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# ToXXicologY: The Importance of Incorporating the Sex Variable in Research Studies

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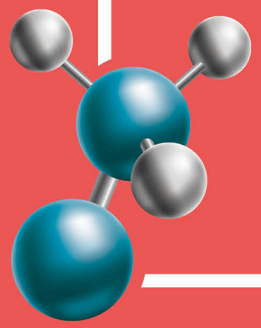


# ToXXicologY: The Importance of Incorporating the Sex Variable in Research Studies

Patricia Silveyra, PhD, ATSF

INDIANA UNIVERSITY BLOOMINGTON

# Learning Objectives

1. Define the terms “sex” and “gender” and their influence on human health
2. Understand the implications of including the sex and gender variables in research studies
3. Identify strategies to incorporate sex as a biological variable in toxicology studies
4. Describe best practices to consider sex differences in experimental designs

# Sex vs. Gender

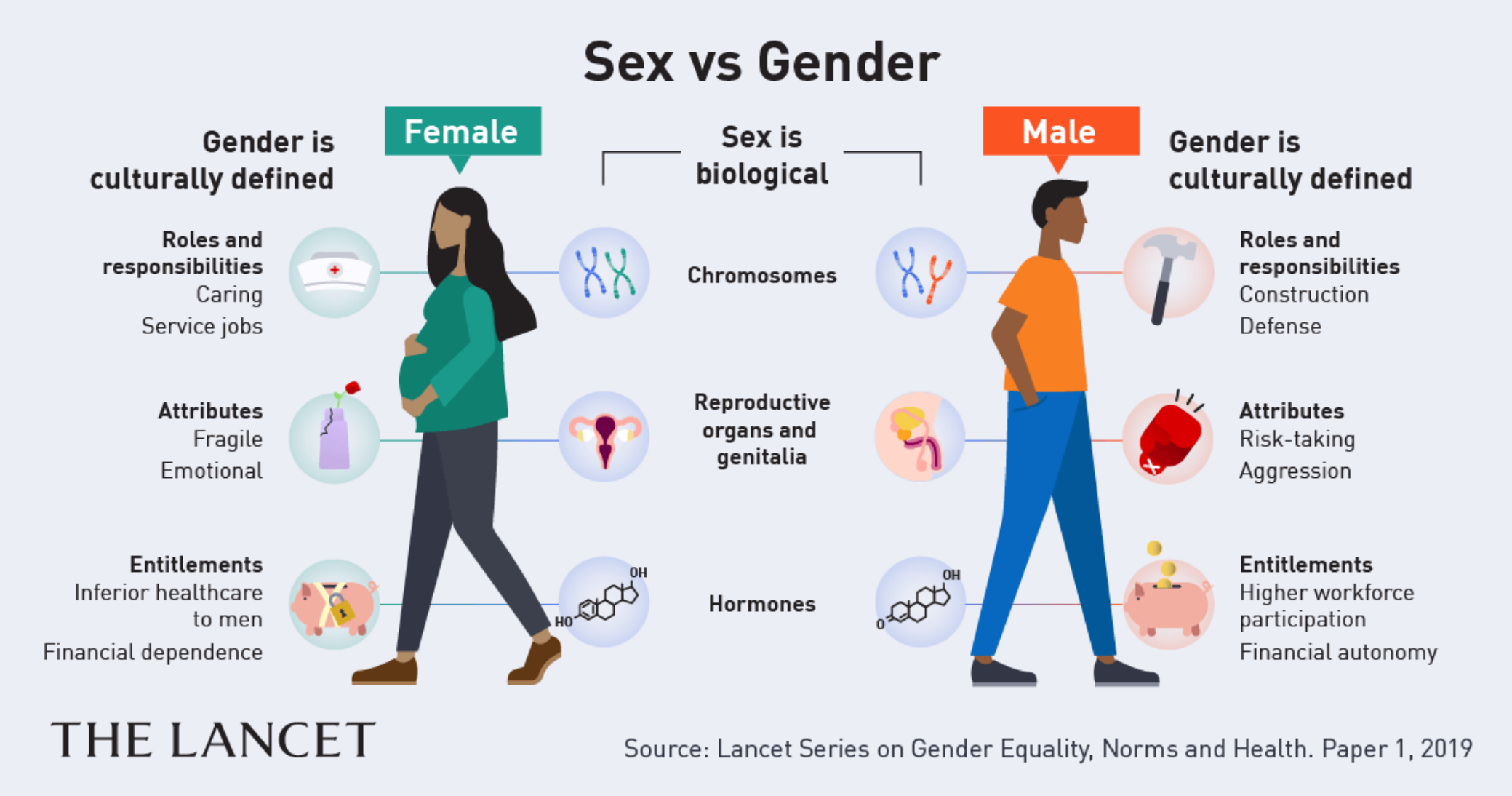
**Sex:**

The biological characteristics that distinguish males and females.

**Gender:**

The socially constructed and enacted roles and behaviors that occur in a historical and cultural context and vary across societies and over time.

# Examples


Sex vs Gender
Female
Male
Gender is culturally defined
Sex is biological
Gender is culturally defined
Roles and responsibilities
Caring
Service jobs
Chromosomes
Roles and responsibilities
Construction
Defense
Attributes
Fragile
Emotional
Reproductive organs and genitalia
Attributes
Risk-taking
Aggression
Entitlements
Inferior healthcare to men
Financial dependence
Hormones
Entitlements
Higher workforce participation
Financial autonomy
OH
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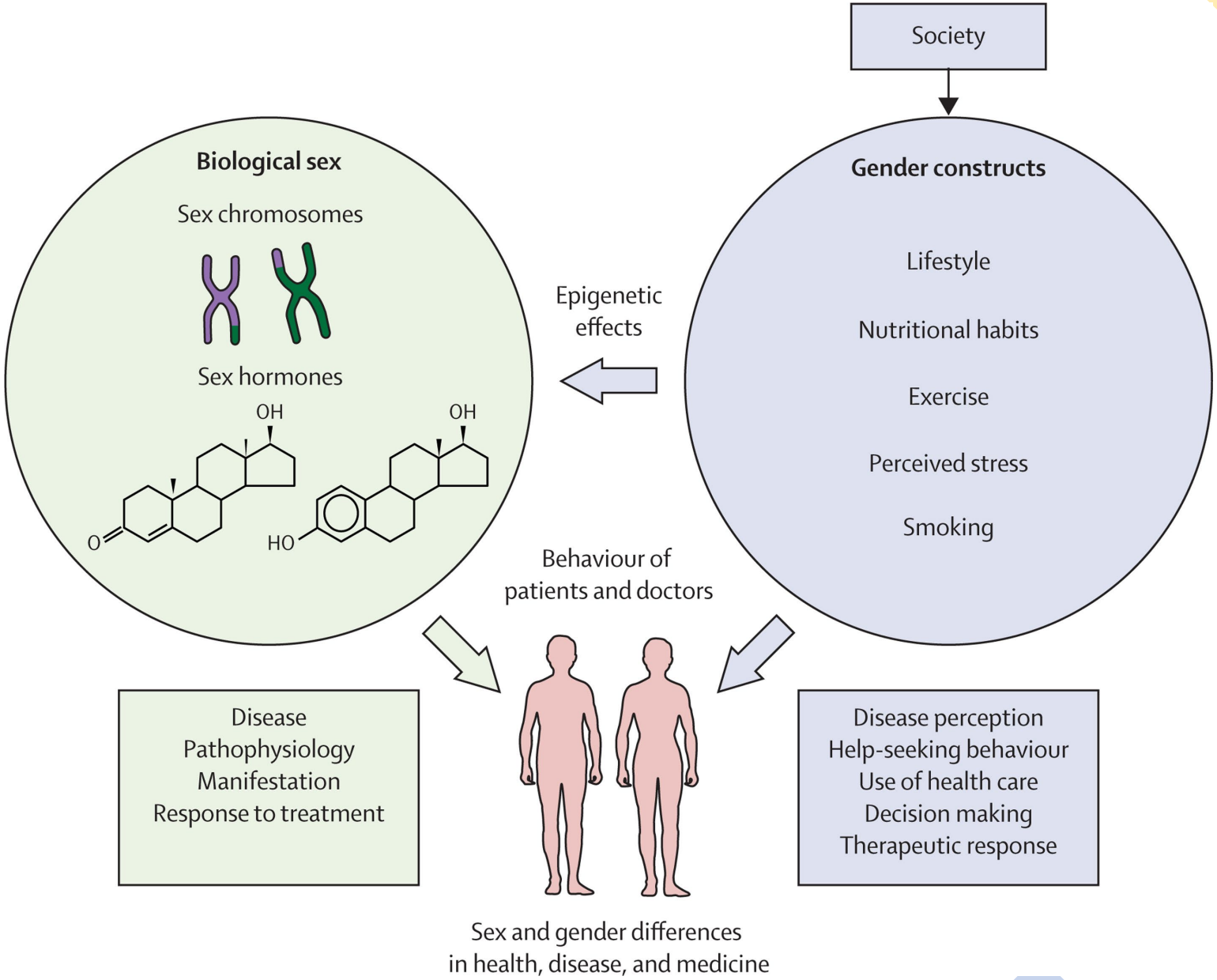
THE LANCET
Source: Lancet Series on Gender Equality, Norms and Health. Paper 1, 2019




https://doi.org/10.1016/S0140-6736(20)31561-0

# NIH Policy on Sex as a Biological Variable

**Consider**

Design studies that take sex into account, or explain why it isn't incorporated

**Collect**

Tabulate sex-based data

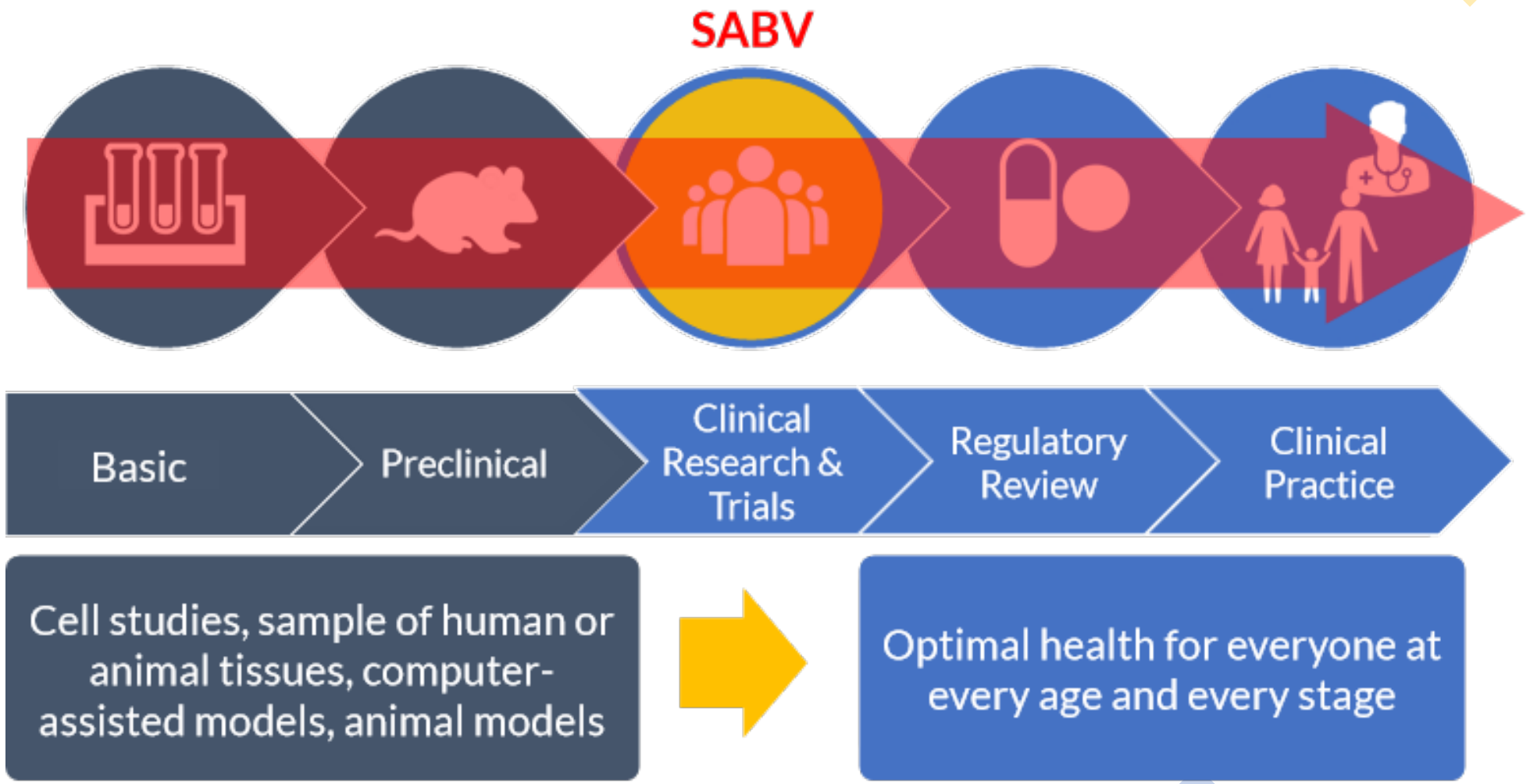
**Characterize**

Analyze sex-based data

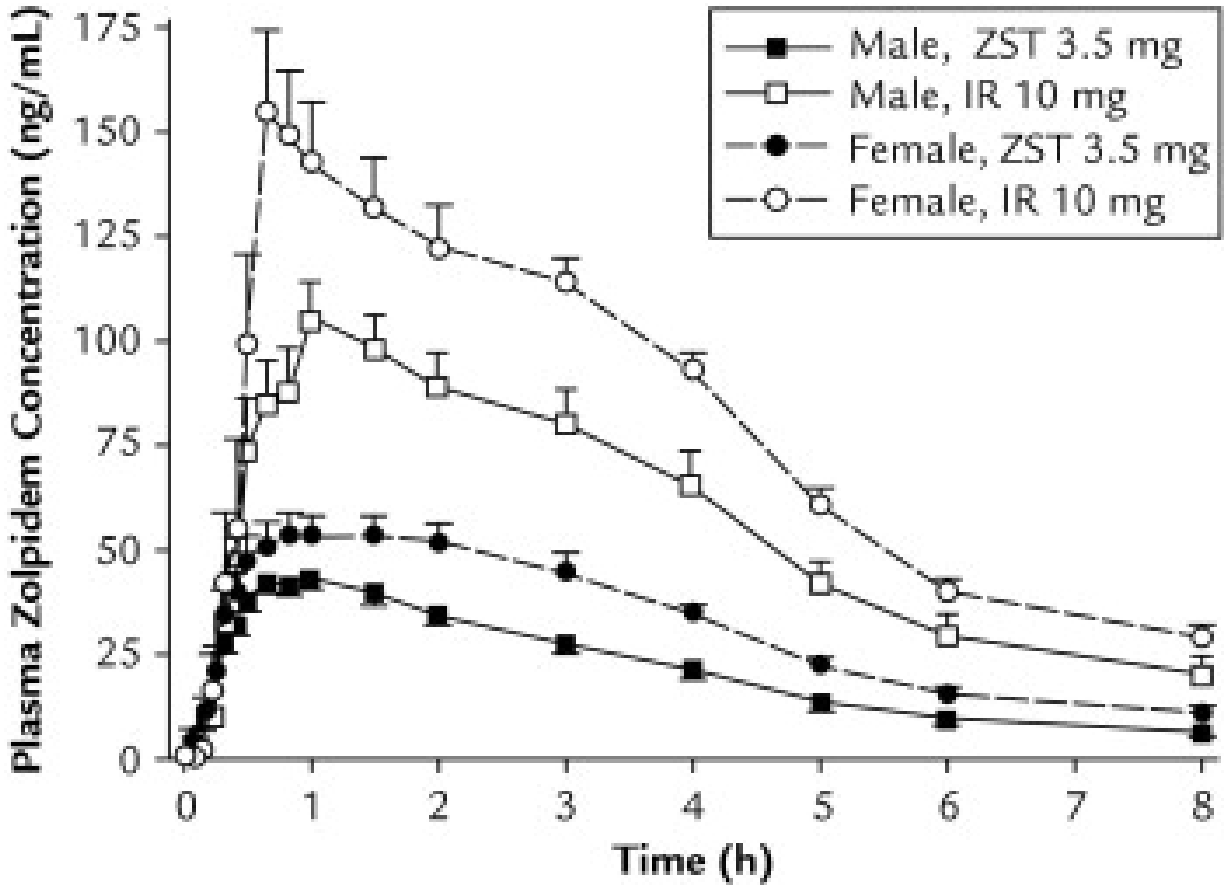
**Communicate**

Report and publish sex-based data

# SABV Across the Biomedical Research Continuum



# Why Is It Important?


DOI: https://doi.org/10.1016/j.clinthera.2013.03.007

## Table 1. CYP450 Enzymes and Their Sex-Dependent Activity

| CYP Enzyme | Enzyme Activity | Example Drugs | Other Characteristics |
|---|---|---|---|
| 1A2 | M > W | Clozapine, olanzapine | Suppressed activity during pregnancy |
| 2A6 | W > M | Nicotine, coumarin | Increased activity in female users of oral contraceptives |
| 2B6 | W > M | Bupropion, tamoxifen | Activity: Hispanic women > Caucasian or African-American women |
| 2C9 | M = W | Imipramine, phenytoin | Increased activity during pregnancy |
| 2C19 | M = W | Imipramine, topiramate | Decreased activity during pregnancy or use of oral contraceptives |
| 2D6 | Mostly W > M | Codeine, fluoxetine, haloperidol | Increased activity during pregnancy |
| 3A4 | Mostly W > M | Cyclosporine, erythromycin, nimodipine | Increased activity during pregnancy |

*M: men; W: women. Source: References 16-24.*

## Table 2. Phase II Enzymes and Their Sex-Dependent Activity

| Enzymes | Enzyme Activity | Example Drugs |
|---|---|---|
| UDP-glucuronosyltransferases (UGTs) | M > W | Oxazepam, acetaminophen |
| Sulfotransferases | M > W | Acetaminophen |
| *N*-acetyltransferases | M < W | Isoniazid, hydralazine |
| Methyltransferases | M > W | L-dopa, azathioprine |

*UDP: uridine diphosphate; M: men; W: women. Source: References 16, 34, 37.*

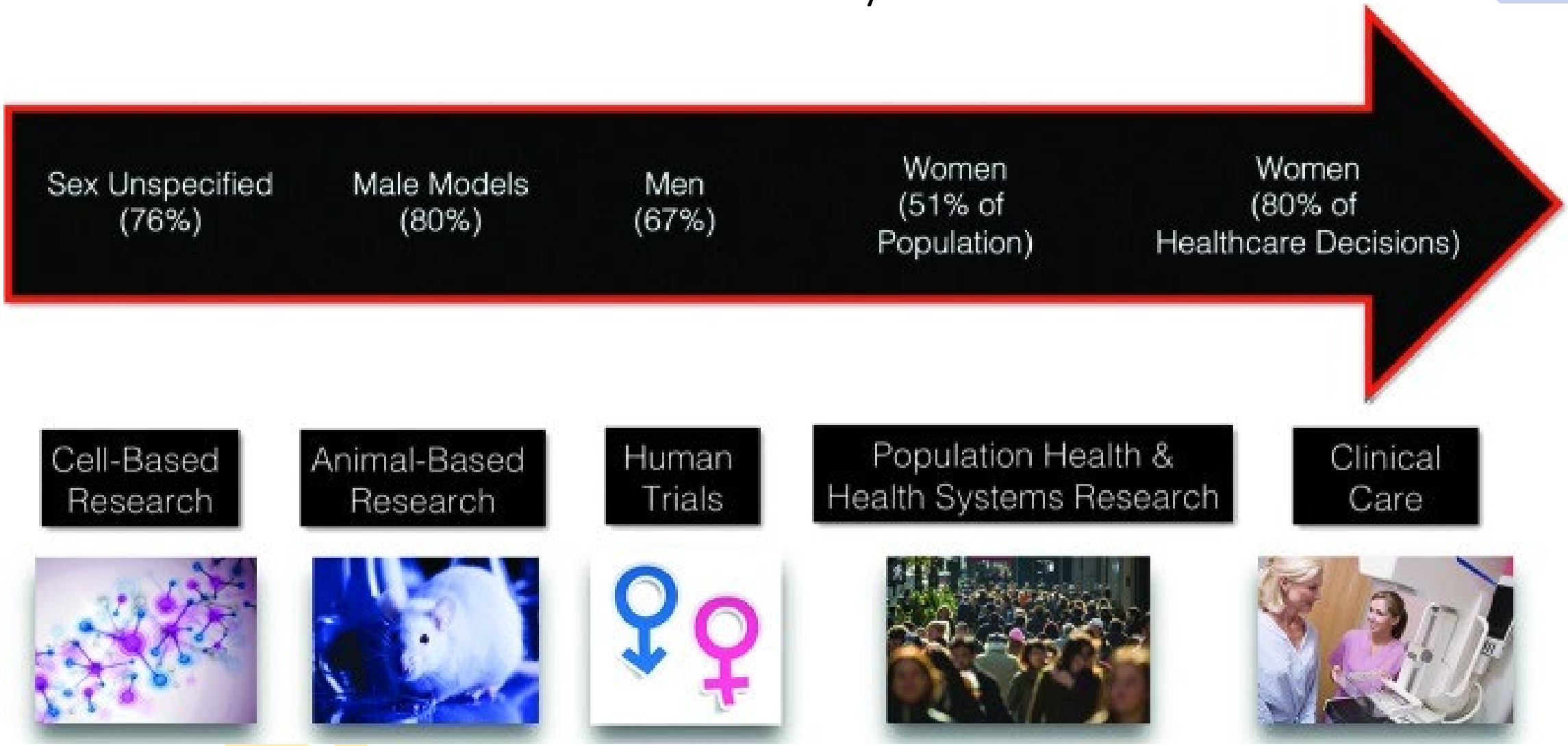
*US Pharm*. 2014;39(9):40-43.

# Are Drug Side Effects Always Different in Men and Women?

Adverse drug reactions are significantly higher in women

80% of severe adverse drug reactions are reported in women!!

# Bias in Evidence-Based Medicine May Be the Reason




J Womens Health 2016 25(2):181-7

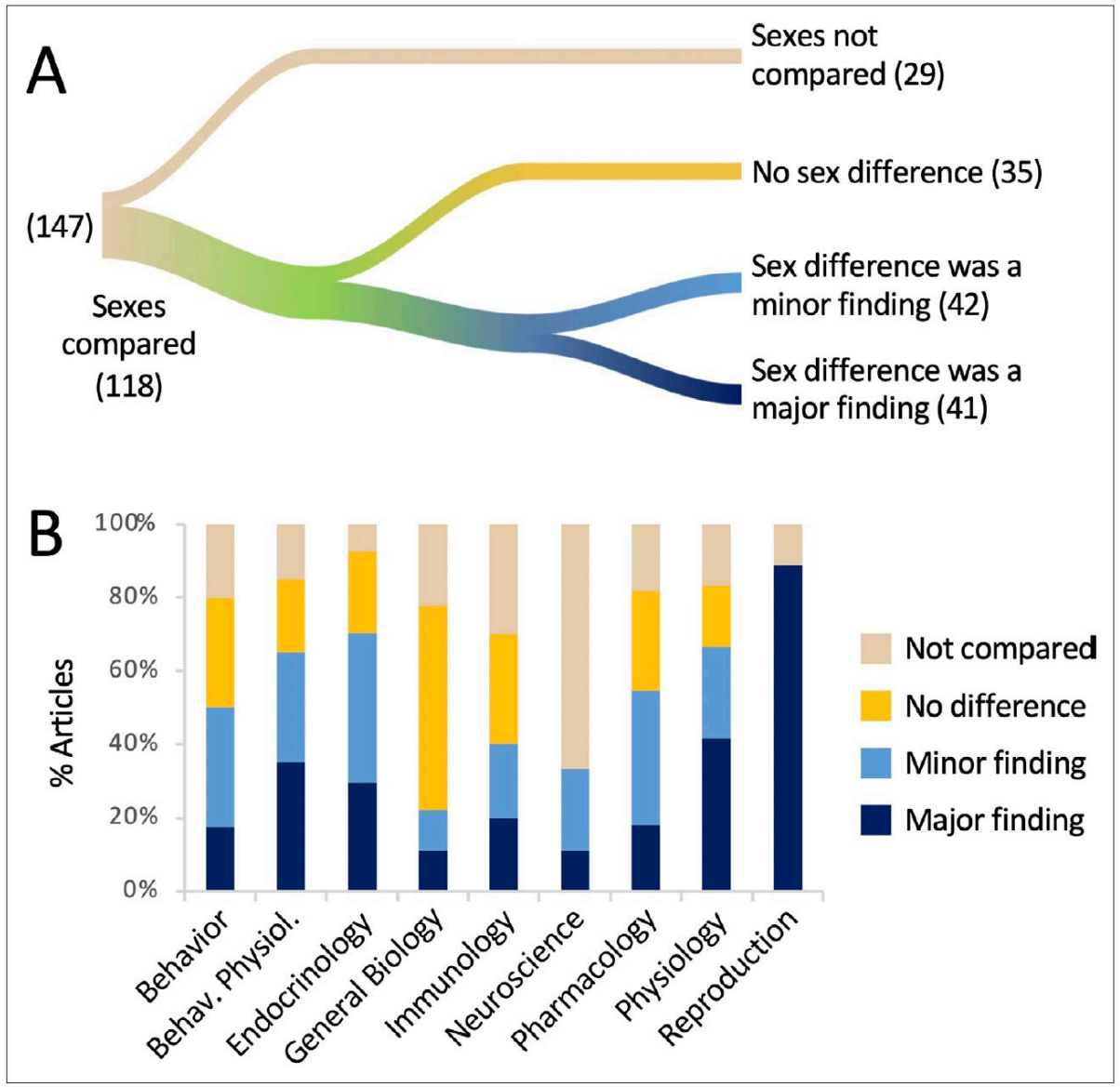
# Do Most Papers in Your Field . . .

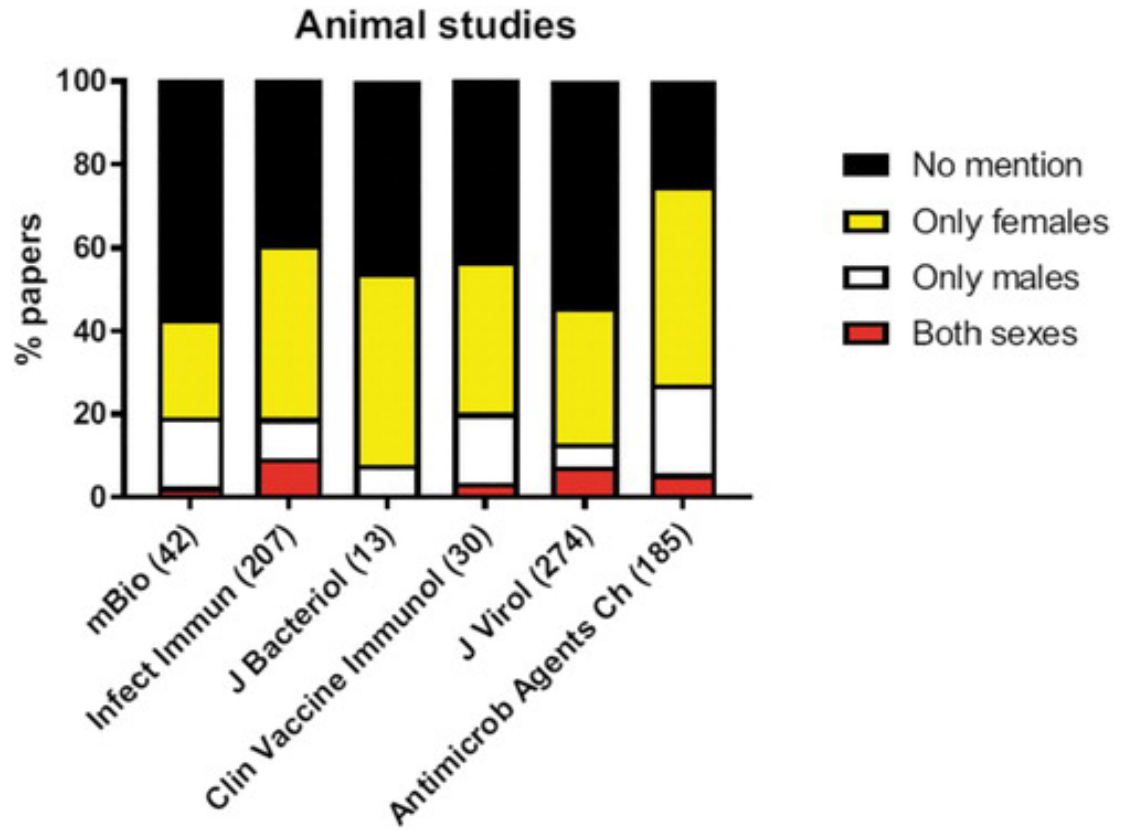
- Analyze data by sex?

- Have design to test SABV?

- Report the sex of cells/animals used?

- Inform sex-specific conclusions?



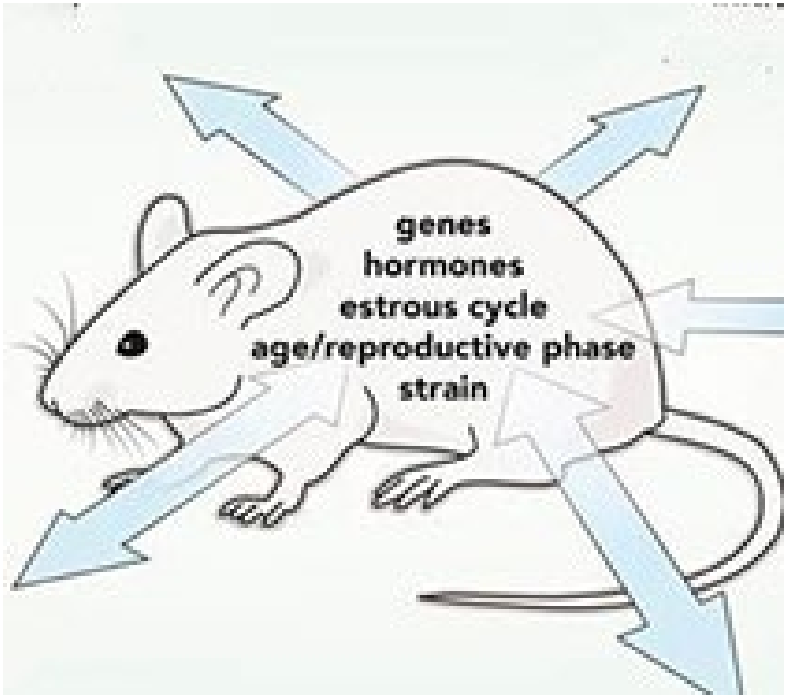



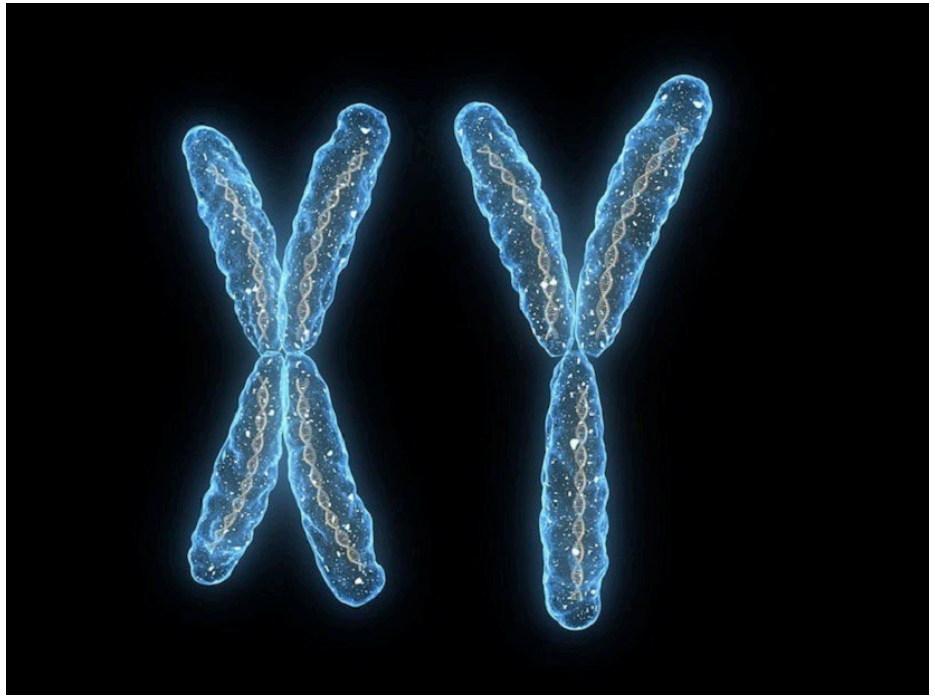

https://doi.org/10.1089/jwh.2019.8114

DOI: https://doi.org/10.7554/eLife.70817


# The Sex Variable in Toxicology Studies

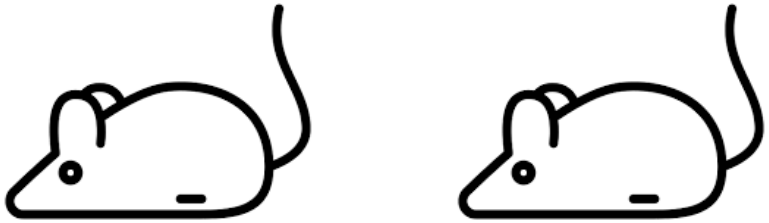
# Studying Males and Females



# Example: Ozone Exposure Effects

*C57BL/6 mice (8 weeks old)*



Males Females

Ozone (2ppm, 3 hours)
or
Filtered Air (3 hours)

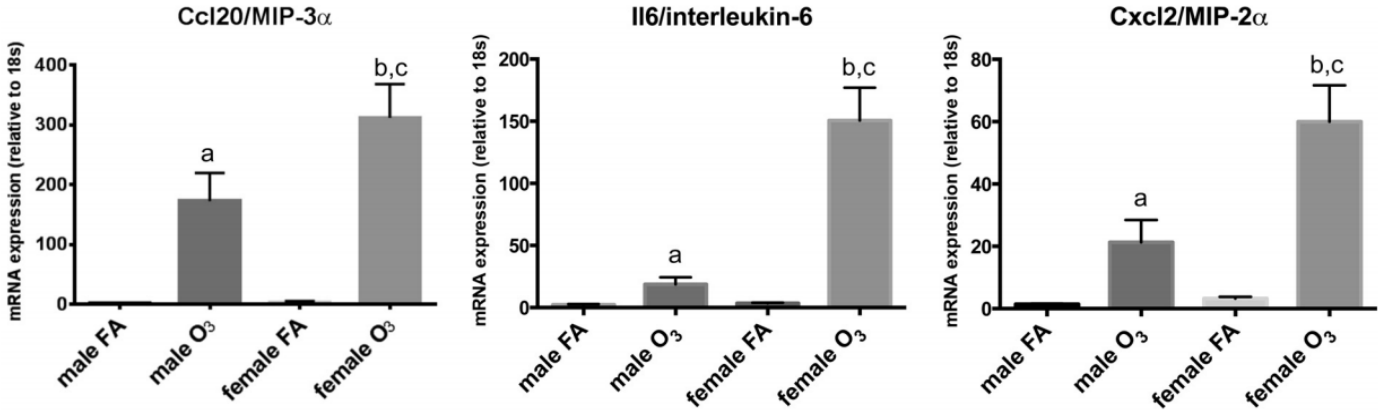
4h

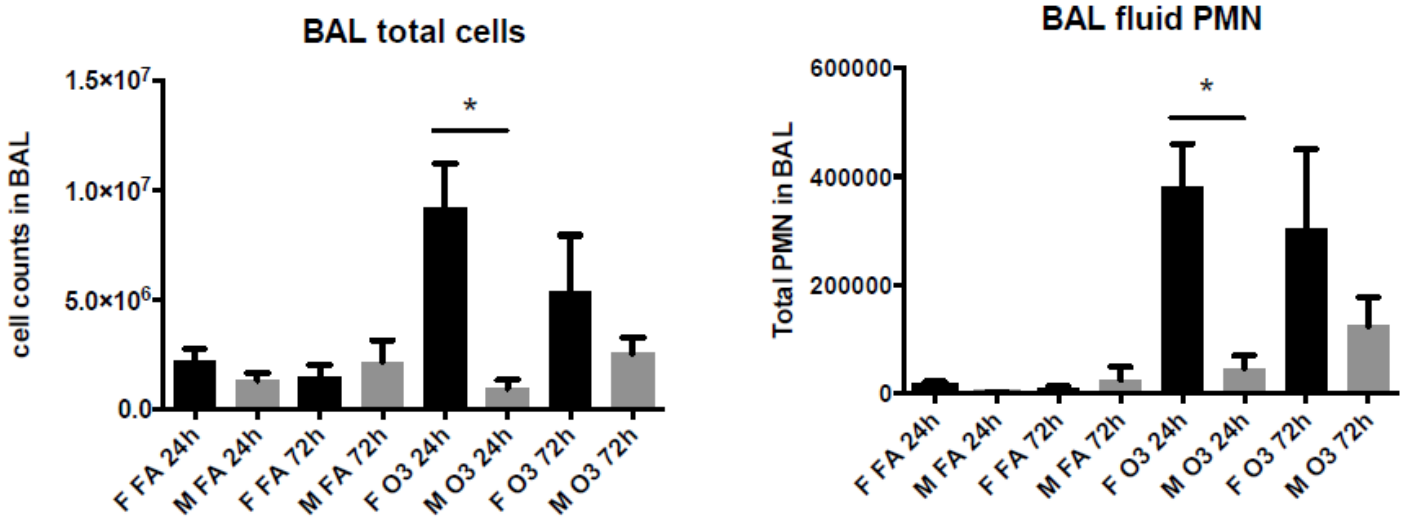
- Lung gene expression

24h

- BALF inflammation

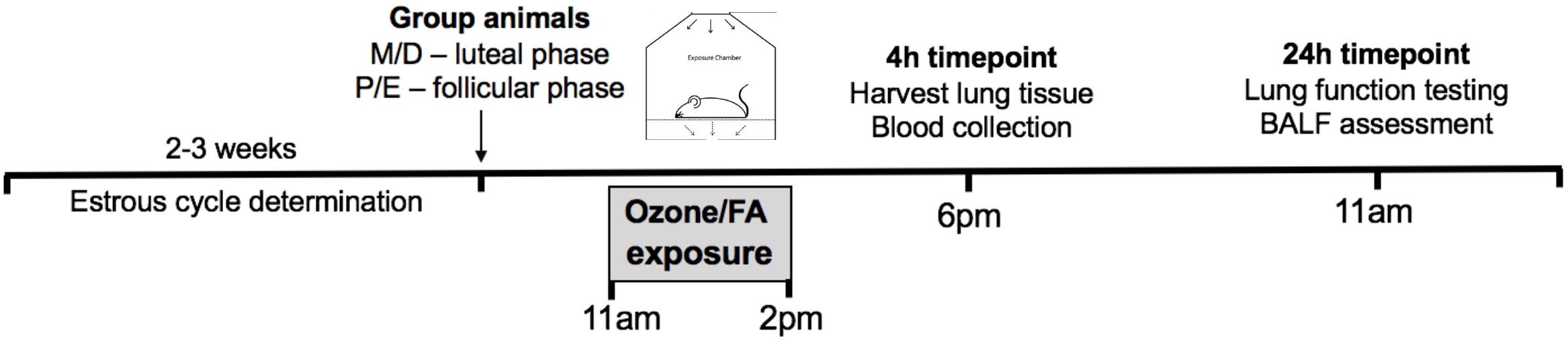
# Example: Ozone Exposure Effects



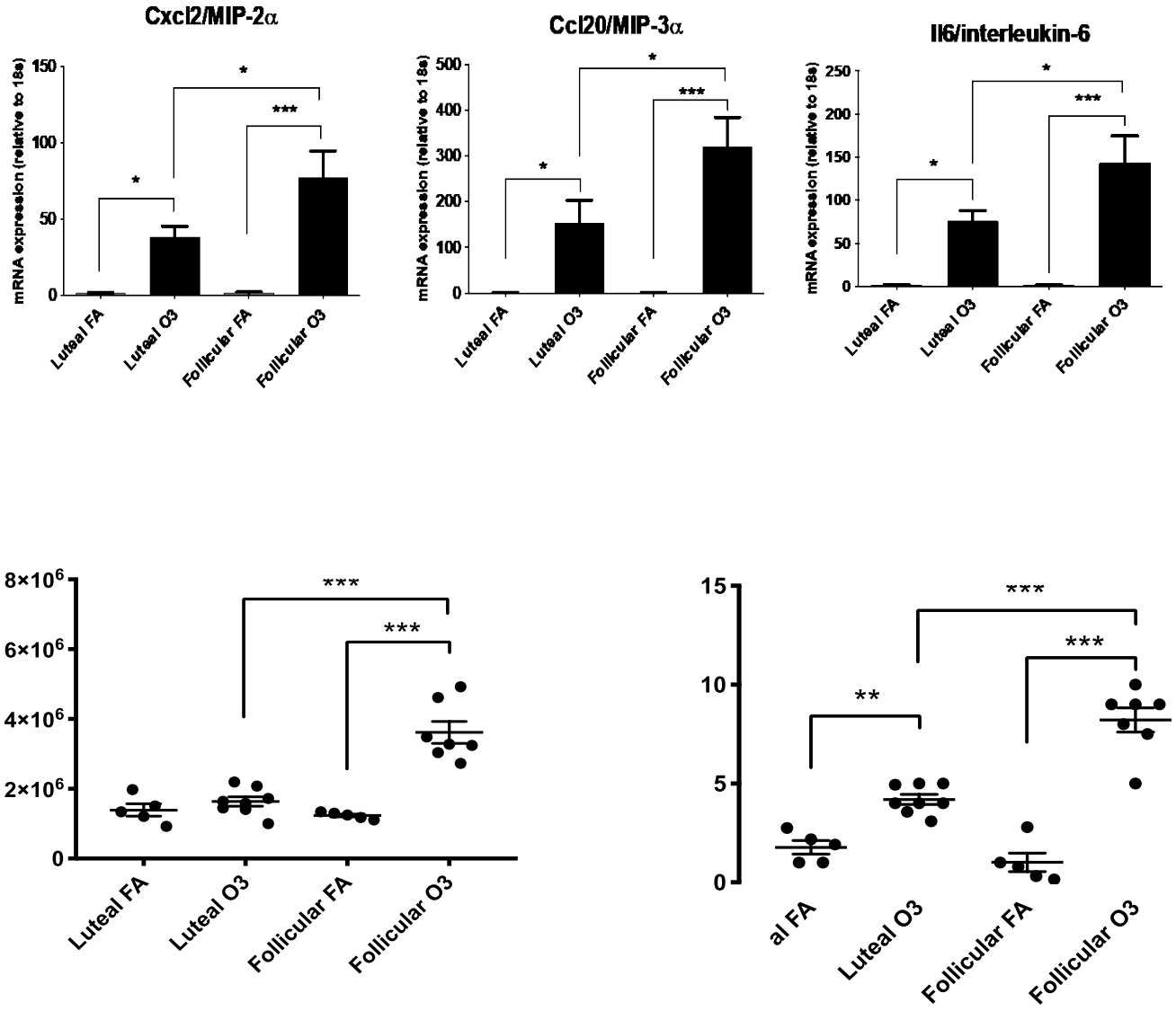

*Cabello et al. 2015*

# Example: Ozone Exposure Effects




Fuentes et al., 2018

# Example: Ozone Exposure Effects

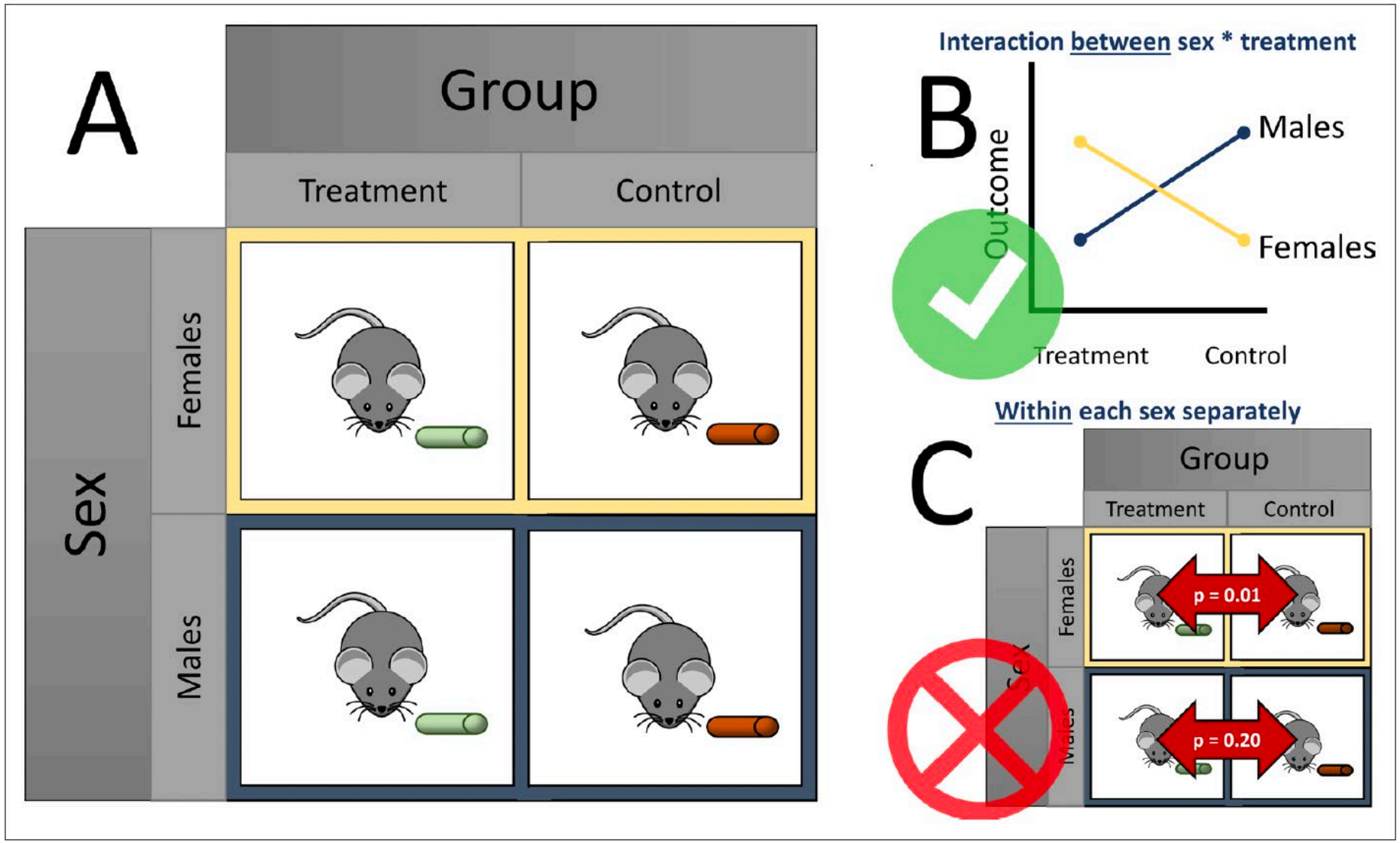



Fuentes et al., 2018

# How to Integrate Your Variable(s) of Interest AND the Sex Variable?

# Factorial Designs

| | | Independent Variable 2 | |
|---|---|---|---|
| | | Level 1 | Level 2 |
| Independent Variable 1 | Level 1 | Dependent Variable | Dependent Variable |
| | Level 2 | Dependent Variable | Dependent Variable |

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# Conclusions

- Sex and gender can influence health in different ways.
- Biological sex can alter drug metabolism and the body's response to a variety of toxicants.
- Incorporating the sex variable in preclinical toxicology studies can reduce the chances of observing negative side effects in women/men.
- Using appropriate research designs can help us identify sex-specific effects, as well as interactions between sex and other variables.

Questions?