Does Early BPA Exposure Cause Hyperactivity in Children?

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Prenatal Origins of Disease

- Chemical exposure in the womb → Disease later in life

https://www.dohadfordoctors.com/what-is-dohad/

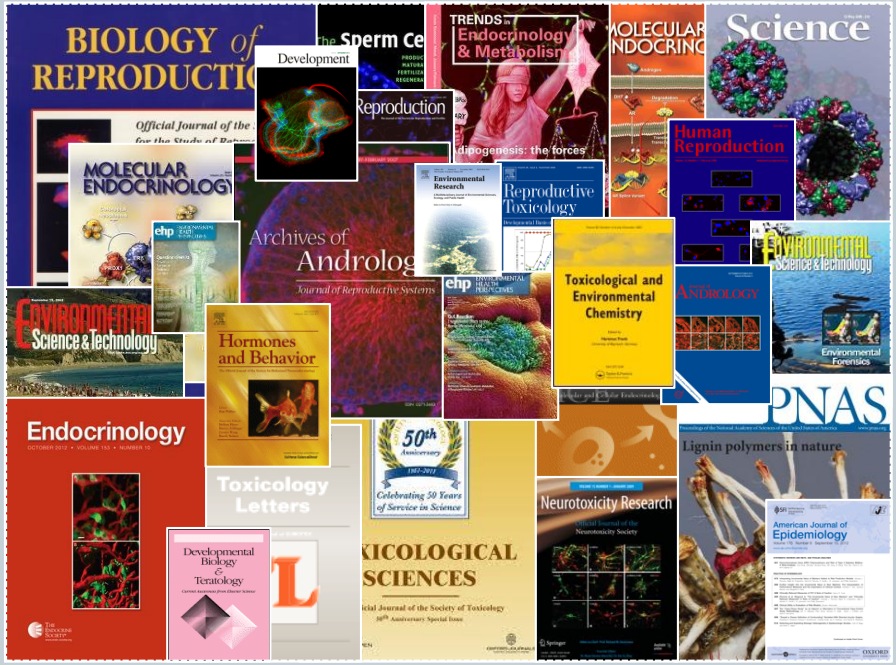
- Humans—difficult to study
- Animals—difficult to relate to human health
- <u>Neurodevelopment</u>

Attention Deficit/Hyperactivity Disorder

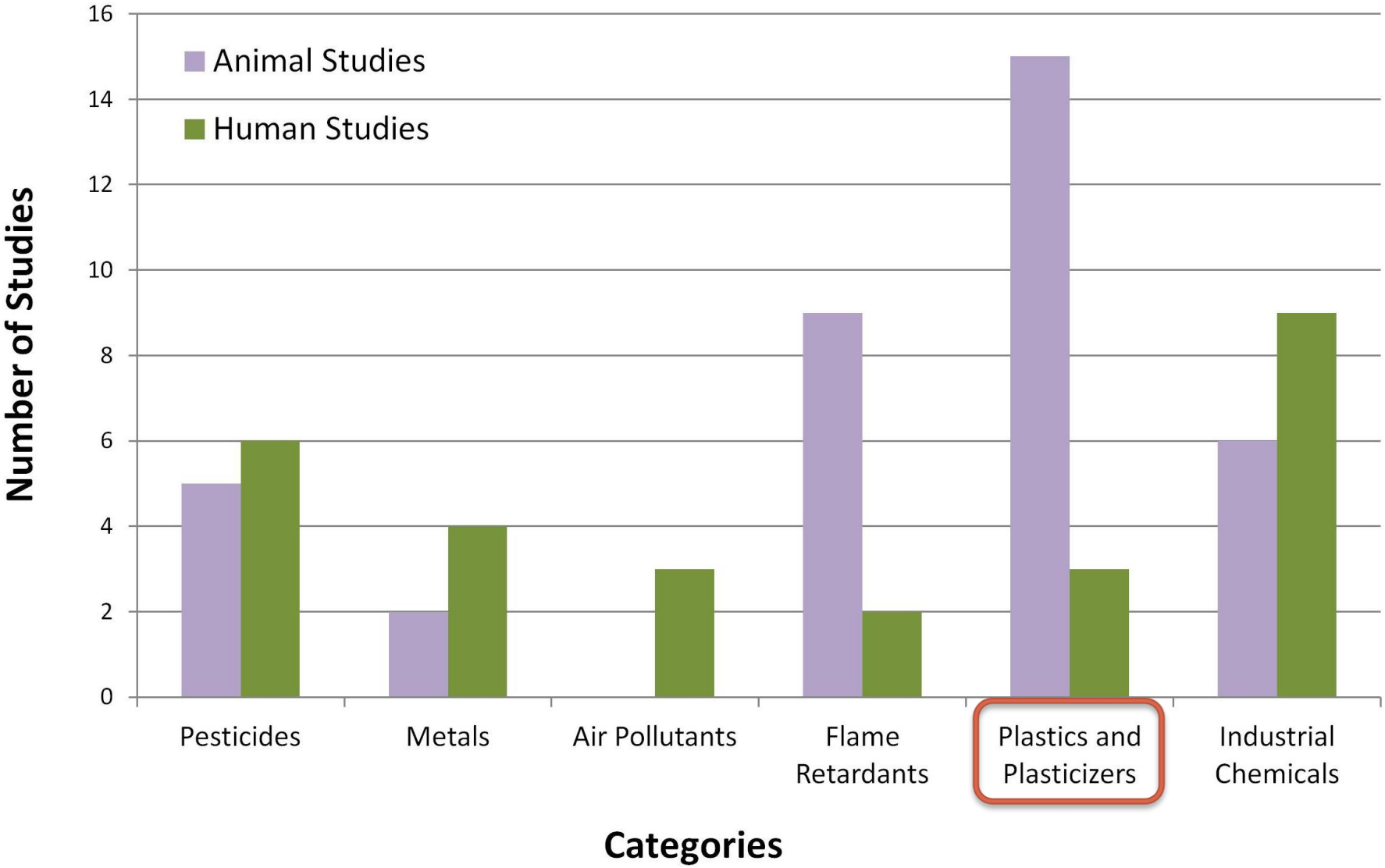
- Hyperactivity, Inattention
- 20% in boys 14-17 years old
- 15% in boys 7% in girls (CDC 2013)
- Costs are high:
  - Estimated at $36-$52 billion per year (cancer is $87 billion)
- Gene-environment interaction?

ADHD and Early Chemical Exposure

- Extensive literature searches
  - Disease/symptom
  - Prenatal
  - Human/rodent
  - Environmental exposure

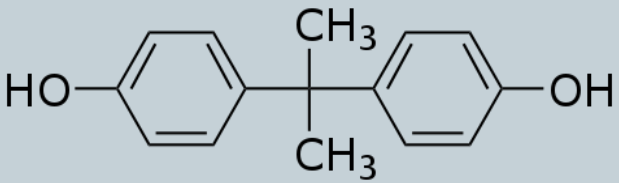


Studies Linking ADHD to Early Chemical Exposure



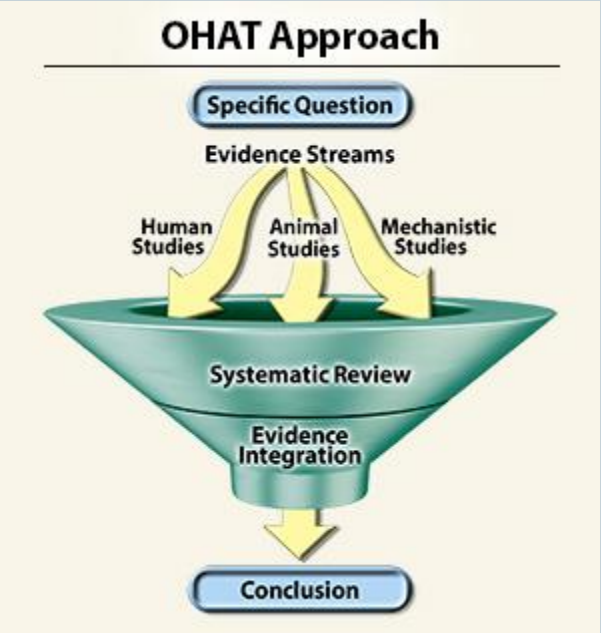
BPA and Human Health

- BPA is a well known endocrine disruptor
  - Estrogen, androgen, thyroid, insulin
- Present in can liners, hard plastics (#7), thermal receipt paper.
- Human health effects (Rochester 2013)
  - Reproduction
  - Thyroid
  - Metabolic Syndrome (obesity, T2D, cardiovascular diseases)
  - Immune effects
  - Neurodevelopment



OHAT Systematic Review Framework

- Office of Health Assessment and Translation (National Toxicology Program, NIEHS)
- 7 Step SR framework
- Hazard ID conclusion
- Can be used with or without meta-analysis
- Integrates animal and human evidence



BPA and Hyperactivity Systematic Review

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Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis

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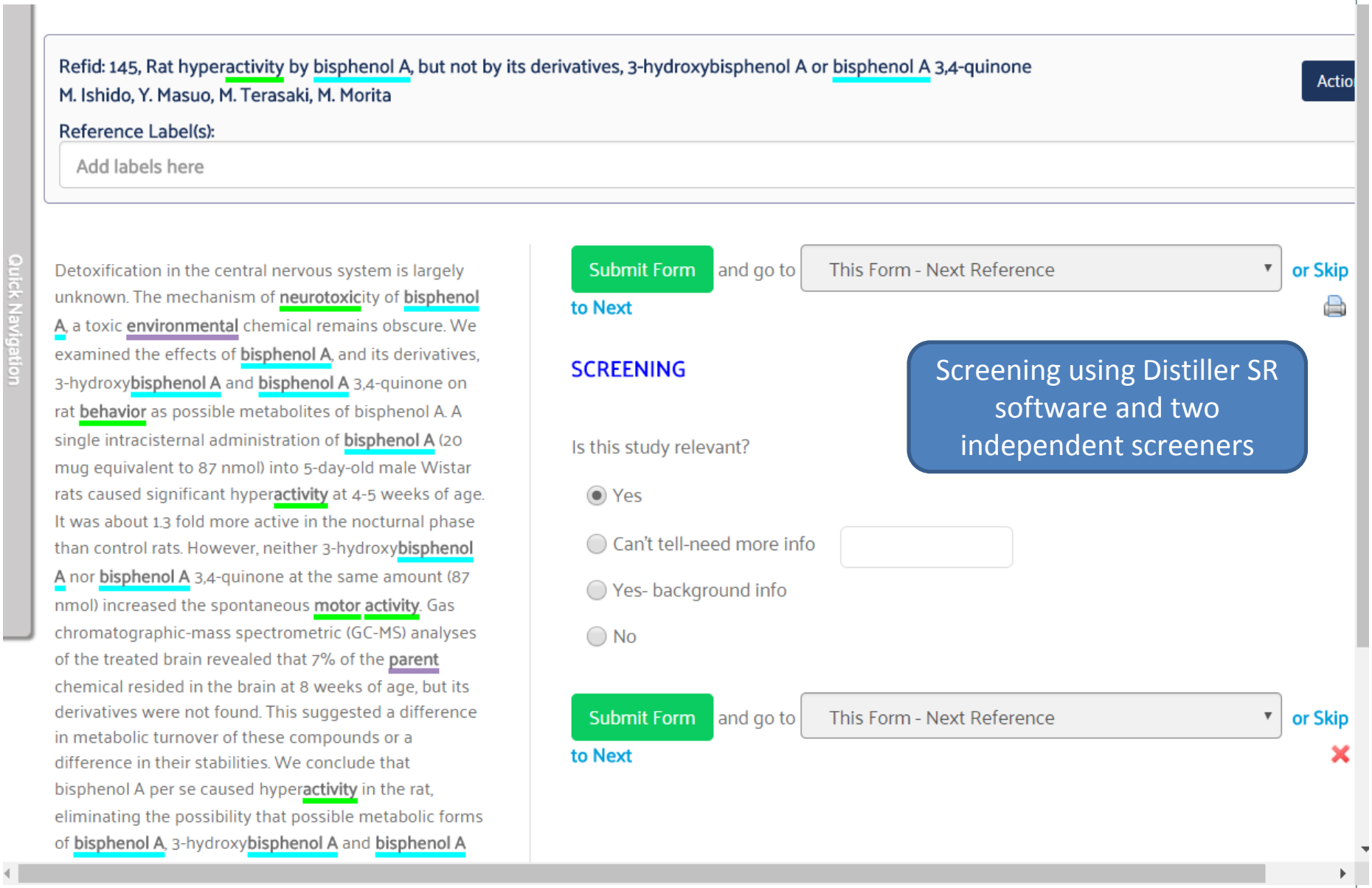
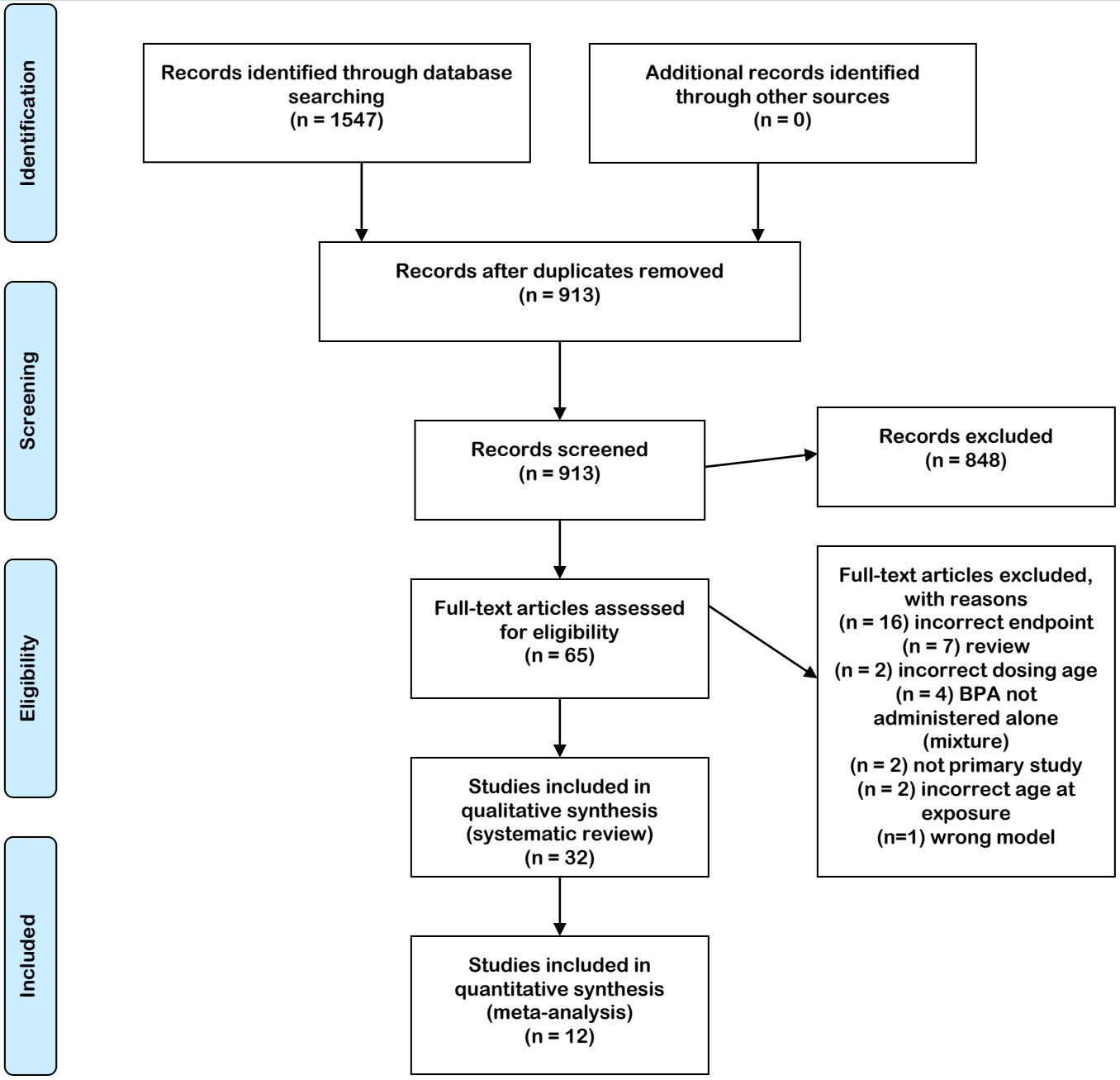
Step 1– Problem Formulation

- Does early BPA exposure cause hyperactivity in humans?

Step 2--Search and Screen Studies



Screening using Distiller SR software and two independent screeners


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1547)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 913)
Records screened (n = 913)
Records excluded (n = 848)
Full-text articles assessed for eligibility (n = 65)
Full-text articles excluded, with reasons
(n = 16) incorrect endpoint
(n = 7) review
(n = 2) incorrect dosing age
(n = 4) BPA not administered alone (mixture)
(n = 2) not primary study
(n = 2) incorrect age at exposure
(n=1) wrong model
Studies included in qualitative synthesis (systematic review) (n = 32)
Studies included in quantitative synthesis (meta-analysis) (n = 12)

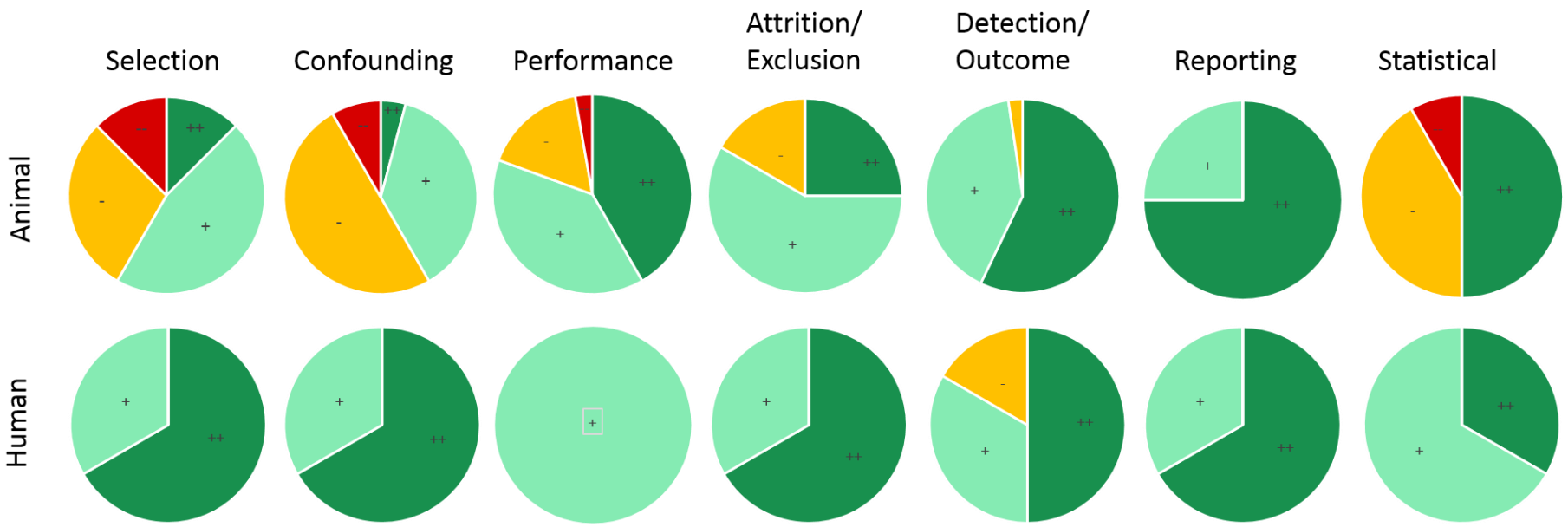
Step 3– Data Extraction

- Rodent models for hyperactivity
- Human surveys

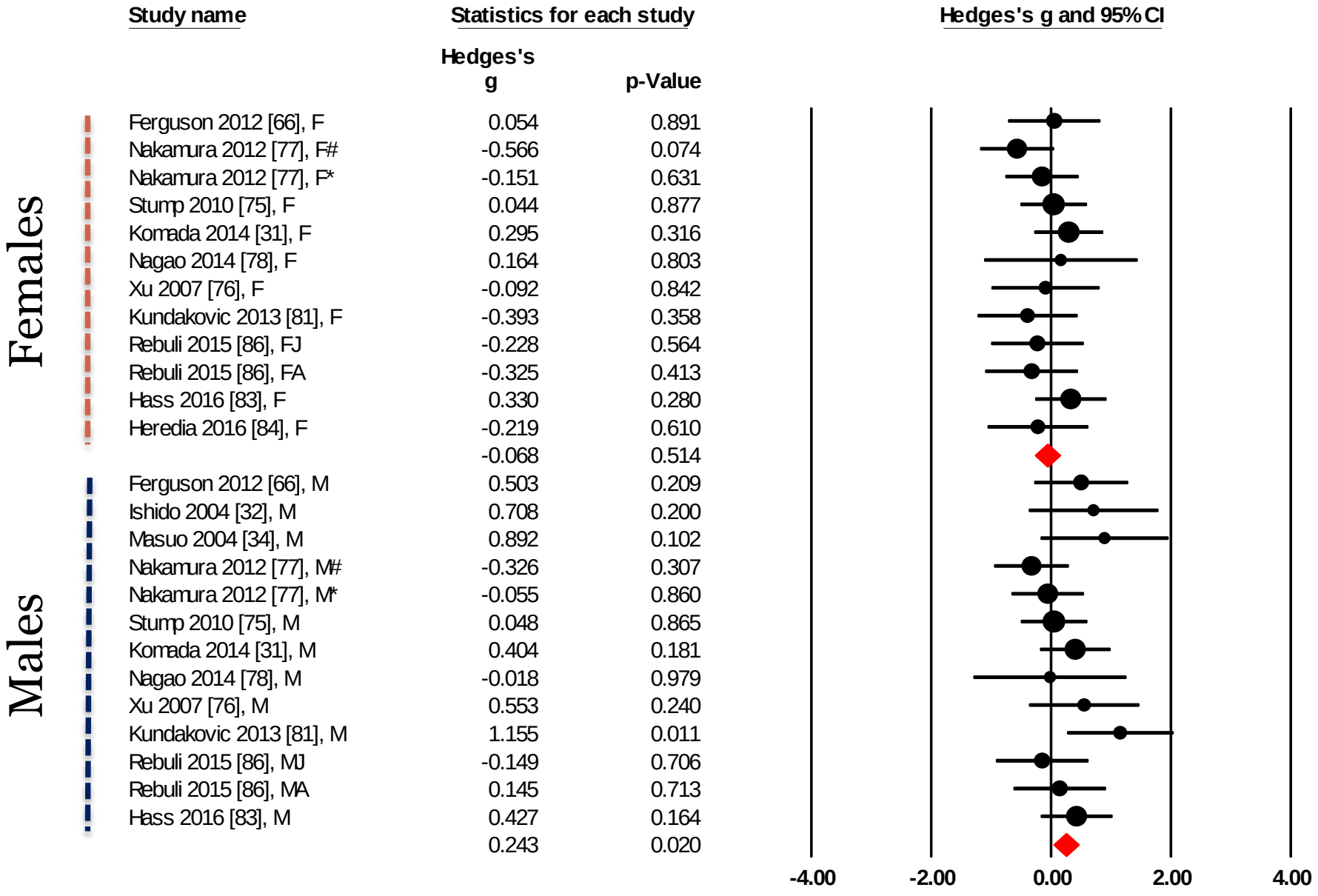
Step 4: "Risk of Bias" (Study Quality)

Study Author & Year	Study Type	Tier	Can we be confident in the exposure assessment?	Can we be confident in outcome assessment?	Was treatment adequately randomized?	Was the allocation of treatment adequately concealed to researchers?	Are baseline characteristics similar between groups?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers rule out any impact from an unintended exposure that might bias results?	Were experimental conditions identical across study groups?	Were the research personnel and human subjects blinded to the study group during the study?	Did variation from the study protocol compromise the conclusions of the study?	Was the attrition rate low and/or similar across groups?	Were the outcome assessors blinded to the intervention or exposure status of participants?	Were confounding variables assessed across groups using valid and reliable measures?	Are the potential outcomes pre-specified and reported by the researchers?	Was an appropriate statistical approach used to analyze the data?
			Key Questions														
Ferguson 2012 [66]*	Animal	1	++	++	+	+	n/a	+	+	++	++	+	++	+	+	++	++
Hass 2016 [83]*	Animal	1	++	++	++	--	n/a	+	NR	++	++	+	++	++	+	++	++
Heredia 2016 [84]*	Animal	1	++	++	+	NR	n/a	+	NR	++	NR	+	NR	+	+	+	++
Hicks 2016 [85]	Animal	1	++	++	+	++	n/a	+	++	++	++	+	++	+	+	++	++
Kiguchi 2007 [68]	Animal	1	++	++	+	-	n/a	+	-	++	++	+	+	++	n/a	++	+
Kiguchi 2008 [69]	Animal	1	++	++	+	-	n/a	+	-	++	++	+	+	++	n/a	++	+
Komada 2014 [31]*	Animal	1	++	+	NR	+	n/a	NR	-	++	+	+	+	+	n/a	++	++
Kundakovic 2013 [81]*	Animal	1	++	++	+	+	n/a	+	-	++	++	+	+	+	n/a	++	++
Masuo 2004 [70]	Animal	1	++	++	--	-	n/a	+	-	++	-	+	+	++	n/a	++	--
Masuo 2004 [34]*	Animal	1	++	++	--	-	n/a	+	-	++	-	+	+	++	n/a	++	--
Nagao 2014 [78]*	Animal	1	++	+	NR	+	n/a	NR	-	-	+	+	+	+	n/a	++	NR
Nakamura 2012 [77]*	Animal	1	++	++	NR	+	n/a	+	-	++	-	+	+	+	+	++	NR
Negishi 2003 [79]	Animal	1	++	++	+	+	n/a	+	NR	++	NR	+	++	+	+	+	NR
Negishi 2004 [71]	Animal	1	++	++	+	-	n/a	+	-	++	-	+	++	++	+	+	--
Rebuli 2015 [86]*	Animal	1	++	++	+	++	n/a	+	++	++	++	+	+	++	+	+	++
Stump 2010 [75]*	Animal	1	++	++	++	+	n/a	+	-	++	-	+	+	+	+	++	NR
Tian 2010 [38]	Animal	1	+	++	+	+	n/a	NR	-	++	-	+	NR	+	n/a	++	NR
Van Esterik 2014 [80]	Animal	1	++	++	--	+	n/a	+	+	++	+	+	++	+	n/a	+	--
Wolstenholme 2013 [72]	Animal	1	++	++	+	--	n/a	+	-	++	--	+	++	++	n/a	++	++
Adriani 2003 [64]	Animal	2	+	++	NR	+	n/a	NR	-	++	-	+	NR	+	n/a	++	NR
Anderson 2013 [65]	Animal	2	NR	++	+	+	n/a	++	+	++	++	+	+	+	+	++	+
Farabollini 1999 [74]	Animal	2	+	++	+	+	n/a	NR	-	++	-	+	NR	NR	n/a	++	NR
Ishido 2004 [32]*	Animal	2	++	++	--	-	n/a	--	--	++	--	+	++	+	n/a	++	NR
Ishido 2005 [33]	Animal	2	++	++	--	-	n/a	--	--	++	--	+	++	+	n/a	+	NR
Ishido 2007 [37]	Animal	2	++	++	--	-	n/a	--	--	+	--	+	++	+	n/a	++	NR
Ishido 2011 [67]	Animal	2	++	++	--	-	n/a	--	--	++	--	+	++	+	n/a	++	NR
Matsuda 2012 [40]	Animal	2	++	++	NR	+	n/a	NR	-	+	-	+	NR	NR	n/a	++	NR
Xu 2007 [76]*	Animal	2	+	++	NR	+	n/a	NR	-	++	-	+	NR	NR	n/a	+	NR
Zhou 2011 [73]	Animal	2	++	++	-	+	n/a	NR	-	++	-	+	NR	+	n/a	++	NR
Braun 2011 [29]*	Human	1	+	++	n/a	n/a	+	++	+	n/a	n/a	+	++	+	++	+	+
Casas 2015 [27]*	Human	1	++	++	n/a	n/a	++	++	++	n/a	n/a	+	+	++	-	++	++
Harley 2013 [30]*	Human	1	+	++	n/a	n/a	++	++	+	n/a	n/a	+	++	+	-	++	+

Step 4: “Risk of Bias”



Meta-Analysis (CMA Software)



Step 5: Determine the confidence in the Body of Evidence for Animal Studies

Step 1: Determine initial confidence in the Body of Evidence	Step 2: Adjust for factors decreasing confidence in the Body of Evidence	Step 3: Adjust for factors increasing confidence in the Body of Evidence
Controlled exposure ✚	Risk of bias ▬	Large Magnitude of Effect
Exposure prior to outcome ✚	Unexplained Inconsistency	Dose Response ✚
Individual outcome data ✚	Indirectness	Residual Confounding
Comparison group used ✚	Imprecision	Consistency
	Publication bias	Other

Overall Confidence in the Body of Evidence	Step 1 Total	Step 2 Total	Step 3 Total	
	+4	-1	+1	High (++++)

Step 5: Determine the confidence in the Body of Evidence for Human Studies

Step 1: Determine initial confidence in the Body of Evidence	Step 2: Adjust for factors decreasing confidence in the Body of Evidence	Step 3: Adjust for factors increasing confidence in the Body of Evidence
Controlled exposure	Risk of bias	Large Magnitude of Effect
Exposure prior to outcome ✚	Unexplained Inconsistency ➖	Dose Response ✚
Individual outcome data ✚	Indirectness	Residual Confounding
Comparison group used ✚	Imprecision	Consistency
	Publication bias	Other

Overall Confidence in the Body of Evidence	Step 1 Total	Step 2 Total	Step 3 Total	
	+3	-1	+1	Moderate (+++)

Step 6- Translate Confidence Rating to Evidence of Health Effects

- Animals: A 'high' rating (from Step 5) and a significant summary measure from the meta-analysis = ***high*** level of evidence.

- Humans: A 'moderate' rating and a significant positive effect = ***moderate*** level of evidence.

Step 7: Identification of Hazard ID conclusion

Level of Evidence for Health Effects in Human Studies	Level of Evidence for Health Effects in Animal Studies		
high	"known"	"known"	"known"
moderate	"suspected"	"presumed"	"presumed"
low	"not classifiable"	"suspected"	"presumed"
	low	moderate	**high**

Conclusions

- SR indicates a **presumed hazard to humans** of early BPA exposure on hyperactivity.
- Heterogeneity: males vs. females
- Data gaps: Timing of exposures
- Risk of Bias

Recommendations/Further Work

- Dose and Risk Assessments
- Pregnant women should avoid BPA
  - Recommended by American College of Obstetricians and Gynecologists
  - BPA is present in: canned food, plastic packaging, thermal receipts
- ADHD/Hyperactivity: sensitive endpoint
- So much BPA research!!

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