Application of US EPA Office of Pesticide Programs (OPP) Framework for Evaluation of Human Epidemiological Literature on Glyphosate Neurotoxicity

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Introduction

Overview

- Why use the U.S. EPA Office of Pesticide Programs (OPP) risk-of-bias framework?
- Why prioritize exposure assessment of direct glyphosate use?
- What does the current epidemiology show in humans?
- How can future epidemiology improve insight?

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REVIEW ARTICLE

Systematic literature review of the epidemiology of glyphosate and neurological outcomes

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Abstract

Purpose Human health risk assessments of glyphosate have focused on animal toxicology data for determining neurotoxic potential. Human epidemiological studies have not yet been systematically reviewed for glyphosate neurotoxicity hazard identification. The objective of this systematic literature review was to summarize the available epidemiology of glyphosate exposure and neurological outcomes in humans.

Methods As of December 2021, 25 eligible epidemiological studies of glyphosate exposure and neurological endpoints were identified and assessed for five quality dimensions using guidance from the U.S. Environmental Protection Agency. Studies that assessed personal use of glyphosate were prioritized, whereas those assessing indirect exposure (other than personal use) were rated as low quality, since biomonitoring data indicate that indirect metrics of glyphosate exposure almost always equate to non-detectable glyphosate doses.

Disclosures

- Work sponsored by the Glyphosate Renewal Group, a European consortium of glyphosate registrants seeming EU Annex 1 Renewal of glyphosate, through a contract with Bayer AG
- Conclusions presented in the paper and this presentation are those of the authors alone
  - Study sponsors did not review or comment on any drafts or versions of the manuscript prior to journal submission or acceptance

- ETC and NUO are employed by Exponent, a science and engineering consulting company that provides consulting support for some members of the Glyphosate Renewal Group
- JFA was employed by Monsanto; ETC and JFA provided consulting support for Bayer; ETC provided consulting support for Monsanto and Syngenta

Methods

U.S. EPA Office of Pesticide Programs Framework

Office of Pesticide Programs'
Framework for Incorporating
Human Epidemiologic & Incident Data in
Risk Assessments for Pesticides

December 28, 2016

Office of Pesticide Programs
US Environmental Protection Agency

U.S. EPA Office of Pesticide Programs Framework

Table 2. Study Quality Considerations [a] (Adapted from Munoz-Quezada et al., 2013; LaKind et al., 2014)

Parameter	High	Moderate	Low
Exposure assessment	Accurate and precise quantitative relationship with external exposure, internal dose, or target dose, possibly associated with an MOA/AOP. If questionnaire utilized, questionnaire and/or interview answered by subjects for chemical-specific exposure	Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose, or target dose. Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Poor surrogate Low-quality questionnaire and/or interview; information collected for groups of chemicals rather than chemical-specific; no chemical-specific exposure information collected; ever/never use of pesticides in general evaluated
Outcome Assessment	Standardized tool, validated in study population; medical record review/diagnosis confirmation by trained staff; appropriate consideration of prevalence/incidence of cases	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated	Selected sections of test, or maternal report, other; or, maternal/paternal self-report; unclear/no consideration for whether prevalent or incident cases are appropriate
Confounder control	Good control for important confounders relevant to scientific question, and standard confounders	Moderately good control confounders, standard variables, not all variables relevant for scientific question	Multi-variable analysis not performed no adjustments; no stratification, restriction, or matching
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (especially sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, effect size magnification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

[a] Overall study quality ranking based on comprehensive assessment across the parameters.

U.S. EPA Office of Pesticide Programs Framework

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U.S. EPA Office of Pesticide Programs Framework

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Overall study quality ranking is based on comprehensive assessment across the parameters.

Glyphosate Exposure Assessment

- “**Direct exposure**”: First-hand or personal application or mixing of a specific pesticide
- “**Indirect exposure**”: Any other exposure routes, e.g., living with a household member who mixed/applied pesticide, working or living on a farm where pesticide was applied, living within a specified distance from a reported pesticide application

Glyphosate Biomonitoring Studies

- Farm Family Exposure Study (Acquavella et al. 2004)
  - 29 (60%) of 48 farmers had detectable 24-hour urinary glyphosate on the day of application (geometric mean = 3 ppb in urine; maximum systemic dose = 0.004 mg/kg, median = 0.0001 mg/kg).
  - 2 (4%) of 48 spouses and 1 (2%) of 52 children not physically present for glyphosate mixing or application had detectable 24-hour urinary glyphosate on the day of application (maximum systemic doses = 0.00004 mg/kg for spouses, 0.0008 mg/kg for children, *including* those participating in mixing/application; median = 0 mg/kg).
- Other biomonitoring studies indicate **no appreciable glyphosate dose from indirect exposure scenarios**, including residing on or near farms with glyphosate use (Curwin et al. 2007, Niemann et al. 2015, Solomon 2016).
  - U.S. general population median urinary glyphosate ~0.4 µg/L = ng/kg range – presumably from dietary exposure, which is not explicitly measured in any epidemiology neurotoxicity studies

Glyphosate Exposure Quality Rating

- **High quality**: Self-reported direct (first-hand) use of glyphosate, with data on frequency and/or duration of use
  - All epidemiological studies involve commercial glyphosate formulations
- **Moderate quality**: Self-reported direct use of glyphosate, without additional data (ever vs. never use)
- **Low quality**: Indirect use of glyphosate, including assessment based on geographic proximity

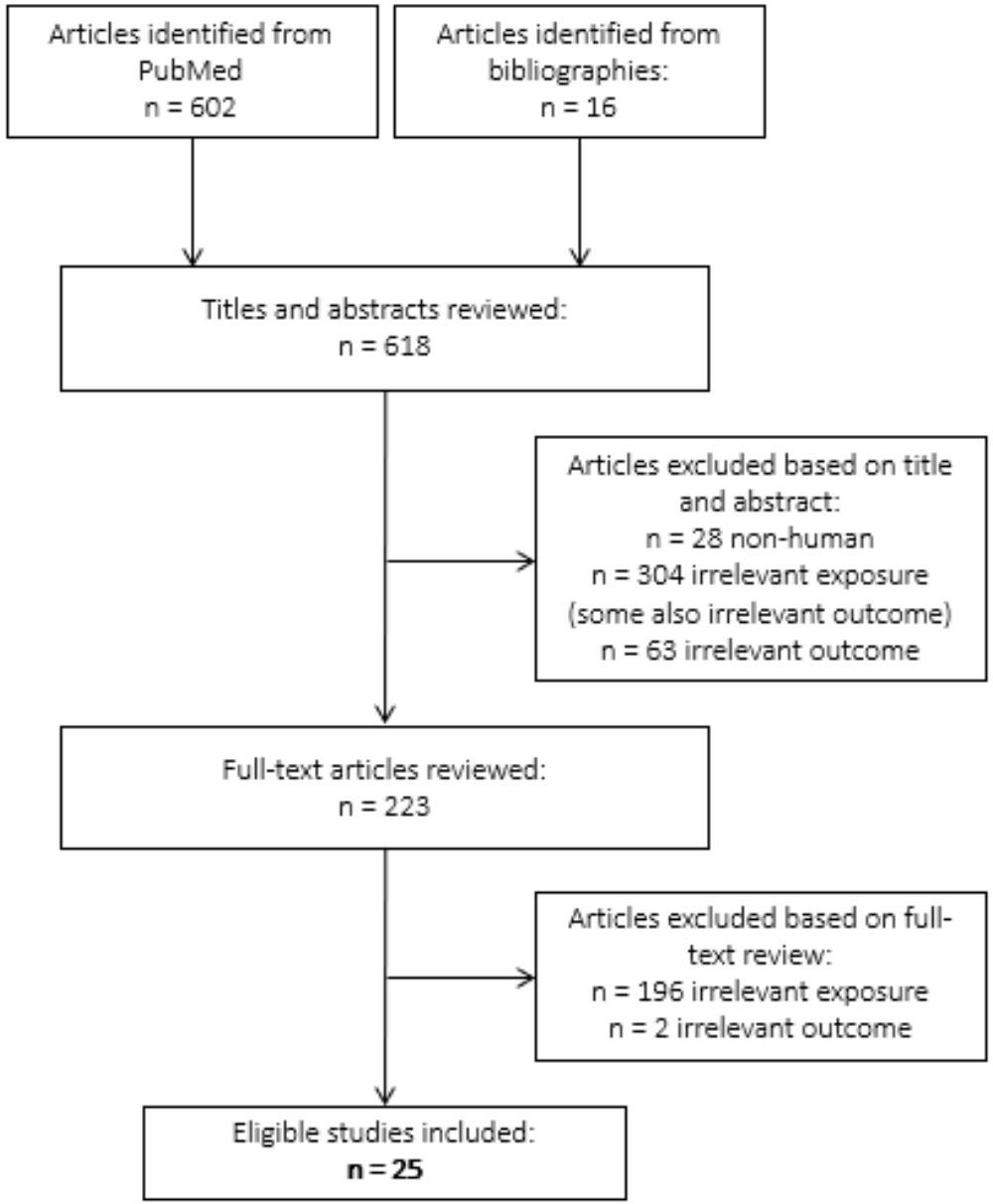
- Studies with low-quality exposure information cannot determine whether individuals received any dose of glyphosate, rendering them uninformative about potential health impacts.
  - Low-quality exposure assessment → Low-quality overall

Literature Search

- PECOS statement
  - **Population**: humans
  - **Exposure**: glyphosate exposure
  - **Comparator**: absence of glyphosate exposure
  - **Outcome**: chronic neurological conditions, including central and peripheral nervous system disorders, excluding acute poisoning and intoxication events, acute nonspecific neurological symptoms, and nervous system neoplasms
  - **Study design**: comparative epidemiological studies, including cross-sectional, case-control, and cohort studies, excluding case reports and case series
- PubMed search on 8 December 2021
  - *(glyphosate OR pesticide* OR herbicide*) AND [various neurological conditions] AND [various epidemiological keywords]*

Results

Literature Search Flow Chart

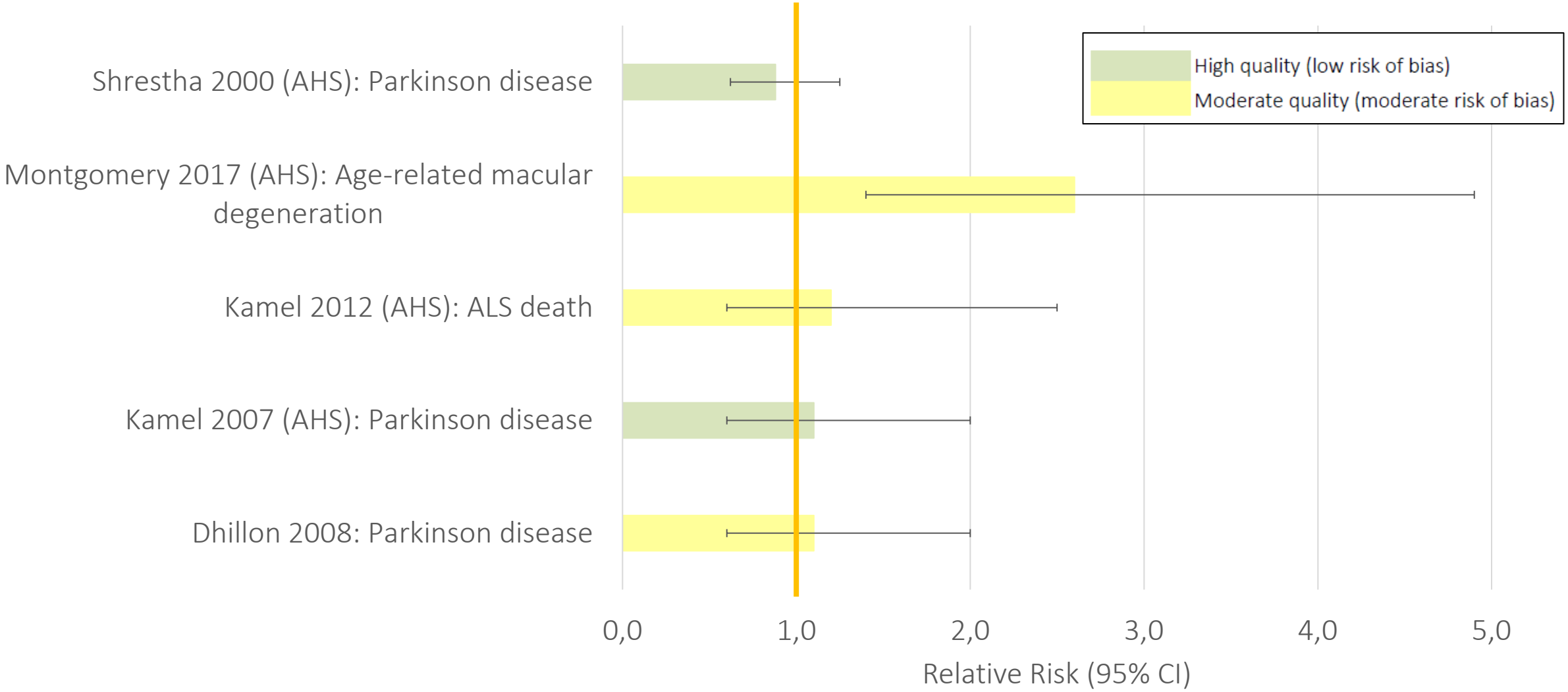


Risk-of-Bias Ratings Summary

Author	Year	Study Design and Population	Exposure Assessment	Outcome Assessment	Confounders Considered	Statistical Approach	Overall Quality
Neurodegenerative outcomes							
Andrew et al.	2021						
Caballero et al.	2018						
Dhillon et al.	2008						
Kamel et al.	2007						
Kamel et al.	2012						
Montgomery et al.	2017						
Shrestha et al.	2020						
Wan & Lin	2016						
Wechsler et al.	1991						
Neurobehavioral outcomes							
Beard et al.	2013						
Beard et al.	2014						
Faria et al.	2014						
Fuhrimann et al.	2021						
Kim et al.	2013						
Neurodevelopmental outcomes							
Garry et al.	2002						
Juntarawijit et al.	2020						
Nevison	2014						
Rull et al.	2006						
von Ehrenstein et al.	2019						
Yang et al.	2014						
Other/mixed neurological outcomes							
Fuhrimann et al.	2022						
Seneff et al.	2015						
Shrestha et al.	2018						
Shrestha et al.	2021						
Zhang et al.	2018						

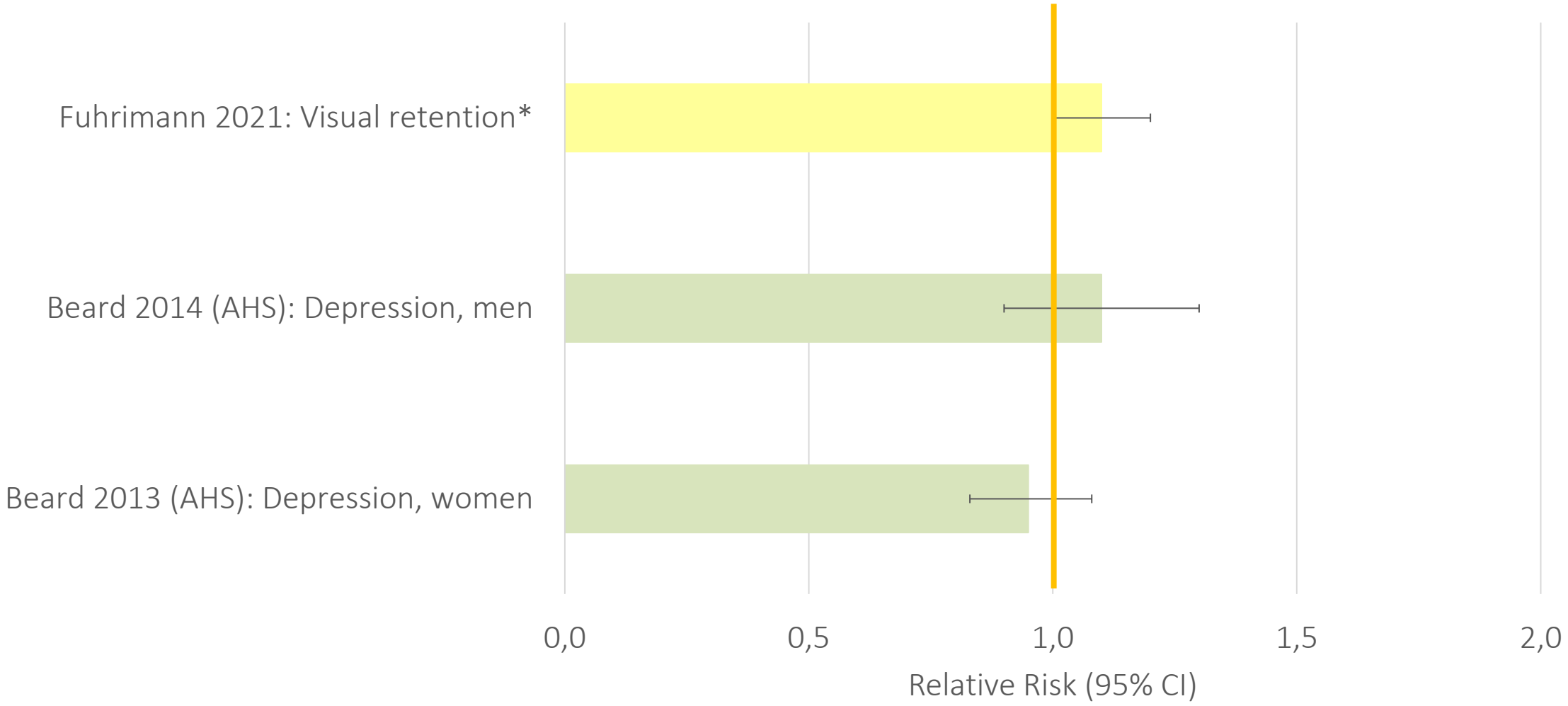
- High quality (low risk of bias)
- Moderate quality (moderate risk of bias)
- Low quality (high risk of bias)

Glyphosate and Neurodegenerative Outcomes



Length of colored bar indicates relative risk for highest exposure contrast
Length of black line indicates 95% confidence interval

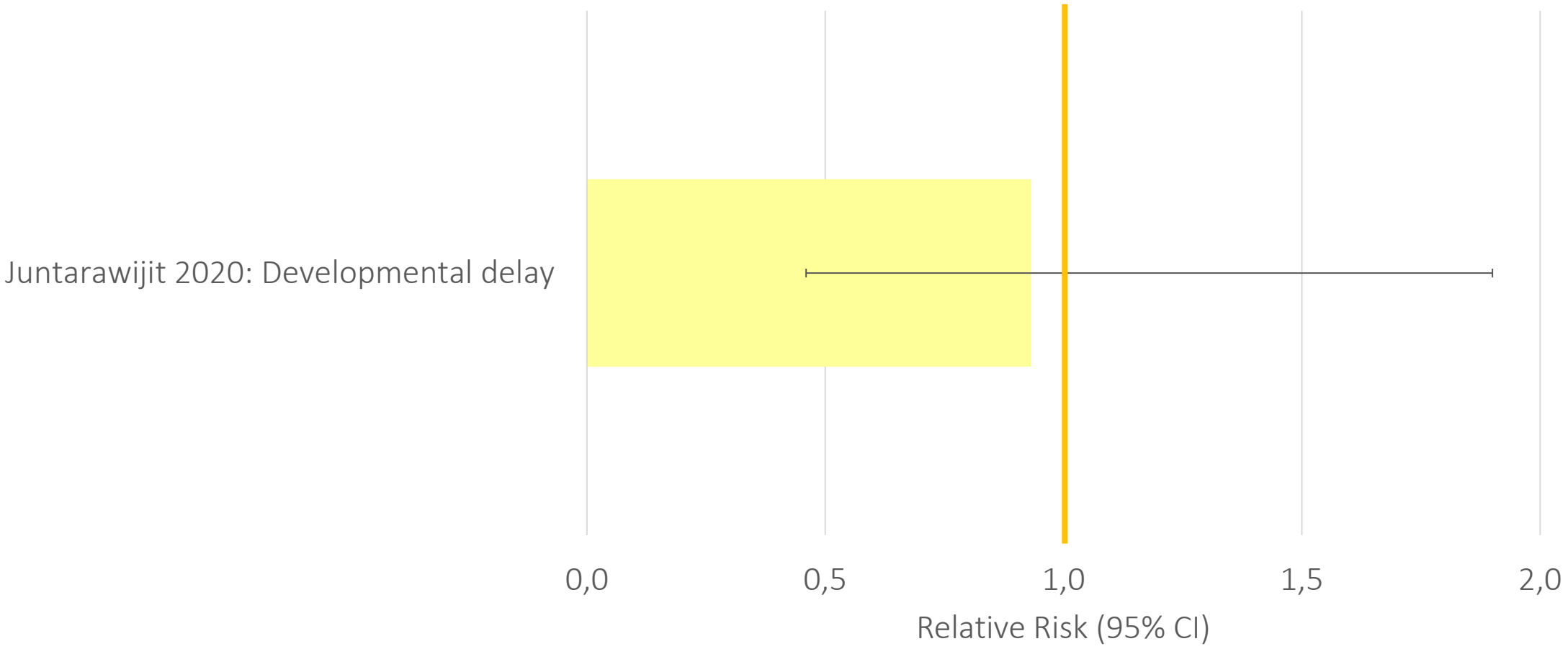
Glyphosate and Neurobehavioral Outcomes



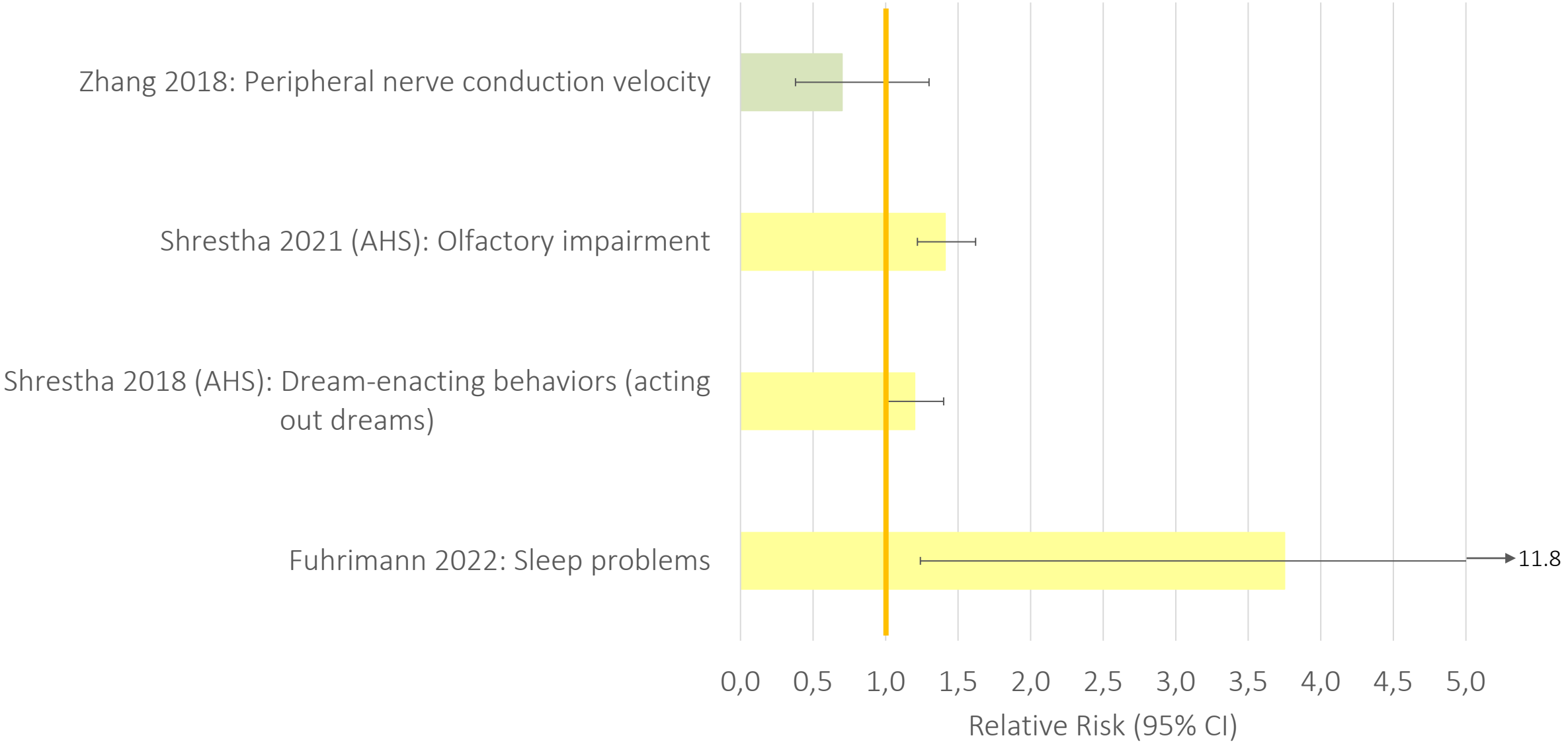
*Change in Benton Visual Retention score per interquartile increase in exposure intensity score = -0.103 (-0.236, 0)

13 other neurobehavioral outcome variables in this study were not significantly associated; adjusted for multiple testing

Glyphosate and Neurodevelopmental Outcomes



Glyphosate and Other Neurological Outcomes



Summary of Results

- 5 high-quality, 8 moderate-quality, 12 low-quality studies
- Among high- and moderate-quality studies, weak or modest statistical associations were detected with 5 different outcomes in one study each (none replicated):
  - Age-related macular degeneration (Montgomery et al. 2017)
  - Visual memory (Fuhrimann et al. 2021)
  - Sleep problems (Fuhrimann et al. 2022)
  - Dream-enacting behaviors (Shrestha et al. 2018)
  - Olfactory impairment (Shrestha et al. 2021)
- Two outcomes were evaluated in more than one study each, all with weak (relative risk < 1.5) and statistically null results:
  - Parkinson disease (Kamel et al. 2007, Dhillon et al. 2008, Shrestha et al. 2020; *some overlap between Kamel and Shrestha*)
  - Depression (Beard et al. 2013, Beard et al. 2014)

Discussion

Overview of Epidemiological Literature

- Sparse
- Mostly methodologically weak
- No consistent association between glyphosate exposure and risk of any specific neurological condition or category of neurological outcomes in humans

Glyphosate Exposure Assessment in Neuroepi Studies

- Only 6 high- or moderate-quality studies with quantitative or semi-quantitative levels of glyphosate use

- 19 studies with little or no information on individual-level exposure frequency or probable dose
  - 7 high- or moderate-quality studies with ever vs. never glyphosate use
  - 2 low-quality studies with ever vs. never glyphosate use
  - 8 low-quality studies with residential proximity-based or ecological exposure assessment
  - 1 low-quality study with ever use of glyphosate on same farm (indirect)
  - 1 low-quality study with occupational pesticide poisoning (misclassification of direct use)

Literature Gaps and Methodological Limitations

- Assessment of residential (nonoccupational) applications of glyphosate in epidemiological studies
  - A biomonitoring study of simulated heavy residential consumer application of Roundup® estimated a worst-case maximum dose of 0.0059 mg/kg/day (Kougias et al. 2021) – comparable to that in occupational applicators
- Assessment of standardized, validated (not self-reported) neurological outcomes
- Adjustment for confounding by other pesticides and aspects of agricultural occupation or lifestyle

Conclusions

- No consistent evidence of a statistical association or causal effect between glyphosate exposure and any neurological outcome in humans
- Epidemiological study needs (in addition to Agricultural Health Study)
  - Populations with frequent direct exposure
  - Validated, quantitative exposure assessment
  - Validated outcome assessment
  - Minimization of selection bias through high participation/follow-up
  - Rigorous statistical adjustment for confounding
- Additional biomonitoring studies for different exposure scenarios
- Validation studies of geographically modeled exposures

THANK YOU