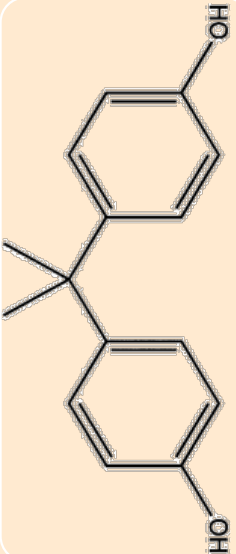


Getting a clear view: Lessons from the CLARITY-BPA study



Laura N Vandenberg, PhD

University of Massachusetts - Amherst



BPA



Canned foods & beverages

Consumer plastics

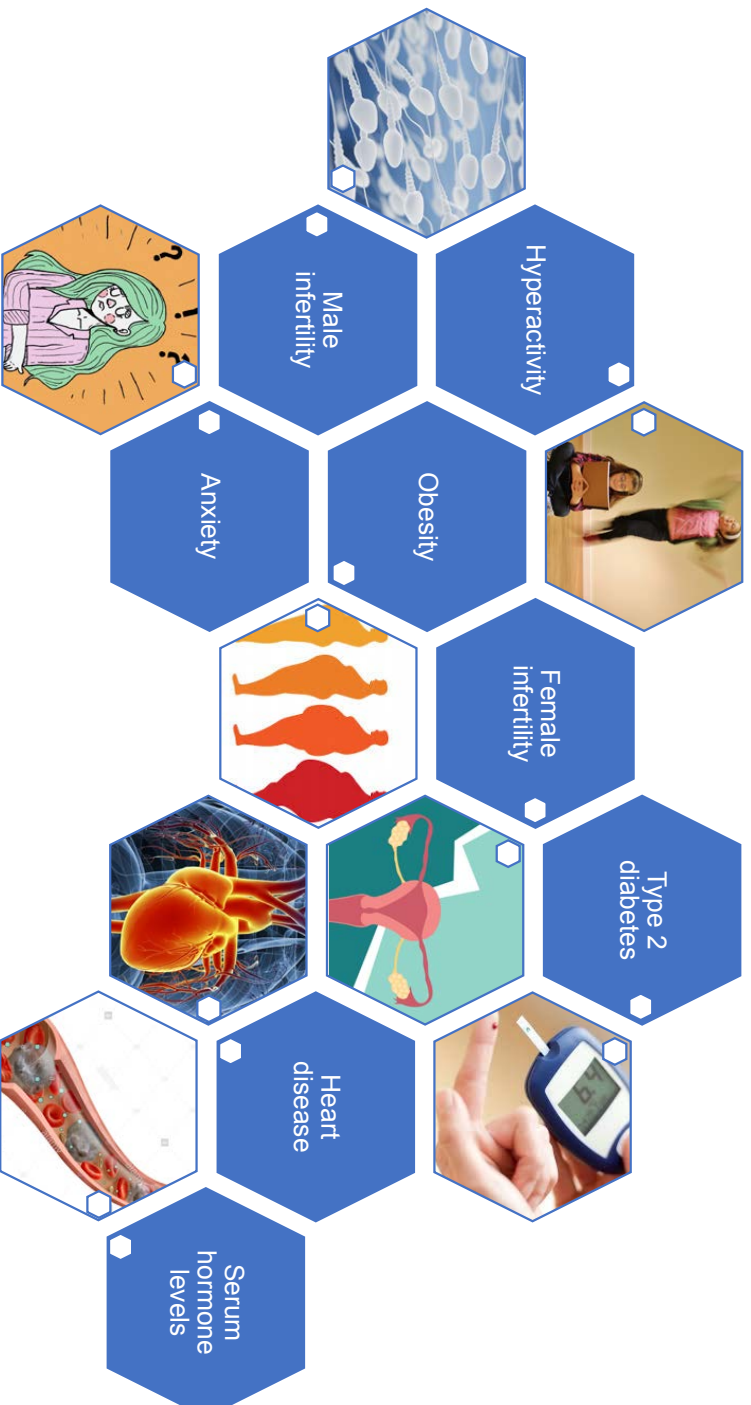


Thermal receipt paper

Sports & medical equipment



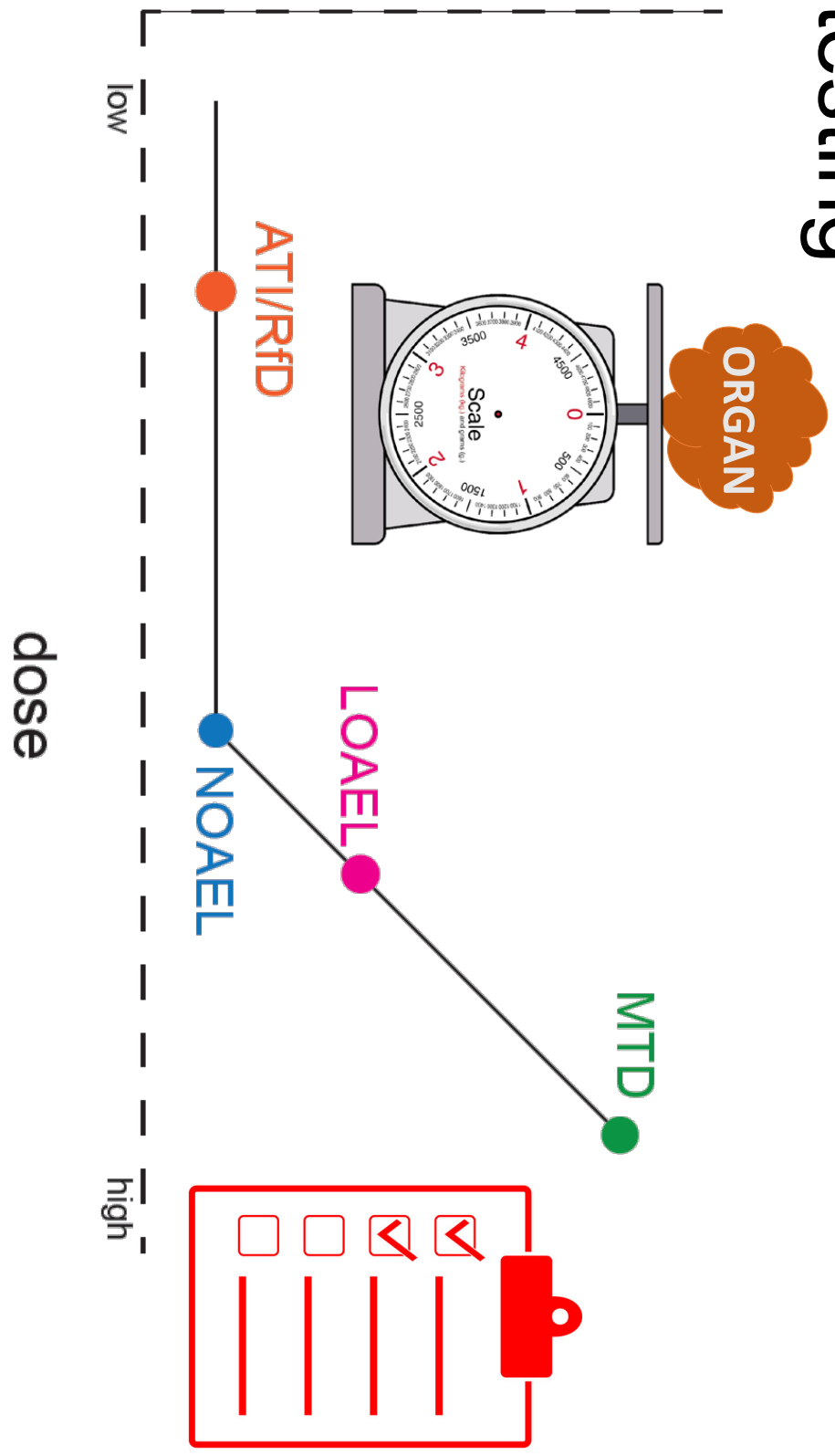
More than 100 human studies suggest associations between BPA and human disease



A 2-minute crash course in chemical safety testing

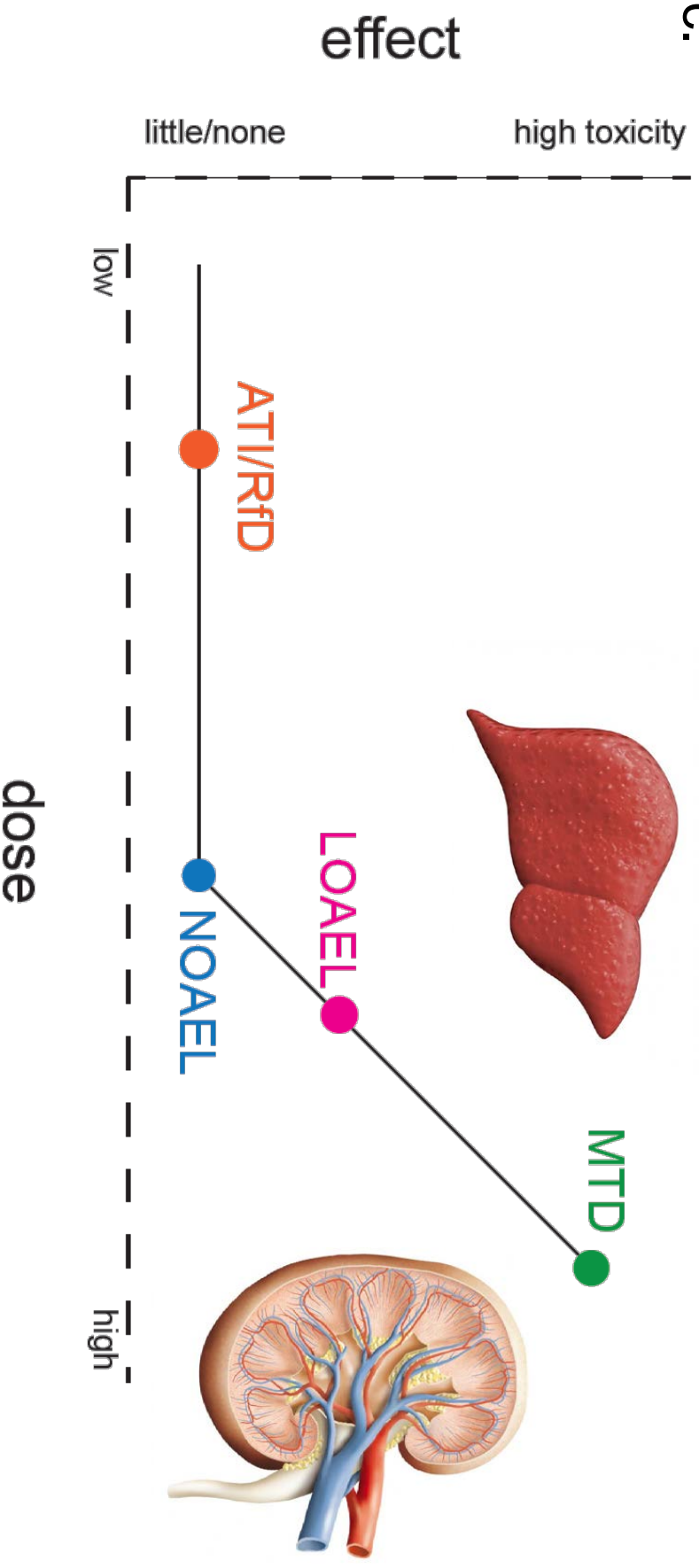


little/none high toxicity



Prior to the CLARITY study ...

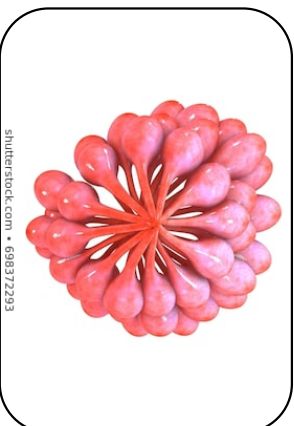
Guideline studies suggested that only high doses of BPA were toxic.



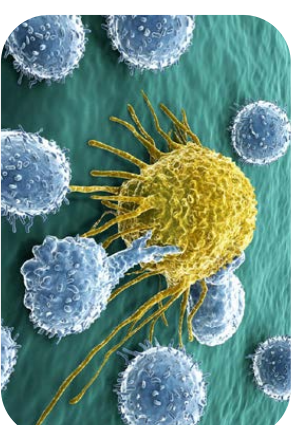
In contrast, hundreds of academic studies revealed effects of BPA on a wide range of hormone-sensitive outcomes



Reproduction



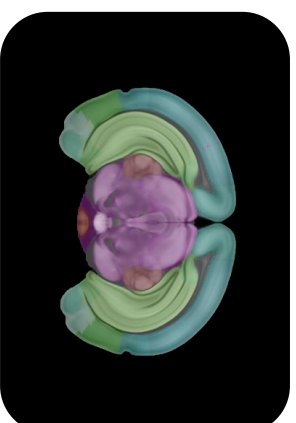
Mammary gland



Immune system

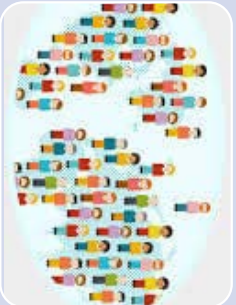


Metabolic endpoints

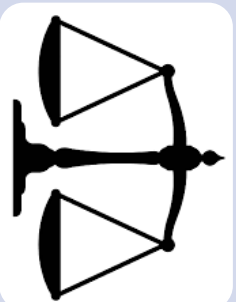


Brain & behavior

Why would guideline and academic studies show vastly different effects of BPA (and other chemicals)?



Differences
in sample
sizes



Differences
in
sensitivity



Differences
in
relevance
to disease



Differences
in study
reliability



Regulatory agencies have focused on the guideline studies to conclude that BPA is safe... but the public, and several scientific societies, disagree.

The logo for the U.S. Food and Drug Administration (FDA). It consists of the letters 'FDA' in a bold, white, stylized font with a double outline, set against a solid blue rectangular background.

CLARITY-BPA: bringing together a guideline study with academic endpoints



Consortium Linking Academic and Regulatory Insights of Toxicity of BPA

Run a guideline study... but add 'academic' endpoints!

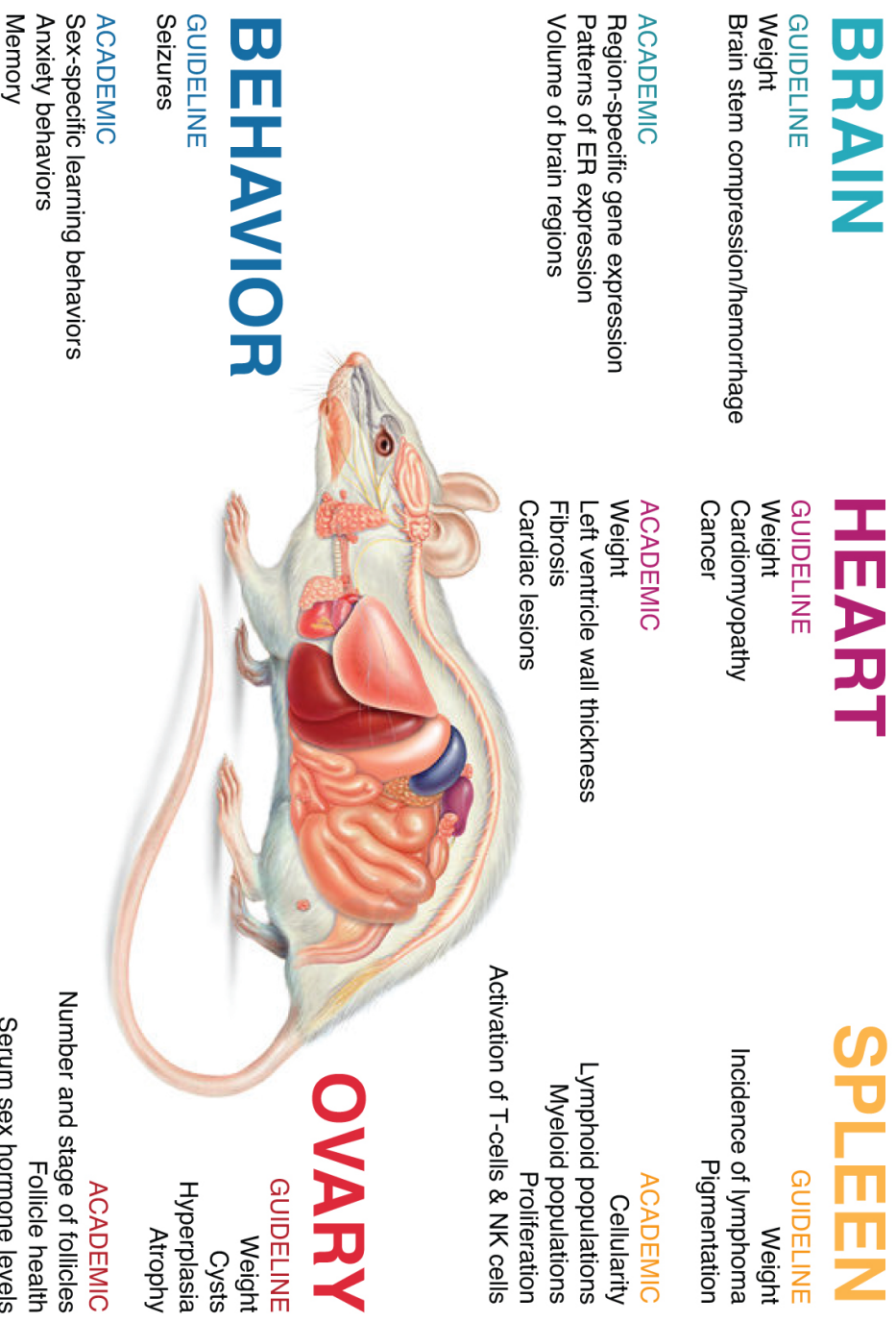
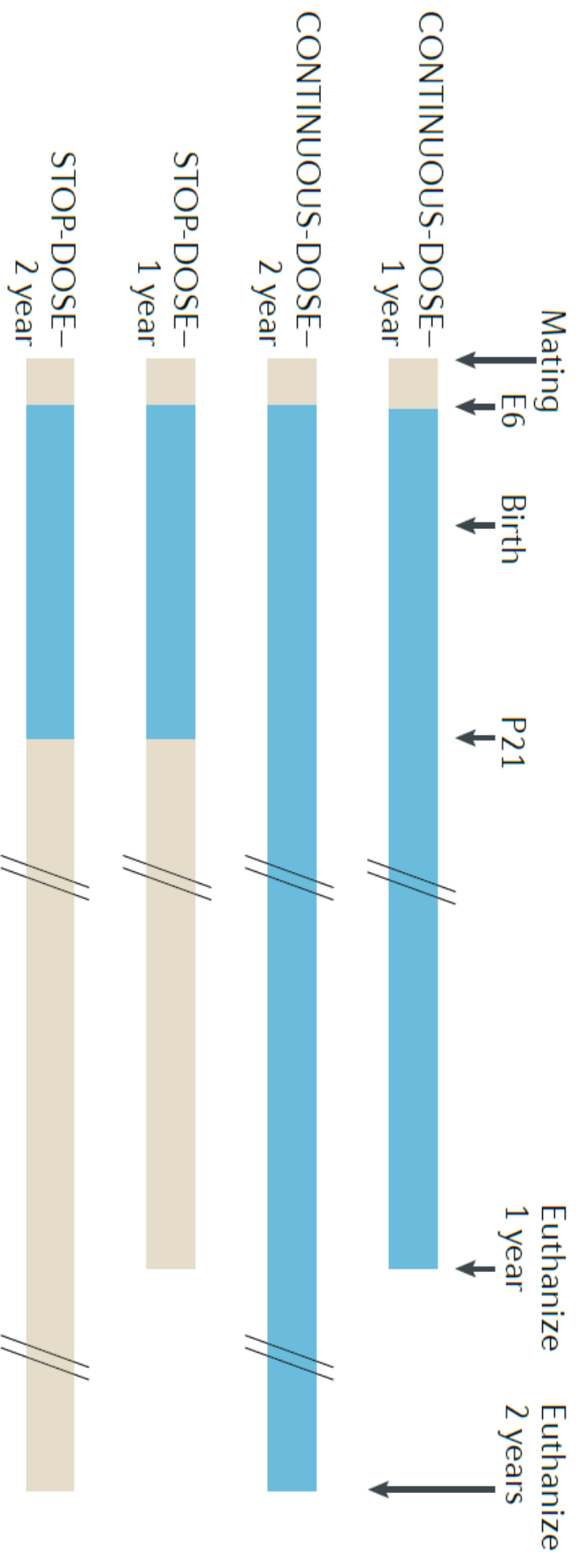


Figure: Pat Hunt

The CLARITY approach:



Vandenberg, Hunt & Gore, Nat Reviews Endocrinol 2019

Broad overview of results from the FDA Core Study

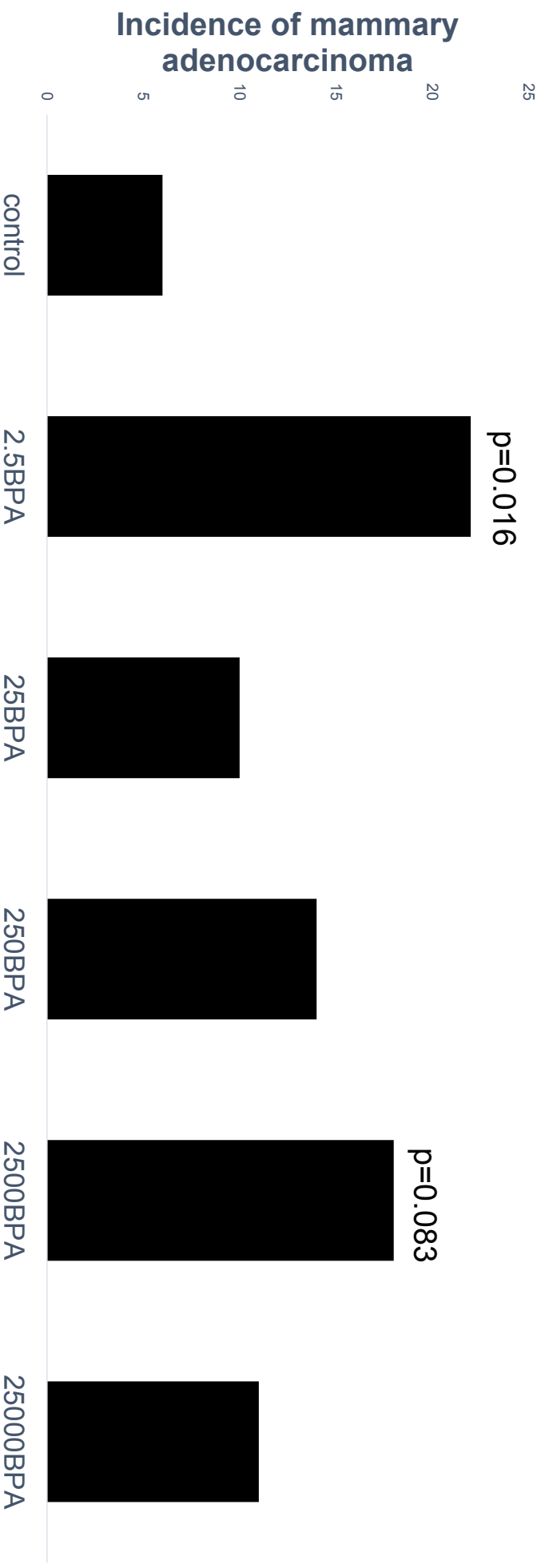
Female							Male						
	2.5	25	250	2,500	25,000		2.5	25	250	2,500	25,000		
Ovary						Testis							
Reproductive tract						Reproductive tract							
Mammary						Mammary							
Liver						Liver							
Kidney						Kidney							
Adrenal						Adrenal							
Thyroid/Parathyroid						Thyroid/Parathyroid							
Pancreas						Pancreas							
Pituitary						Pituitary							
Spleen						Spleen							

Vandenberg, Hunt & Gore, Nat Reviews Endocrinol 2019

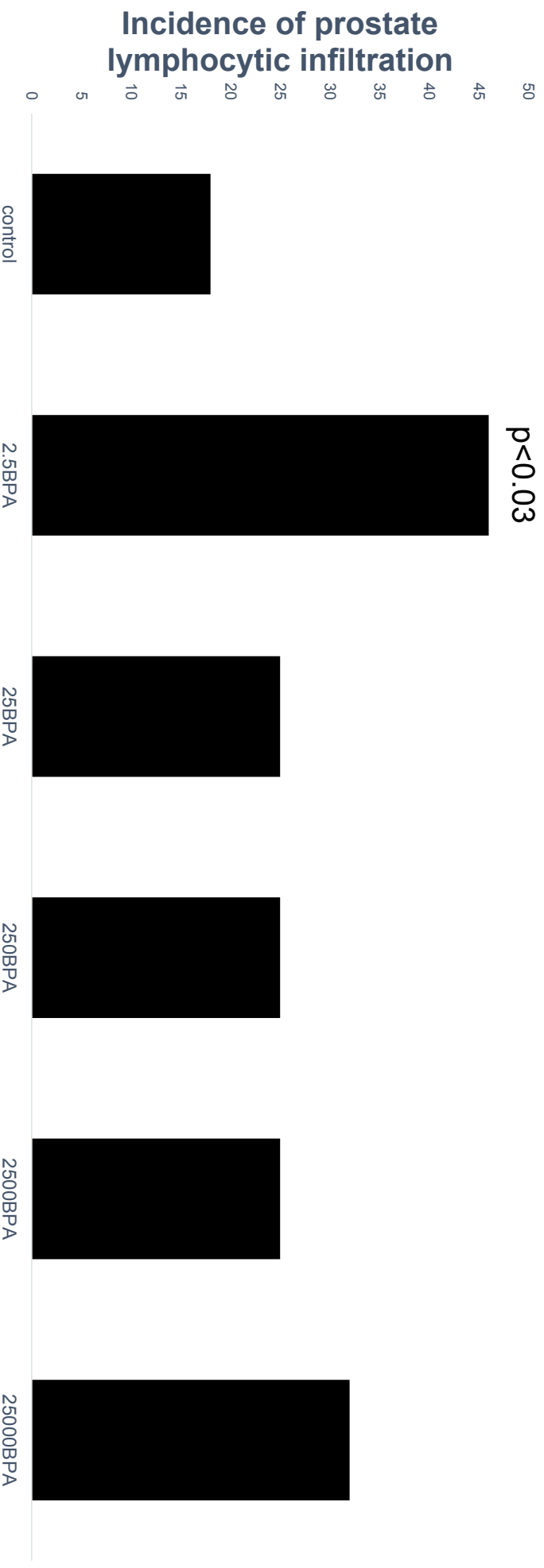
Several serious adverse effects of BPA were observed in the FDA-Core study at low doses

- increases in the incidence of **mammary adenocarcinoma** (at 2.5 µg/kg/day in the STOP group)
- **inflammation of the dorsal and lateral lobes of the prostate** (at 2.5 µg/kg/day in the CONTINUOUS group)
- **kidney nephropathy** in females (at 2.5 µg/kg/day in the CONTINUOUS group)
- increased **body weight** in adult females (at 250 µg/kg/day in the CONTINUOUS group)

Example 1: Low dose BPA exposure increased mammary cancer



Example 2: Low dose BPA exposure increased prostate inflammation (a cancer risk factor)



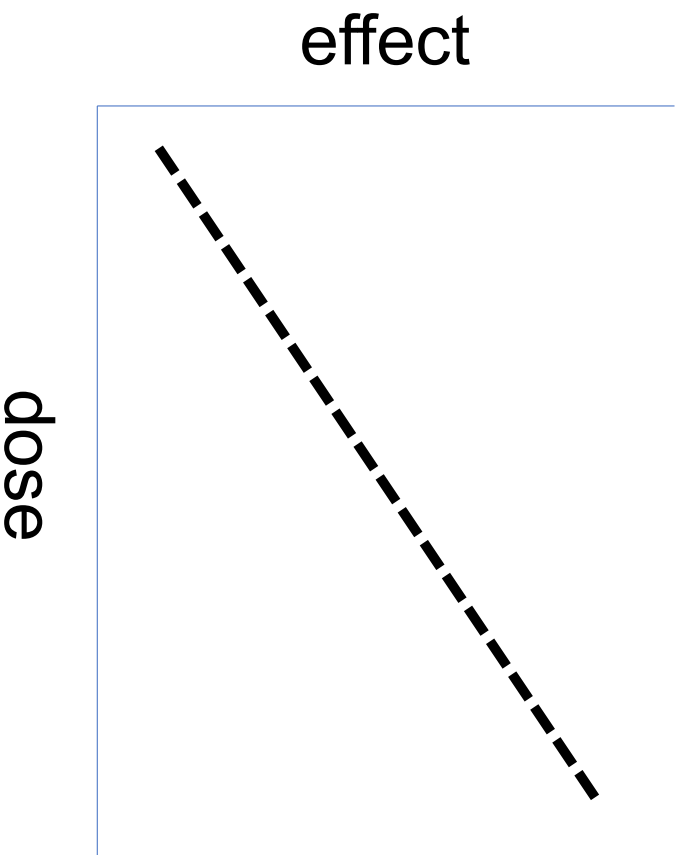
There are serious effects of BPA reported in the FDA Core Study.

This contrasts with the FDA's conclusions

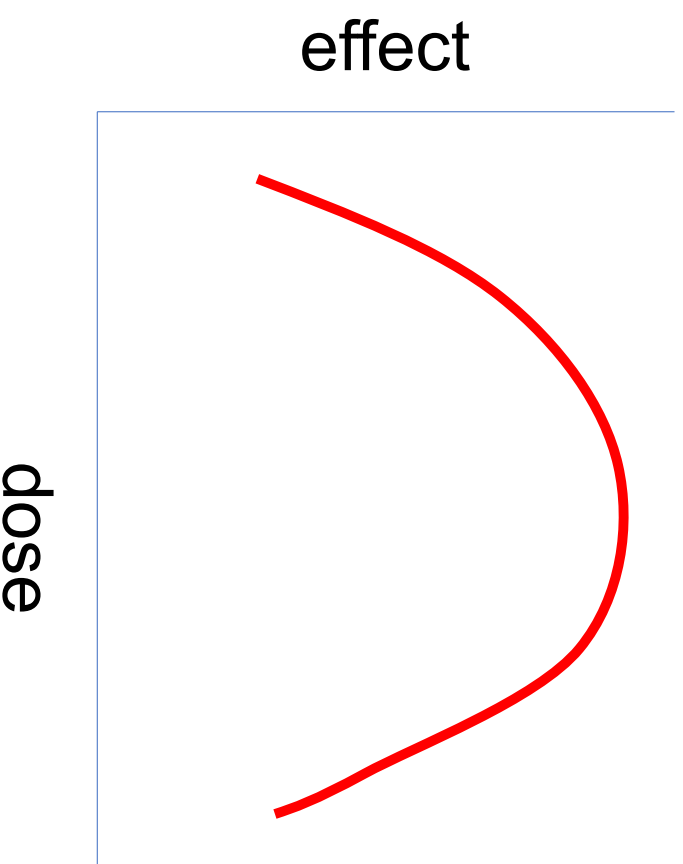
“Results of the [core study] indicated that BPA produced adverse effects at high doses, but not at the low end of the dose range tested, consistent with its activity as a weak estrogen.”

Why does the FDA ignore low dose effects of BPA observed in the FDA-Core study?

expectation:



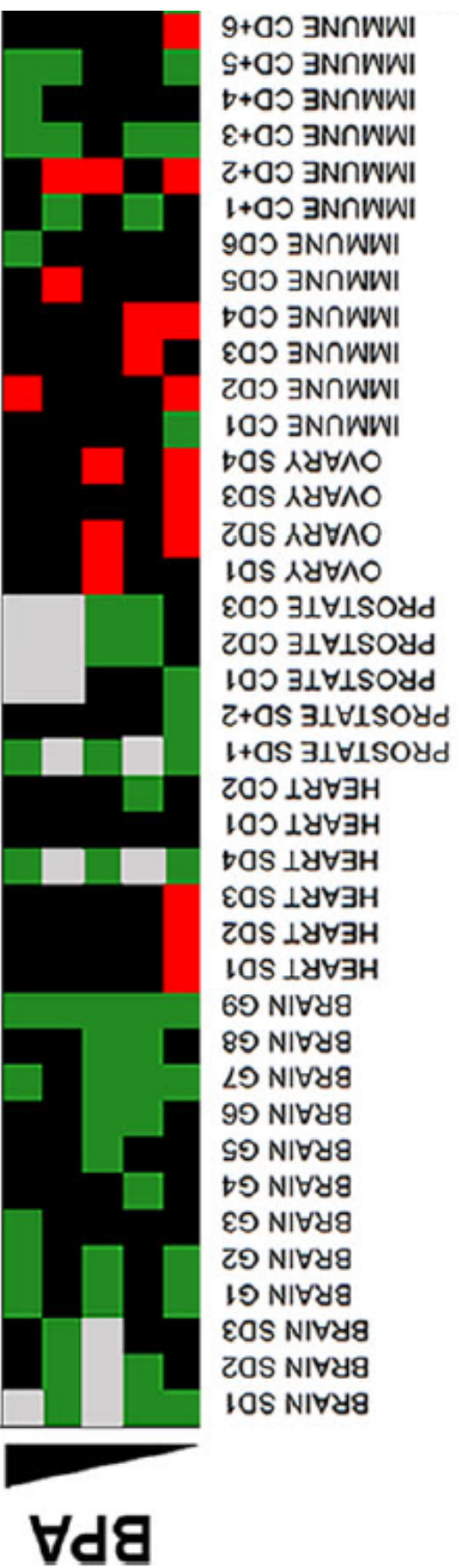
reality:



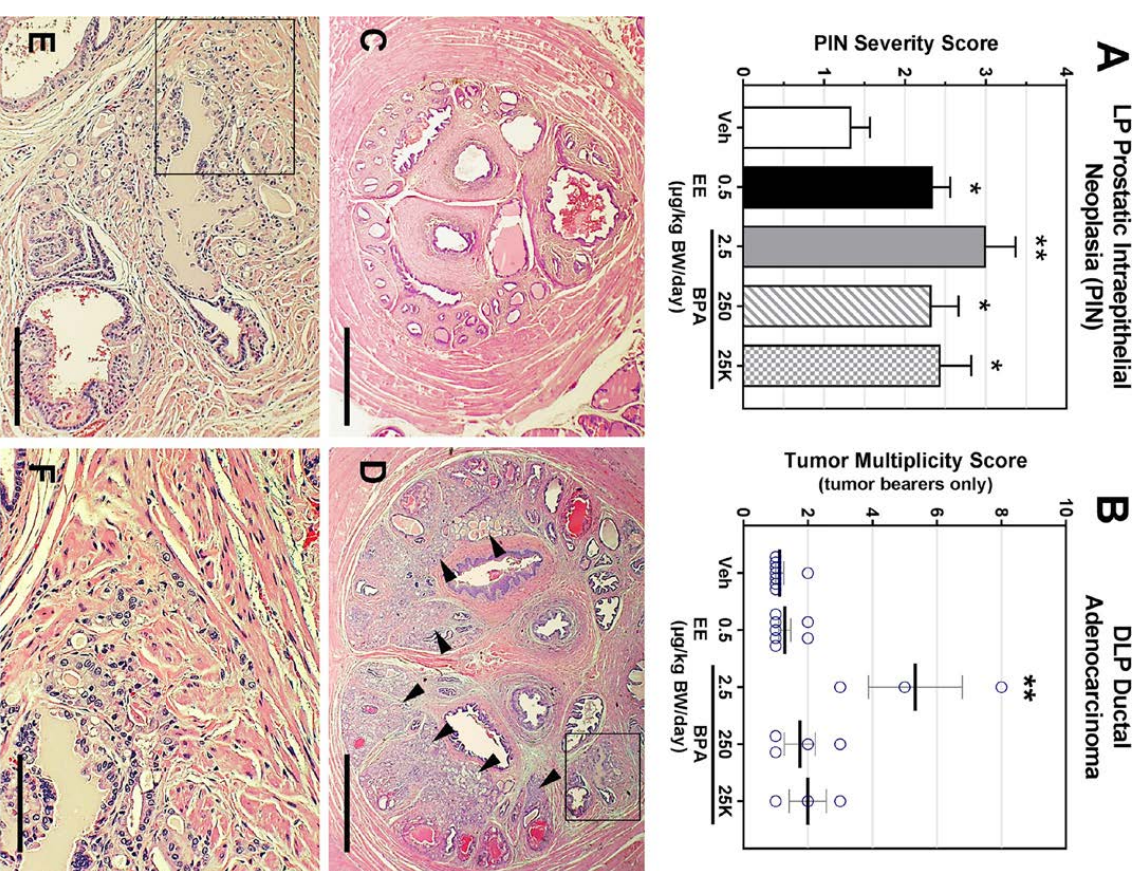
Finding anything in
the low dose
groups of the
guideline study is
surprising, based
on the prior
guideline studies on
BPA!!



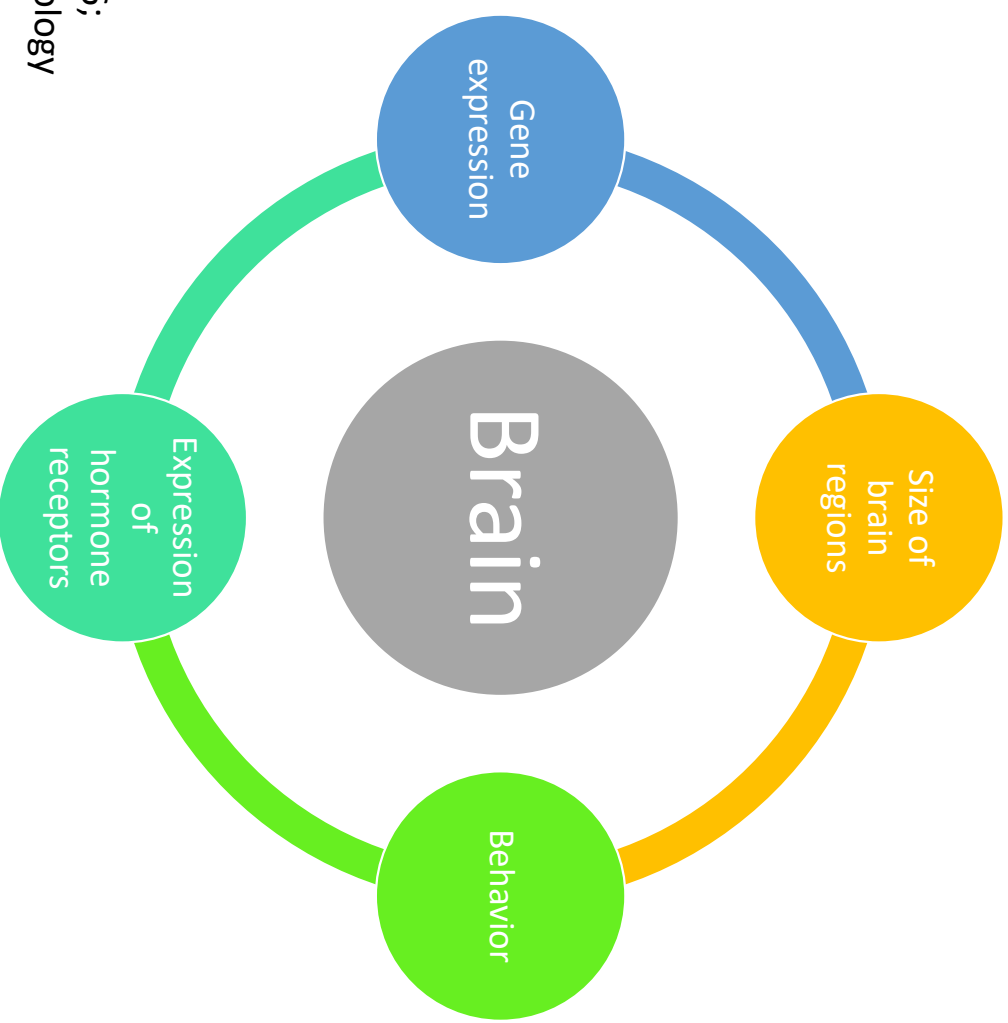
Many, many effects were observed in academic studies



Example 1: Low dose BPA exposure induces neoplasia (PIN) and adenocarcinoma in the prostate



Example 2: Seven academic CLARITY publications document effects of BPA on brain and behavior



Rebuli et al. Tox Sci 2015; Arambula et al. Endocrinology 2016;
Johnson et al. Horm Behav 2016; Arambula et al. Neurotoxicology
2017; Cheong et al. Epigenetics 2018; Arambula et al.
Neurotoxicology 2018; Withey et al. Neurotoxicology 2019

CLARITY was an imperfect study

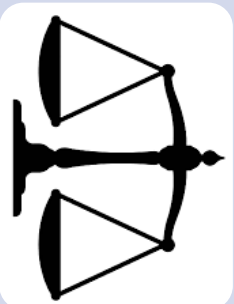


Vandenberg, Hunt & Gore, Nat Reviews Endocrinol 2019

What can we conclude from the CLARITY study?



Differences
in sample
sizes



Differences
in
sensitivity



Differences
in
relevance
to disease



Differences
in study
reliability

Conclusions – CLARITY-BPA (to date)

- There are serious effects observed in the FDA Core study after exposure to low doses of BPA
 - These effects are ignored or dismissed by FDA because they were not observed at high doses, or because they were only observed in one group (stop-dose versus continuous)
- There are many, many effects observed in the academic studies after exposure to low doses of BPA
- **Let's learn from CLARITY and develop endpoints that are sensitive & more accurately reflect human diseases!!!**

