrate		60.0	63.9
Fat		7.2	17.3
Kcal/g	3.8		

[1] Values are calculated from ingredient analysis or manufacturer data

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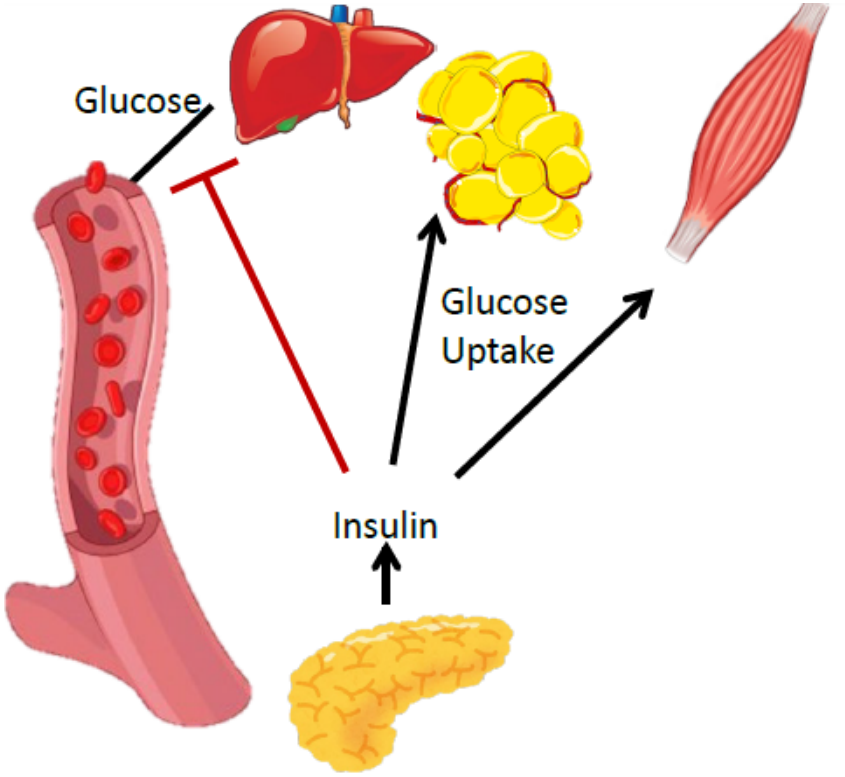
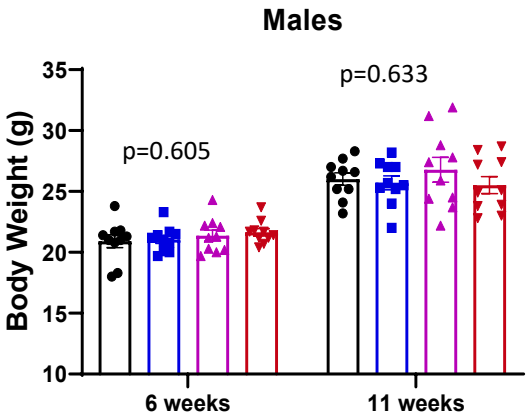
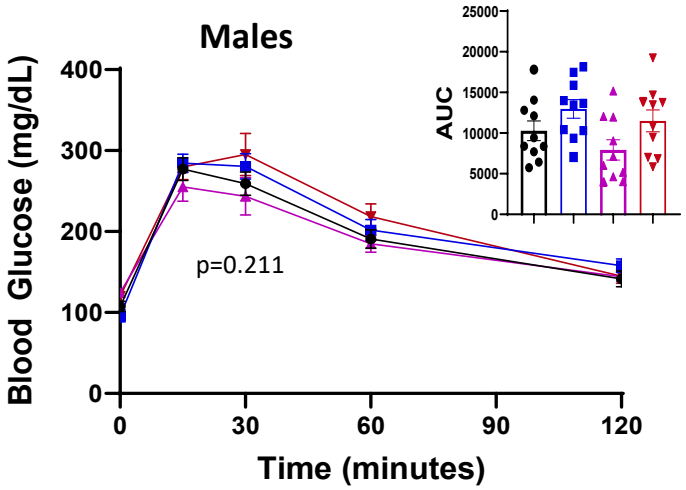
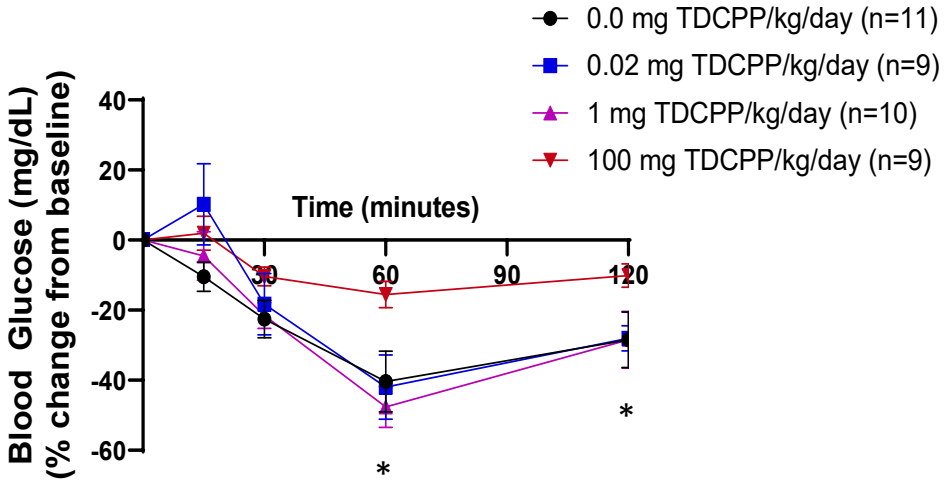


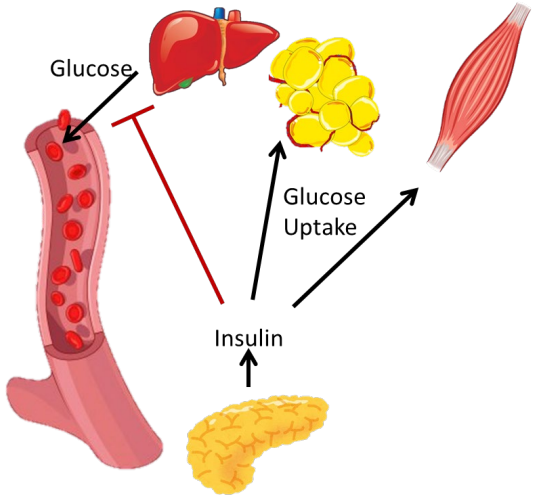
TDCPP causes male-specific and dose-dependent adiposity

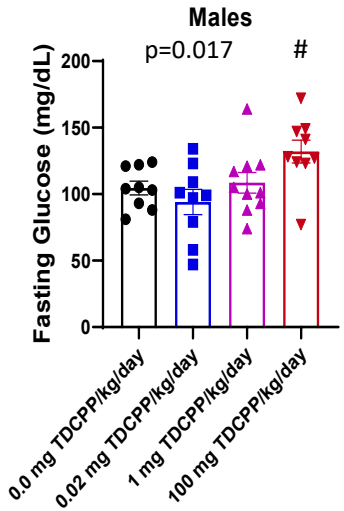


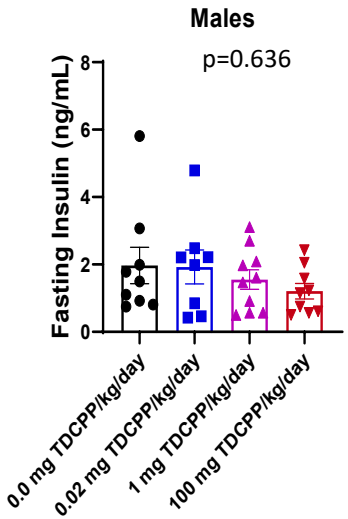
TDCPP causes insulin resistance and fasting hyperglycemia in males



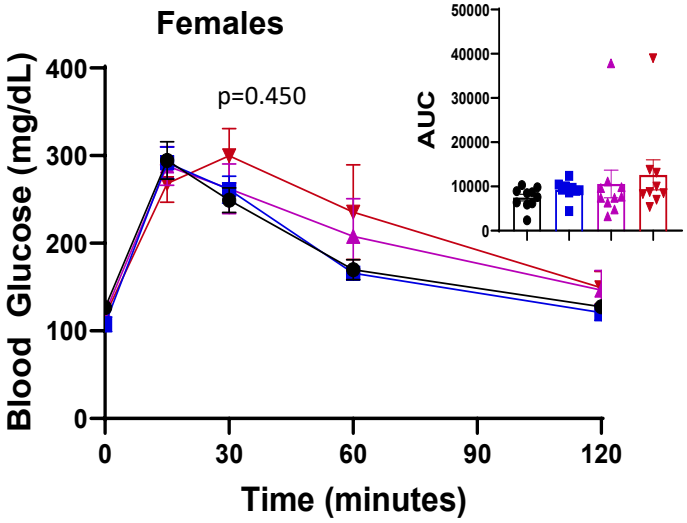


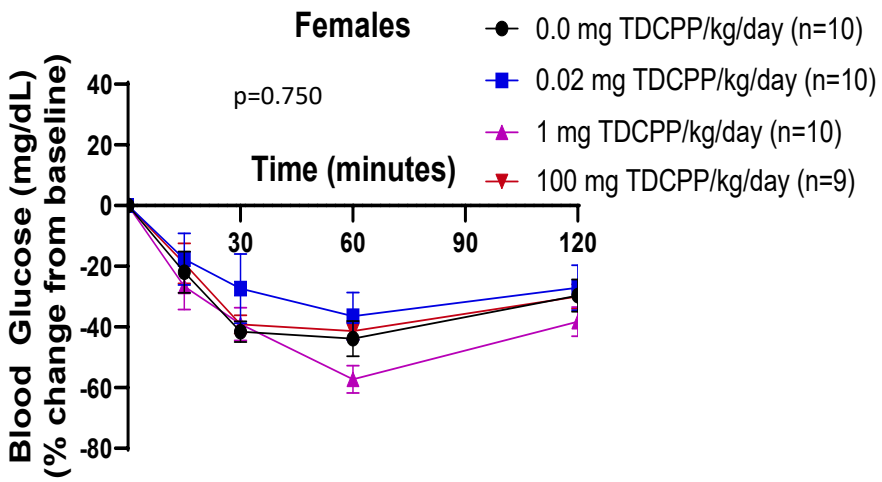


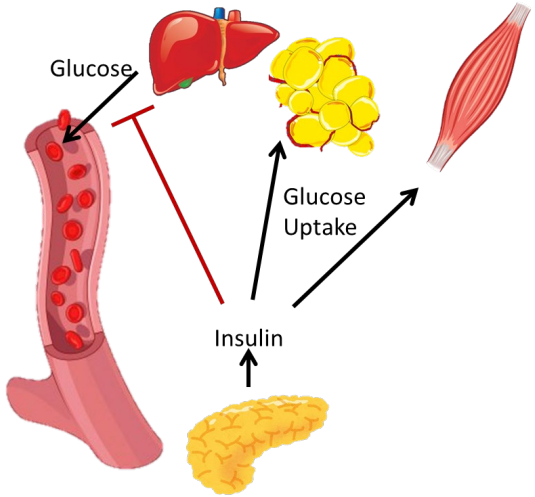


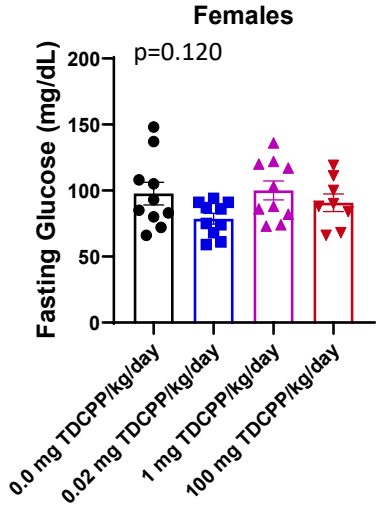


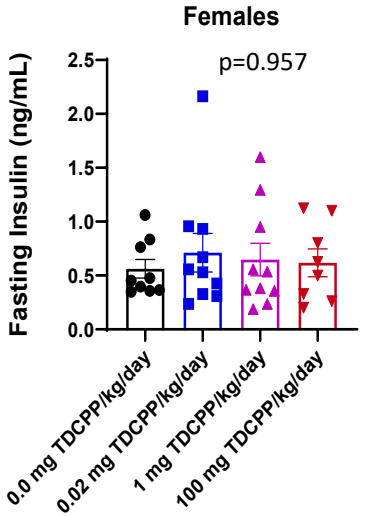
Females are resistant to TDCPP-induced perturbations of glucose homeostasis



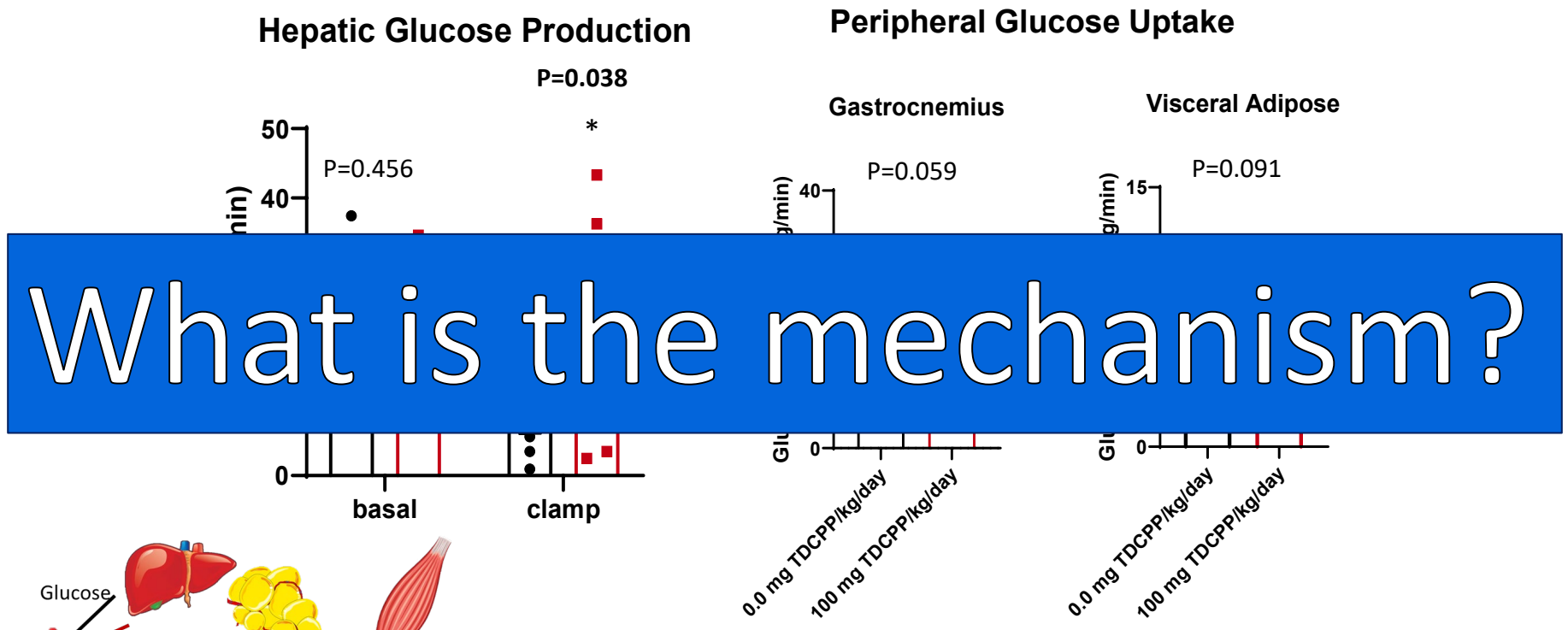




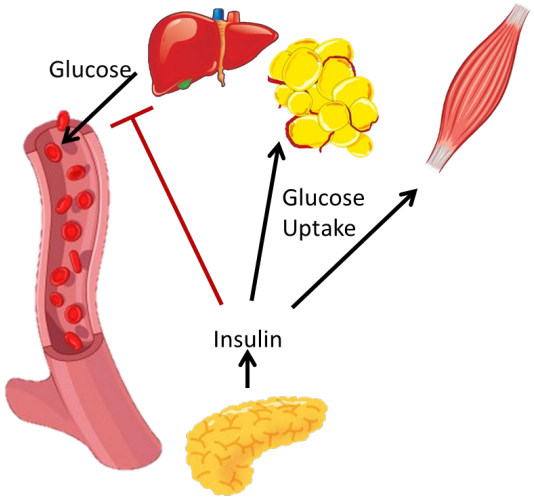




Males have hepatic insulin resistance



What is the mechanism?



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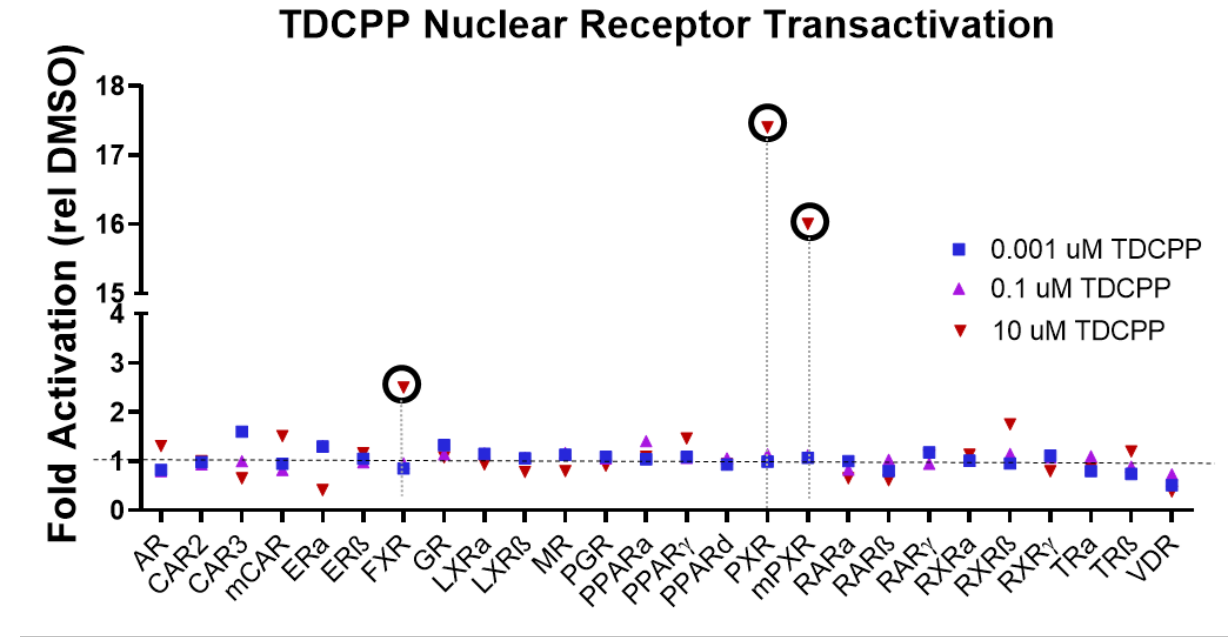
MMPC
Mouse Metabolic Phenotyping Centers

Nuclear Receptor Agonist Activity



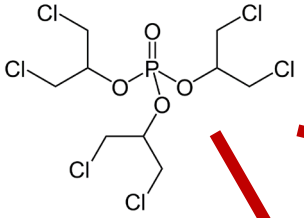
Summary

♂

Adiposity
Insulin resistance

?

PXR



TDCPP

<u>Metabolic Syndrome</u>

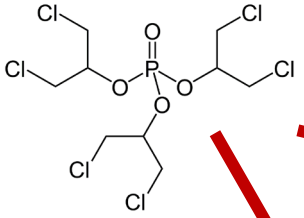
Insulin resistance

- Hyperglycemia
- Central obesity

Summary

?

PXR



TDCPP

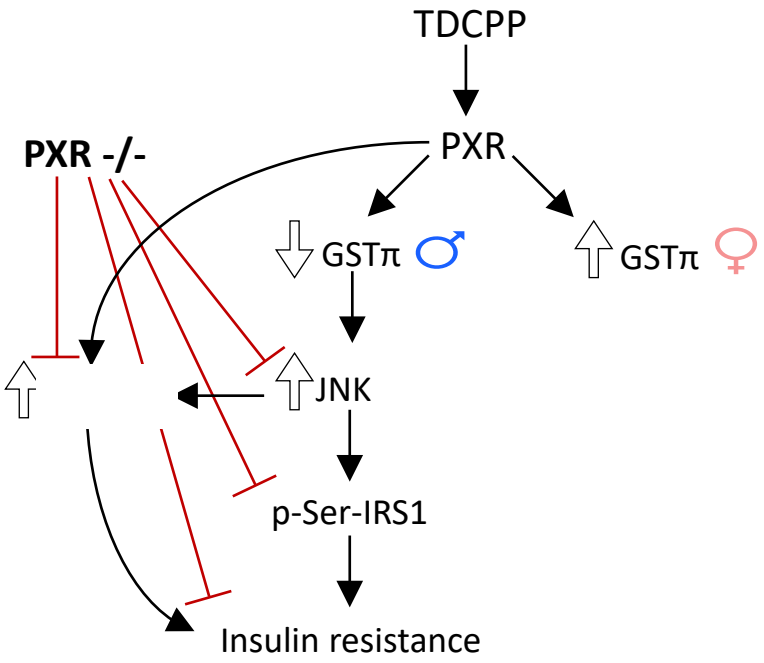
Metabolic Syndrome

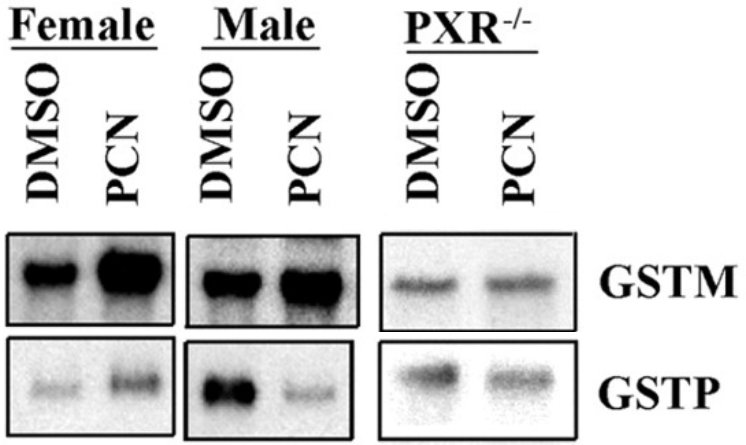
Insulin resistance

- Hyperglycemia
- Central obesity

Future studies to elucidate mechanisms of sex-specific TDCPP-induced metabolic disruption

Hypothesis-Driven Approach





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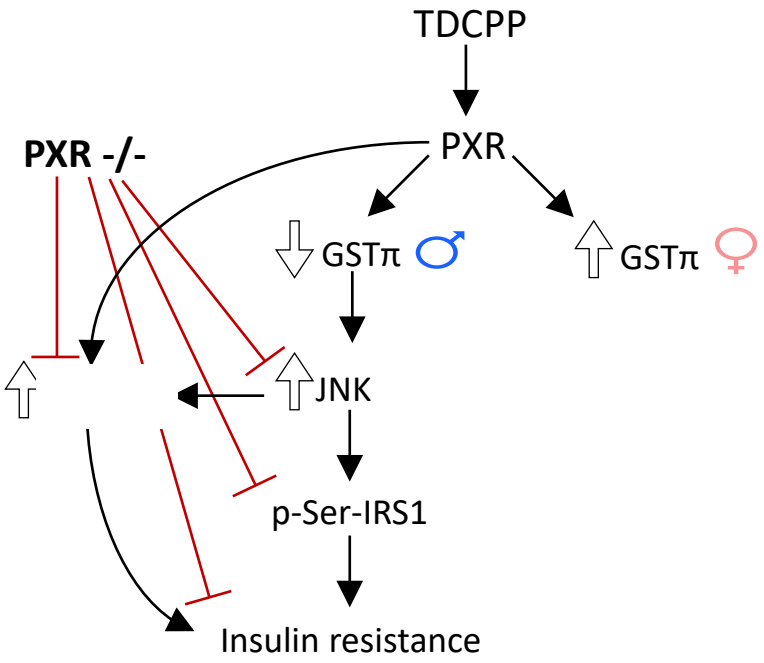
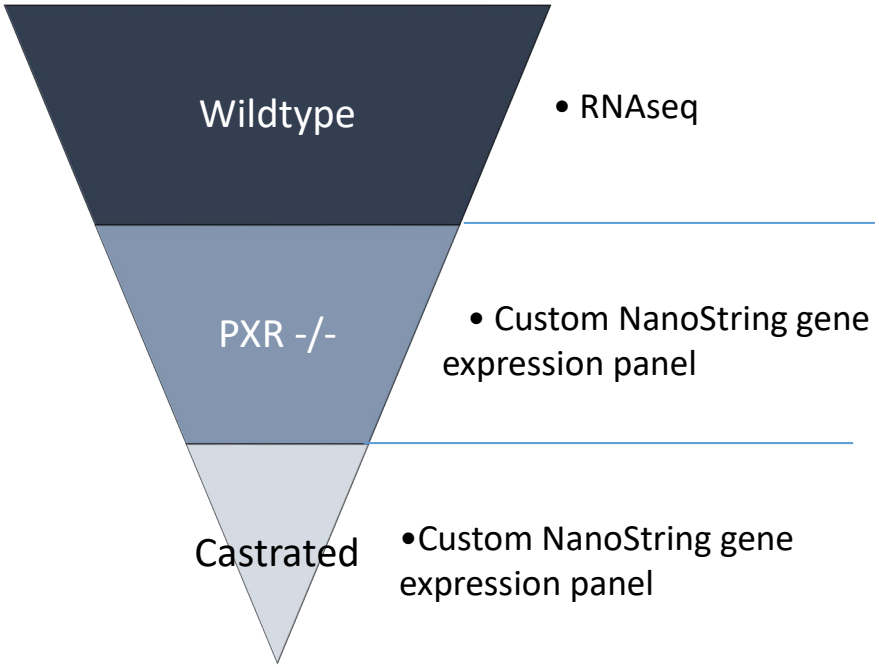
Future studies to elucidate mechanisms of sex-specific TDCPP-induced metabolic disruption

Hypothesis-Driven Approach



Unbiased Funneling Approach



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- Andrew Morris
- Olga Vsevolozhskaya
- Kevin Pearson
- UK-CARES

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QUESTIONS?