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Commissioned Systematic Reviews: Final Report

The committee contracted with the Texas A&M University Evidence Practice Center to conduct an update of two systematic reviews from the USDA Nutrition Evidence Systematic Review—one on seafood consumption during childhood and adolescence and neurocognitive development and the other on seafood consumption during pregnancy and lactation and neurocognitive development in the child. In addition, the committee requested a *de novo* systematic review on toxicants in seafood and neurocognitive development in children and adolescents. This appendix provides the final report and 11 supplemental files prepared by the Evidence Practice Center.

Supplemental File List

Supplemental file 2-1. Seafood consumption during pregnancy and lactation and neurocognitive development in the child – A systematic review: Data files

Supplemental file 2-2. Seafood consumption during pregnancy and lactation and neurocognitive development in the child – A systematic review: Risk of bias assessment results

Supplemental file 2-3. Seafood consumption during pregnancy, lactation, childhood and adolescents and neurocognitive development in the child – Full text excluded articles with rationale

Supplemental file 3-1. Seafood consumption during childhood and adolescence and neurocognitive development in the child – A systematic review: Data files

Supplemental file 3-2. Seafood consumption during childhood and adolescence and neurocognitive development in the child – A systematic review: Risk of bias assessment results

Supplemental file 4-1. Seafood toxicant exposure during pregnancy, lactation, and childhood and child growth and development – A preliminary scoping review: Data files

Supplemental file 4-2. Seafood toxicity during pregnancy, lactation, childhood and adolescents and child health and development outcomes – Special categories of excluded articles

Supplemental file 4-3. Seafood toxicity during pregnancy, lactation, childhood and adolescents and child health and development outcomes – Full text excluded articles with rationale

Supplemental file 5-1. Seafood and mercury exposure during pregnancy, lactation, and childhood and child growth and development – Identifying existing systematic reviews: Data files

Supplemental file 6-1. Maternal seafood and lead exposure during pregnancy or lactation and child development outcomes – A systematic review: Data files

Supplemental file 7-1. Maternal seafood and PCB exposure during pregnancy or lactation and child growth outcomes – A systematic review: Data files

The Role of Seafood Consumption in Child Growth and Development: A series of systematic reviews

Texas A&M Agriculture, Food, and Nutrition Evidence Center

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AGRICULTURE, FOOD, & NUTRITION
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Chapter 1: Introduction

The FDA and EPA provide advice related to the health benefits of eating fish in pregnancy, during lactation or in childhood to help individuals make informed choices regarding the types of fish (i.e., finfish and shellfish) that are nutritious and safe to eat. The goal is to look more holistically at the role of fish in the diet, considering both components that are beneficial (such as nutrients) and detrimental (such as environmental contaminants) and evaluating their respective and interacting roles in child development.

The National Academies of Sciences, Engineering, and Medicine (NASEM) was commissioned to review the state of scientific evidence in nutrition and toxicology of associations between seafood intake and child growth and relevant aspects of development. This NASEM review will include a study of the associations between seafood intake (maternal and child) and child growth and development. As part of this review, the Texas A&M Agriculture, Food, and Nutrition Evidence Center (Evidence Center) has been sub-contracted to perform a series of systematic reviews examining the associations between seafood nutrition and toxicant intake during pregnancy, lactation and child growth and development, addressed by three key questions (**Text box 1-1**). Specifically, the Evidence Center will update two existing systematic reviews previously published by the USDA Nutrition Evidence Systematic Review Center conducted to inform the *2020-2025 Dietary Guidelines for Americans* that examined the relationship between seafood nutrition and health outcomes among 1) pregnant and lactating individuals, and 2) children. *These two reviews are collectively referred to as the "Nutrition reviews"*. In addition, a third de novo systematic review will examine the association between seafood-related contaminants (toxicological) and health outcomes during pregnancy, lactation and childhood on child growth and development, *referred to as the "Toxicology review".* A scoping review will be used to prioritize exposure-outcome associations with sufficient evidence to warrant systematic review.

This report outlines the methodology and results of the Evidence Center work conducted to provide data to the NASEM committee on The Role of Seafood in Child Growth and Development (herein referred to as "the Committee").

Text box 1-1. Systematic review questions

1. What are the associations between seafood consumption *during pregnancy and lactation* and child growth and development?

2. What are the associations between seafood consumption *during childhood and child growth* and development?

3. What are the associations between seafood toxicant exposure during pregnancy, lactation, and childhood and child growth and development?

Chapter 2: Seafood consumption during pregnancy and lactation and neurocognitive development in the child: A systematic review

Methodology

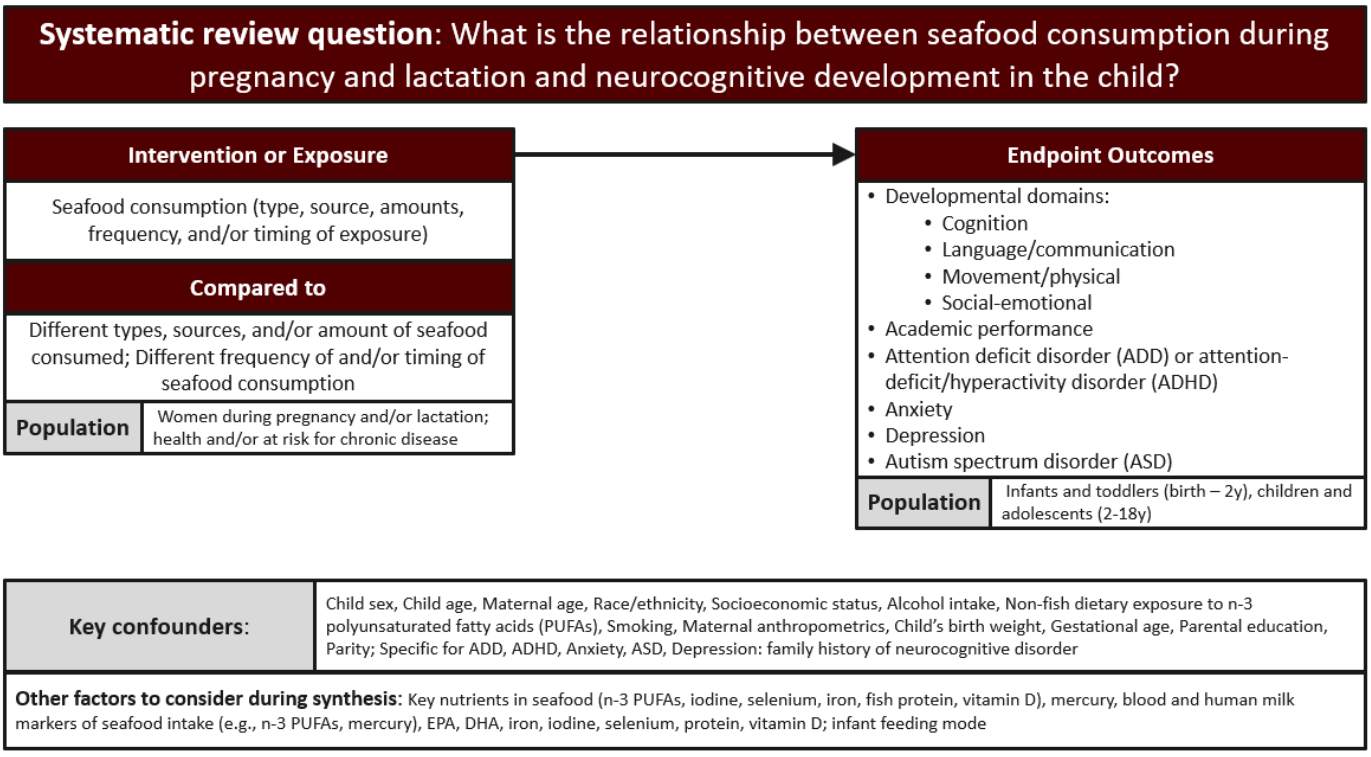
Protocol development

Relevant data and information to create the systematic review protocol was provided to the Evidence Center by NASEM. This information included the PECOD framework, inclusion/exclusion criteria, and the search strategy. The search was run by the NASEM librarian and search results were provided to the Evidence Center. The Evidence Center drafted the protocol including relevant methodology based on the provided information and registered the protocol in PROSPERO (CRD42023432844).

Because the nutrition reviews (1. seafood consumption in women who are pregnant or lactating and 2. seafood consumption in children) were updates of existing USDA NESR systematic reviews, the protocols reflected those of the existing reviews.

Analytic framework

***Figure 2-1**. Analytic framework for examining the relationship between seafood consumption during pregnancy and lactation and neurocognitive development in the child.*



Inclusion and exclusion criteria

Table 2-1. Inclusion and exclusion criteria for nutrition reviews

Category	Inclusion Criteria	Exclusion Criteria

Population	Individuals living in countries ranked as high or very high on the human development index[a] during the study.
	
	• Exposed population: Individuals in the general population who are pregnant or lactating. Subgroups of interest:
	  ○ By race/ethnicity
	  ○ By income
	  ○ By cumulative exposure to non-chemical and environmental stressors (e.g., stress, depression, neighborhood or locale, food security)
	  ○ By pre-existing disease burden
	
	• Outcome population: Children and adolescents (up to age 18 years). Subgroups of interest:
	  ○ Infants (ages 0 to 12 months)
	  ○ Toddlers (ages 1 to 3 years)
	  ○ Early childhood (ages 4 to 8 years)
	  ○ Puberty (ages 9 to 13 years)
	  ○ Adolescents (ages 14 to 18 years)
		• Studies exclusively of participants with a chronic condition, hospitalized with an illness or injury. Examples include:
		• Diabetes (not including gestational diabetes)
		• Cancer
		• Cardiometabolic disorders
		• Chronic kidney disease
		• Malabsorption (any disorder that causes malabsorption from the gastrointestinal tract)
		• Asthma

Exposure	• Seafood consumption: • Types (e.g., salmon, tuna, bass) • Sources (e.g., sea, fresh water, farmed, canned, wild) • Amount (e.g., ounces per day, grams per meal) • Frequency (e.g., daily, twice a week) • Duration (e.g., length of time consuming seafood) • Preparation (e.g., fried, baked) • Timing (e.g., by trimester, age)	• Supplements • Infant formula
Comparator	• Different types, sources, amounts, frequencies, durations, preparations, or timings of seafood consumption • No seafood consumption	No comparator

Outcome	Neurodevelopment and Neurodevelopmental Disorders: ● Developmental domains: cognition, language/communication, movement/physical, social-emotional ● Social/emotional outcomes ● Academic performance ● Autism spectrum disorders (ASD) ● Anxiety ● Depression ● Attention deficit hyperactivity disorder (ADHD)	
Study Designs	● Randomized controlled trials ● Controlled (nonrandomized) trials ● Cohort (observational) studies, prospective or retrospective ● Case-cohort studies	● Case reports ● Studies reported in theses or conference abstracts only ● Studies not reported in English ● Studies without primary data, such as systematic reviews, narrative reviews, editorials, and commentaries

[a] https://worldpopulationreview.com/country-rankings/hdi-by-country

Screening

All records captured in the search were screened independently by two reviewers. Screening occurred within a web-based program (DistillerSR) using screening forms developed based on the inclusion and exclusion criteria determined *a priori*. Each article was reviewed to determine if it met the inclusion criteria, in which case the article was included, or if any of the exclusion criteria were met, in which case the article was excluded.

Screening was conducted in 3 stages or levels following the methodology of the original existing review. In the first level, the title of the article was reviewed. Title screening was used to exclude clearly irrelevant studies. Potential reasons for exclusion at the title level included wrong study population or country, as examples. If there was not a clear reason for exclusion, the article was included and moved to level 2, abstract screening. If there was no reason to exclude the article based on information in the abstract, it was included and moved to level 3, full text screening. When an article was excluded at level 2 (abstract) or level 3 (full text) the screener indicated at least one reason for exclusion. Any disagreements on whether to include or exclude an article were discussed and resolved by the two screeners. If necessary, a third party was consulted to resolve differences.

Piloting was done to ensure the screening forms were adequate and that screeners interpreted the eligibility criteria similarly. For the pilot, screeners reviewed a common set of references (25 references to start) at each screening level. The screeners discussed their responses, any questions or uncertainties they had when making their decision, and any concerns regarding the screening form. If necessary, this was repeated with another common set of references.

Manual searching (or hand-searching) was performed on all articles included after full-text screening. Manual searching is a process whereby the reference list from each included article is reviewed. If a reference is found to be relevant to the present review that was not identified in the electronic search it proceeds through the screening process as detailed above. If an article identified through manual searching was included in the review, the librarian was notified to determine why the article was not found through the electronic search. If necessary, the search strategy would have been updated and rerun, in which case newly identified articles would go through the screening process as described above.

Data extraction

Data from all included articles were extracted by a trained analyst using a systematic approach. Only data relevant to the review was extracted. To ensure data was extracted in a consistent manner for all papers, standard data extraction forms were used. Data fields for extraction were based on information outlined in the protocol and included important characteristics of the study design, methodology, results, and limitations. Data extraction was piloted on 2 to 3 articles (varying in study design, when appropriate) by all reviewers to ensure all relevant information was recorded and done so in a consistent manner. For the nutrition reviews, data extraction forms included similar fields as the existing reviews (**Text box 2-1**). A second analyst reviewed the extracted data for accuracy and completeness. Any suggested changes were discussed between the reviewers. If necessary, a third analyst was consulted.

Text box 2-1. Data extraction fields for the nutrition review update

Study characteristics:

- Author name, publication year
- Study design
- Study name, if applicable
- Country

- Baseline n

Participant characteristics:

- Mother's age
- Child sex (% female)
- Race/ethnicity
- Socioeconomic Status
- Maternal anthropometrics
- Gestational weight gain
- Infant feeding practices

Exposure details:

- Exposure definition/description
- Exposure assessment method

Exposure level:

- Seafood intake amount
- Maternal/infant levels of nutrients from seafood: omega-3 polyunsaturated fatty acids [PUFAs], iodine, selenium, iron, fish protein, and vitamin D
- Maternal/infant levels of mercury

Confounders:

- Key confounders accounted for
- Key confounders NOT accounted for
- Other confounders accounted for

Outcome(s) and Results:

- Outcome domain (e.g. developmental domain-cognition, developmental domain-language/communication)
- Outcome assessment tool

- Outcome assessment methods including subscale
- Child age at outcome assessment
- Results, including analytic n

Study limitations

Summary of results

Funding source

Risk of bias assessment

Risk of bias was assessed independently by two analysts using standardized tools specific to each study's design for all included studies. If a study included multiple relevant results, the analysts assessed the risk of bias pertinent to each. If there were differences in risk of bias for the different results, more than one risk of bias assessment was reported for a paper.

For this project, Cochrane risk of bias tools specific to the included study designs were used. These included: ROB 2.0 for randomized controlled trials, ROBINS-I for non-randomized studies of interventions, and ROBINS-E for non-randomized studies of exposures. These tools are designed to assess risk of bias by domain and then determine an overall risk of bias rating for the study. The analysts piloted the tools on 2 to 3 articles per study design to ensure a consistent approach and interpretation. Further, upon completion of the dual, independent risk of bias assessments, domain-level ratings and the overall rating were compared between the two reviewers to assess inter-rater reliability. If there were differences, the reviewers discussed and determined the appropriate rating. If necessary, a third reviewer was consulted.

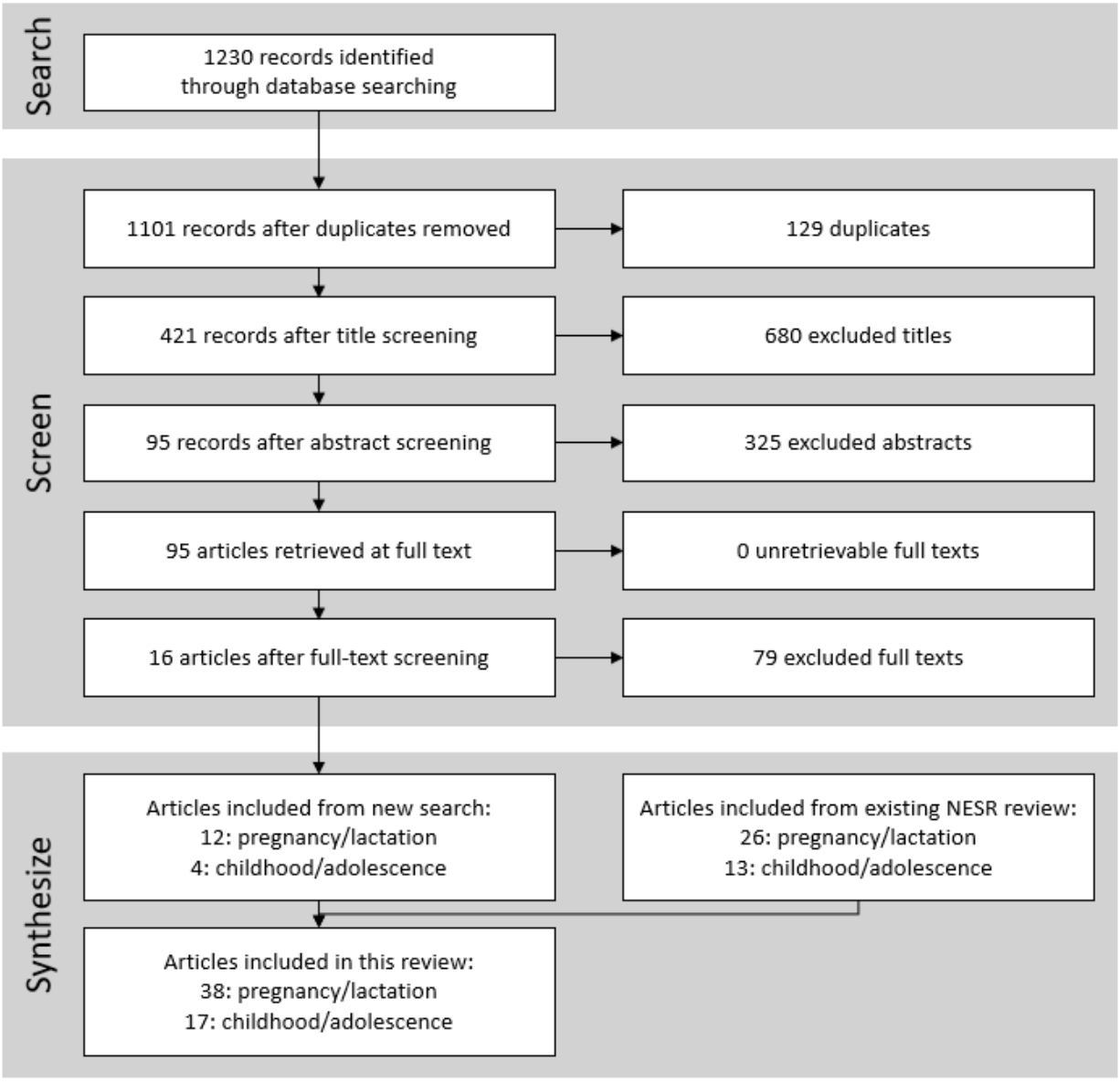
Synthesis

Synthesis was conducted by the Committee. To prepare for synthesis, a description of the evidence was drafted to provide details on the body of evidence including but not limited to, the number of included articles, the number of included studies, study designs, country of origin, participant characteristics, description of the exposure across studies, outcomes, and outcome assessment tools. A description of the evidence and data tables were provided to the Committee.

Results

PRISMA flow chart

Figure 2-2. *PRISMA flow chart outlining the number of articles included after searching, screening and synthesis.*



Description of evidence

***Table 2-2**. Studies included in the nutrition review in women who are pregnant or lactating; 38 articles included (26 from existing NESR review, 12 from update)*

Study Design	Cohort/Study Name	Article (Author, year)
Randomized Control Trials	Mommy's Food Study	2 articles: • Kvestad, 2021 • Markhus, 2021
Longitudinal Cohort Study	Avon Longitudinal Study of Children and Parents (ALSPAC)	5 articles: • Daniels, 2004 • Golding, 2018 • Hibbeln, 2007 • Mesirow, 2017 • Williams, 2001
	Project Viva	3 articles: • Oken, 2016 • Oken, 2005 • Oken, 2008b
	Spanish Childhood and Environment Project (Infancia y Medio Ambiente; INMA)	3 articles: • Llop, 2012 • Julvez, 2020 • Julvez, 2016
	PHIME (Public Health Impact of long-term, low level, Mixed Element exposure in susceptible population strata)	2 articles: • Nišević, 2019 • Barbone, 2019
	Health Outcomes and Measures of the Environment (HOME)	2 articles: • Xu, 2016 • Vecchione, 2020 (also includes data from the Early Autism Risk Longitudinal Investigation (EARLI) cohort)
	Danish National Birth Cohort (DNBC)	1 article: • Oken, 2008a
	Étude Longitudinale Française depuis l'Enfance (ELFE) study	1 article: • De Lauzon-Guillain, 2022

	Fish Oil and Probiotics in Pregnancy study (FOPP study)	1 article: • Saros, 2023
	Generation R study	1 article: • Steenweg-de Graaff, 2016
	Japan Environment and Children's Study	1 article: • Hamazaki, 2020
	LW Birth Cohort	1 article: • Hu, 2016
	Mount Sinai Children's Environmental Health Study	1 article: • Furlong, 2018
	Norwegian Mother and Child Cohort Study (MoBa)	1 article: • Verjrup, 2018
	Seychelles Child Development Study	1 article: • Conway, 2023
	The New Bedford Cohort	1 article: • Sagiv, 2012
	Unnamed cohort/study	1 article: • Barbone, 2020
	Unnamed cohort/study	1 article: • Davidson, 2008
	Unnamed cohort/study	1 article: • Gale, 2008
	Unnamed cohort/study	1 article: • Lederman, 2008
	Unnamed cohort/study	1 article: • Mendez, 2009
	Unnamed cohort/study	1 article: • Deroma, 2013
	Unnamed cohort/study:	1 article: • Hisada, 2017

	Unnamed cohort/study:	1 article: • Normia, 2018
	Unnamed cohort/study:	1 article: • Rothenberg, 2021
	Unnamed cohort/study	1 article: • Valent, 2013
	Unnamed cohort/study	1 article: • Varsi, 2021

***Table 2-3**. Studies included in the nutrition review in women who are pregnant or lactating organized by outcome; 38 articles included (26 from existing NESR review, 12 from update)*

Outcome Domain	Sub-Domain	Article (Author, year)
Development Domain	Cognition	28 articles: • Barbone, 2019 • Conway, 2023 • Davidson, 2008 • De Lauzon-Guillain, 2022 • Deroma, 2013 • Furlong, 2018 • Gale, 2008 • Hamazaki, 2020 • Hibbeln, 2007 • Hu, 2016 • Julvez, 2016 • Lederman, 2008 • Llop, 2012 • Markhus, 2021 • Mendez, 2009 • Nišević, 2019 • Normia, 2018 • Oken, 2005 • Oken, 2008b • Oken, 2016 • Rothenberg, 2021 • Sagiv, 2012 • Saros, 2023 • Steenweg-de Graaff, 2016 • Valent, 2013 • Vecchione, 2020 • Williams, 2001 • Xu, 2016

	Language/Communication	13 articles: • Barbone, 2019 • Barbone, 2020 • Conway, 2023 • Daniels, 2004 • De Lauzon-Guillain, 2022 • Hamazaki, 2020 • Hibbeln, 2007 • Hu, 2016 • Markhus, 2021 • Nišević, 2019 • Saros, 2023 • Valent, 2013 • Verjrup, 2018
	Movement/physical	16 articles: • Barbone, 2019 • Barbone, 2020 • Conway, 2023 • Hamazaki, 2020 • Hibbeln, 2007 • Hu, 2016 • Lederman, 2008 • Llop, 2012 • Markhus, 2021 • Mendez, 2009 • Nišević, 2019 • Oken, 2008a • Rothenberg, 2021 • Saros, 2023 • Valent, 2013 • Varsi, 2021
	Social-emotional	10 articles: • Barbone, 2020 • Daniels, 2004 • Gale, 2008 • Hamazaki, 2020 • Hibbeln, 2007 • Hu, 2016 • Kvestad, 2021 • Mesirow, 2017 • Oken, 2008a • Valent, 2013

	Total/aggregate scores	5 articles: • Daniels, 2004 • De Lauzon-Guillain, 2022 • Hisada, 2017 • Kvestad, 2021 • Oken, 2008a
Academic Performance	NA	0 articles
Attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD)	NA	4 articles: • Conway, 2023 • Julvez, 2020 • Mesirow, 2017 • Sagiv, 2012
Anxiety	NA	0 articles
Depression	NA	0 articles
Autism spectrum disorder (ASD)	NA	4 articles: • Golding, 2018 • Julvez, 2016 • Steenweg-de Graaff, 2016 • Vecchione, 2020

Extracted data

Analysts extracted data that was relevant to the review question from each included article. During extraction, results were organized by the outcome domains listed in the Analytic Framework and further by the outcome assessment tool (e.g., Bayley Scale of Infant Development) and the subscale (e.g., mental development index, psychomotor development index). Therefore, when an article reported multiple domains, assessment tools, and/or subscales, data is presented in multiple rows within the extracted data file. This allows for organization of the evidence by outcome category. **SEE SUPPLEMENTAL FILE 2-1.**

Note that there is a large amount of data in many cells (particularly results). Data cells need to be expanded to see all data. For results, significant findings are **bolded**, with significant findings indicating a beneficial association between seafood intake on child development in **green**, and significant findings indicating a detrimental association between seafood intake on child development in **red**.

Within the data table file, data is organized in separate tabs:

- All-sorted by author
- Cohort+Participant characteristics (no results)
- All-sorted by outcome (results for all outcomes can be reviewed to assess for trends)
- Each outcome domain with included articles:
  - Cognition
  - Language/Communication
  - Movement/physical
  - Social-emotional
  - Total/aggregate scores
  - Academic performance
  - Attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD)
  - Autism spectrum disorder (ASD)

Risk of bias assessments

Risk of bias was assessed for each included article. Results from the risk of bias assessments can be found in **SUPPLEMENTAL FILE 2-2.**

Included articles

1. Barbone, F., Rosolen, V., Mariuz, M., Parpinel, M., Casetta, A., Sammartano, F., et al. (2019). Prenatal mercury exposure and child neurodevelopment outcomes at 18 months: Results from the Mediterranean PHIME cohort. Int J Hyg Environ Health, 222(1), 9-21. doi:10.1016/j.ijheh.2018.07.011.
2. Barbone, F., Valent, F., Pisa, F., Daris, F., Fajon, V., Gibicar, D., et al. (2020). Prenatal low-level methyl mercury exposure and child development in an Italian coastal area. NeuroToxicology, 81, 376-381. doi: 10.1016/j.neuro.2020.09.033.
3. Conway, M. C., Yeates, A. J., Love, T. M., Weller, D., McSorley, E. M., Mulhern, M. S., et al. (2023). Maternal fish consumption and child neurodevelopment in Nutrition 1 Cohort: Seychelles Child Development Study. Br J Nutr, 1-7. doi: 10.1017/S0007114523000375.
4. Daniels, J. L., Longnecker, M. P., Rowland, A. S., Golding, J., & ALSPAC Study Team-University of Bristol Institute of Child Health. (2004). Fish intake during pregnancy and early cognitive development of offspring. Epidemiology, 15(4), 394-402. doi:10.1097/01.ede.0000129514.46451.ce.

5. Davidson, P. W., Strain, J. J., Myers, G. J., Thurston, S. W., Bonham, M. P., Shamlaye, C. F., et al. (2011). Neurodevelopmental effects of maternal nutritional status and exposure to methyl mercury from eating fish during pregnancy. NeuroToxicology, 32(6), 989-989. doi:10.1016/j.neuro.2008.06.001.
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8. Furlong, M., Herring, A. H., Goldman, B. D., Daniels, J. L., Wolff, M. S., Engel, L. S., et al. (2018). Early life characteristics and neurodevelopmental phenotypes in the Mount Sinai children's environmental health center. Child Psychiatry Hum Dev, 49(4), 534-550. doi:10.1007/s10578-017-0773-5.
9. Gale, C. R., Robinson, S. M., Godfrey, K. M., Law, C. M., Schlotz, W., & O'Callaghan, F. J. (2008). Oily fish intake during pregnancy–association with lower hyperactivity but not with higher full-scale IQ in offspring. J Child Psychol Psychiatry, 49(10), 1061-1068. doi:10.1111/j.1469-7610.2008.01908.x.
10. Golding, J., Rai, D., Gregory, S., Ellis, G., Emond, A., Iles-Caven, Y., et al. (2018). Prenatal mercury exposure and features of autism: a prospective population study. Mol Autism, 9(1), 1-9. doi:10.1186/s13229-018-0215-7.
11. Hamazaki, K., Matsumura, K., Tsuchida, A., Kasamatsu, H., Tanaka, T., Ito, M., et al. (2020). Maternal dietary intake of fish and PUFAs and child neurodevelopment at 6 months and 1 year of age: a nationwide birth cohort—the Japan Environment and Children's Study (JECS). Am J Clin Nutr, 112(5), 1295-1303. doi: 10.1093/ajcn/nqaa190.
12. Hibbeln, J. R., Davis, J. M., Steer, C., Emmett, P., Rogers, I., Williams, C., et al. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet, 369(9561), 578-585. doi:10.1016/s0140-6736(07)60277-3.
13. Hisada, A., Yoshinaga, J., Zhang, J., Katoh, T., Shiraishi, H., Shimodaira, K., et al. (2017). Maternal exposure to pyrethroid insecticides during pregnancy and infant development at 18 months of age. Int J Environ Res Public Health, 14(1), 52. doi:10.3390/ijerph14010052.

14. Hu, Y., Chen, L., Wang, C., Zhou, Y., Zhang, Y., Wang, Y., et al. (2016). Prenatal low-level mercury exposure and infant neurodevelopment at 12 months in rural northern China. Environ Sci Pollut Res Int, 23(12), 12050-12059. doi:10.1007/s11356-016-6395-9.
15. Julvez, J., Mendez, M., Fernandez-Barres, S., Romaguera, D., Vioque, J., Llop, S., et al. (2016). Maternal consumption of seafood in pregnancy and child neuropsychological development: a longitudinal study based on a population with high consumption levels. Am J Epidemiol, 183(3), 169-182. doi:10.1093/aje/kwv195.
16. Julvez, J., Fernandez-Barres, S., Gignac, F., Lopez-Vicente, M., Bustamante, M., Garcia-Esteban, R., et al. (2020). Maternal seafood consumption during pregnancy and child attention outcomes: a cohort study with gene effect modification by PUFA-related genes. Int J Epidemiol, 49(2), 559-571. doi: 10.1093/ije/dyz197.
17. Kvestad, I., Hysing, M., Kjellevold, M., Næss, S., Dahl, L., & Markhus, M. W. (2021). Maternal cod intake during pregnancy and infant development in the first year of life: secondary analyses from a randomized controlled trial. J Nutr, 151(7), 1879-1885. doi: 10.1093/jn/nxab083.
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19. Llop, S., Guxens, M., Murcia, M., Lertxundi, A., Ramon, R., Riano, I., et al. (2012). Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: study of potential modifiers. Am J Epidemiol, 175(5), 451-465. doi:10.1093/aje/kwr328.
20. Markhus, M. W., Hysing, M., Midtbo, L. K., Nerhus, I., Næss, S., Aakre, I., et al. (2021). Effects of two weekly servings of cod for 16 weeks in pregnancy on maternal iodine status and infant neurodevelopment: Mommy's Food, a randomized-controlled trial. Thyroid, 31(2), 288-298. doi: 10.1089/thy.2020.0115.
21. Mendez, M. A., Torrent, M., Julvez, J., Ribas-Fito, N., Kogevinas, M., & Sunyer, J. (2009). Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years. Public Health Nutr, 12(10), 1702-1710. doi:10.1017/s1368980008003947.
22. Mesirow, M. S., Cecil, C., Maughan, B., & Barker, E. D. (2017). Associations between prenatal and early childhood fish and processed food intake, conduct problems, and co-occurring difficulties. J Abnorm Child Psychol, 45(5), 1039-1049. doi:10.1007/s10802-016-0224-y.

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24. Normia, J., Niinivirta-Joutsa, K., Isolauri, E., Jaaskelainen, S. K., & Laitinen, K. (2019). Perinatal nutrition impacts on the functional development of the visual tract in infants. Pediatr Res, 85(1), 72-78. doi:10.1038/s41390-018-0161-2.
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33. Valent, F., Mariuz, M., Bin, M., Mazej, D., Tognin, V., Tratnik, J., et al. (2013). Associations of prenatal mercury exposure from maternal fish consumption and polyunsaturated fatty acids with child neurodevelopment: a prospective cohort study in Italy. J Epidemiol, 23(5), 360-370. doi:10.2188/jea.je20120168.
34. Varsi, K., Torsvik, I. K., Huber, S., Averina, M., Brox, J., & Bjorke-Monsen, A. L. (2022). Impaired gross motor development in infants with higher PFAS concentrations. Environ Res, 204, 112392. doi: 10.1016/j.envres.2021.112392.
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36. Vejrup, K., Brandlistuen, R. E., Brantsæter, A. L., Knutsen, H. K., Caspersen, I. H., Alexander, J., et al. (2018). Prenatal mercury exposure, maternal seafood consumption and associations with child language at five years. Environ Int, 110, 71-79. doi:10.1016/j.envint.2017.10.008.
37. Williams, C., Birch, E. E., Emmett, P. M., Northstone, K., & Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) Study Team. (2001). Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population–based cohort study. Am J Clin Nutr, 73(2), 316-322. doi:10.1093/ajcn/73.2.316.
38. Xu, Y., Khoury, J. C., Sucharew, H., Dietrich, K., & Yolton, K. (2016). Low-level gestational exposure to mercury and maternal fish consumption: Associations with neurobehavior in early infancy. Neurotoxicol Teratol, 54, 61-67. doi:10.1016/j.ntt.2016.02.002.

Chapter 3: Seafood consumption during childhood and adolescence and neurocognitive development in the child: A systematic review

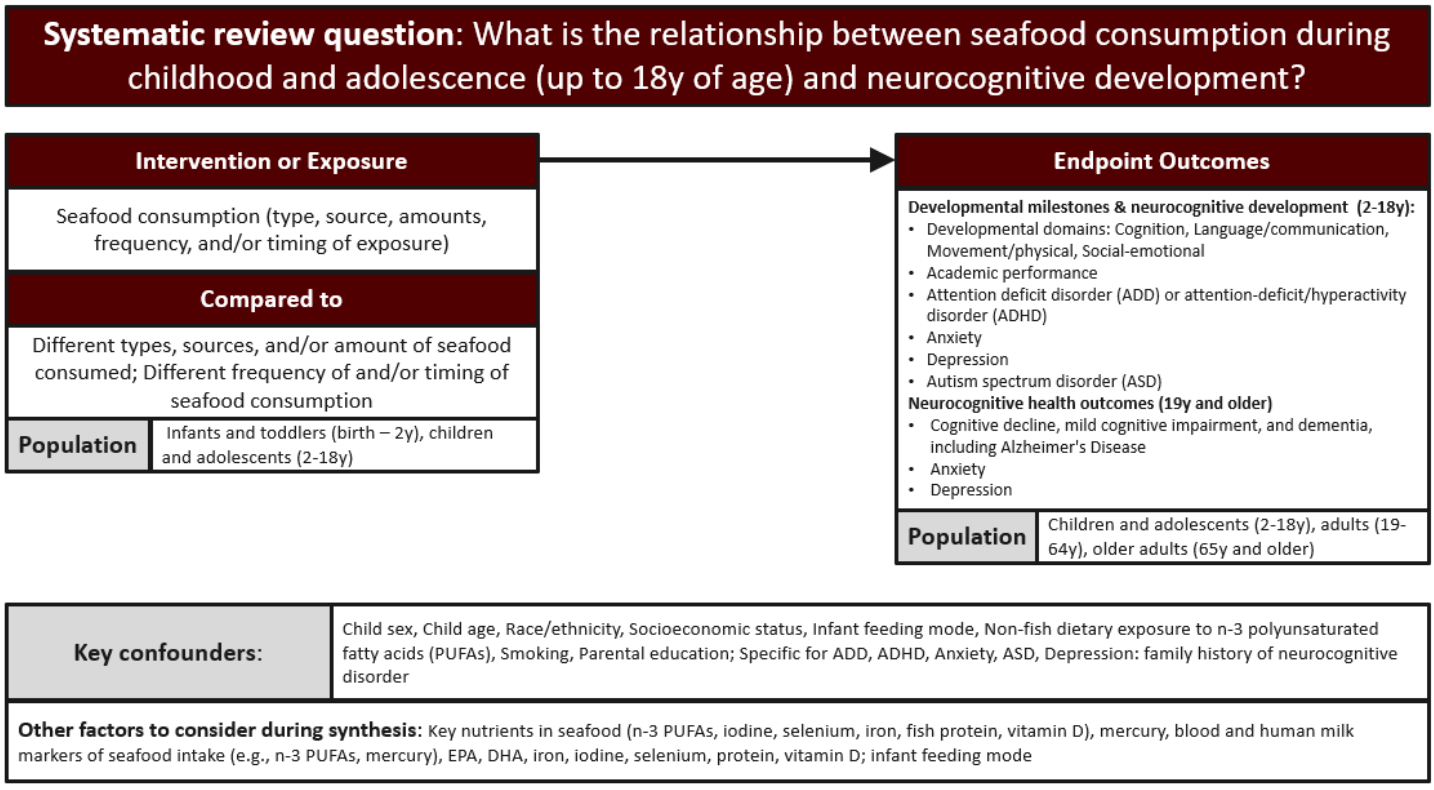
Methodology

Relevant data and information to create the systematic review protocol was provided to the Evidence Center by NASEM. This information included the PECOD framework, inclusion/exclusion criteria, and the search strategy. The search was run by the NASEM librarian and search results were provided to the Evidence Center. The Evidence Center drafted the protocol including relevant methodology based on the provided information and registered the protocol in PROSPERO (CRD42023432844).

Because the nutrition reviews (1. seafood consumption in women who are pregnant or lactating and 2. seafood consumption in children) were updates of existing USDA NESR systematic reviews, the protocols reflected those of the existing reviews.

Analytic framework

***Figure 3-1**. Analytic framework for examining the relationship between seafood consumption during childhood and adolescence and neurocognitive development.*



Inclusion and exclusion criteria

Table 3-1. *Inclusion and exclusion criteria for nutrition reviews*

Category	Inclusion Criteria	Exclusion Criteria
Population	Individuals living in countries ranked as high or very high on the human development index[a] during the study. ● Exposed population: Individuals in the general population who are infants, children, or adolescents up to age 18 years. Subgroups of interest: ○ By race/ethnicity ○ By income ○ By cumulative exposure to non-chemical and environmental stressors (e.g., stress, depression, neighborhood or locale, food security) ○ By pre-existing disease burden ● Outcome population: Children and adolescents (up to age 18 years). Subgroups of interest: ○ Infants (ages 0 to 12 months) ○ Toddlers (ages 1 to 3 years) ○ Early childhood (ages 4 to 8 years) ○ Puberty (ages 9 to 13 years) ○ Adolescents (ages 14 to 18 years)	Studies exclusively of participants with a chronic condition, hospitalized with an illness or injury. Examples include: ● Diabetes (not including gestational diabetes) ● Cancer ● Cardiometabolic disorders ● Chronic kidney disease ● Malabsorption (any disorder that causes malabsorption from the gastrointestinal tract) ● Asthma
Exposure	Seafood consumption: ● Types (e.g., salmon, tuna, bass) ● Sources (e.g., sea, fresh water, farmed, canned, wild) ● Amount (e.g., ounces per day, grams per meal) ● Frequency (e.g., daily, twice a week) ● Duration (e.g., length of time consuming seafood) ● Preparation (e.g., fried, baked) ● Timing (e.g., by trimester, age)	● Supplements ● Infant formula
Comparator	● Different types, sources, amounts, frequencies, durations, preparations, or timings of seafood consumption ● No seafood consumption	No comparator

Outcome	• Neurodevelopment and Neurodevelopmental Disorders: • Developmental domains: cognition, language/communication, movement/physical, social-emotional • Social/emotional outcomes • Academic performance • Autism spectrum disorders (ASD) • Anxiety • Depression • Attention deficit hyperactivity disorder (ADHD)	
Study Designs	• Randomized controlled trials • Controlled (nonrandomized) trials • Cohort (observational) studies, prospective or retrospective • Case-cohort studies	• Case reports • Studies reported in theses or conference abstracts only • Studies not reported in English • Studies without primary data, such as systematic reviews, narrative reviews, editorials, and commentaries

[a] https://worldpopulationreview.com/country-rankings/hdi-by-country

Screening

All records captured in the search were screened independently by two reviewers. Screening occurred within a web-based program (DistillerSR) using screening forms developed based on the inclusion and exclusion criteria determined *a priori*. Each article was reviewed to determine if it met the inclusion criteria, in which case the article was included, or if any of the exclusion criteria were met, in which case the article was excluded.

Screening was conducted in 3 stages or levels following the methodology of the original existing review. In the first level, the title of the article was reviewed. Title screening was used to exclude clearly irrelevant studies. Potential reasons for exclusion at the title level included wrong study population or country, as examples. If there was not a clear reason for exclusion, the article was included and moved to level 2, abstract screening. If there was no reason to exclude the article based on information in the abstract, it was included and moved to level 3, full text screening. When an article was excluded at level 2 (abstract) or level 3 (full text) the screener indicated at least one reason for exclusion. Any disagreements on whether to include or exclude an article were discussed and resolved by the two screeners. If necessary, a third party was consulted to resolve differences.

Piloting was done to ensure the screening forms were adequate and that screeners interpreted the eligibility criteria similarly. For the pilot, screeners reviewed a common set of references (25 references to start) at each screening level. The screeners discussed their responses, any questions or uncertainties they had when making their decision, and any concerns regarding the screening form. If necessary, this was repeated with another common set of references.

Manual searching (or hand-searching) was performed on all articles included after full-text screening. Manual searching is a process whereby the reference list from each included article is reviewed. If a reference is found to be relevant to the present review that was not identified in the electronic search it proceeds through the screening process as detailed above. If an article identified through manual searching was included in the review, the librarian was notified to determine why the article was not found through the electronic search. If necessary, the search strategy would have been updated and rerun, in which case newly identified articles would go through the screening process as described above.

Data extraction

Data from all included articles were extracted by a trained analyst using a systematic approach. Only data relevant to the review was extracted. To ensure data was extracted in a consistent manner for all papers, standard data extraction forms were used. Data fields for extraction were based on information outlined in the protocol and include important characteristics of the study design, methodology, results, and limitations. Forms were piloted on 2 to 3 articles (varying in study design, when appropriate) by all reviewers to ensure all relevant information is being recorded and done so in a consistent manner. For the nutrition reviews, data extraction forms include similar fields as the existing reviews (**Text box 3-1**). A second analyst reviewed the extracted data for accuracy and completeness. Any suggested changes were discussed between the reviewers. If necessary, a third analyst was consulted.

Text box 3-1*. Data extraction fields for the nutrition review update*

Study characteristics:

- Author name, publication year
- Study design
- Study name, if applicable
- Country

- Baseline n

Participant characteristics:

- Mother's age
- Child sex (% female)
- Race/ethnicity
- Socioeconomic Status
- Maternal anthropometrics
- Gestational weight gain
- Infant feeding practices

Exposure details:

- Exposure definition/description
- Exposure assessment method

Exposure level:

- Seafood intake amount
- Maternal/infant levels of nutrients from seafood: omega-3 polyunsaturated fatty acids [PUFAs], iodine, selenium, iron, fish protein, and vitamin D
- Maternal/infant levels of mercury

Confounders:

- Key confounders accounted for
- Key confounders NOT accounted for
- Other confounders accounted for

Outcome(s) and Results:

- Outcome domain (e.g. developmental domain-cognition, developmental domain-language/communication)
- Outcome assessment tool

- Outcome assessment methods including subscale
- Child age at outcome assessment
- Results, including analytic n

Study limitations

Summary of results

Funding source

Risk of bias assessment

Risk of bias was assessed for all included studies independently by two analysts using standardized tools specific to each study's design. If a study included multiple relevant results, the analysts assessed the risk of bias pertinent to each. If there were differences in risk of bias for the different results, more than one risk of bias assessment may be reported for a paper.

For this project, Cochrane risk of bias tools specific to the included study designs were used. These include: ROB 2.0 for randomized controlled trials, ROBINS-I for non-randomized studies of interventions, and ROBINS-E for non-randomized studies of exposures. These tools are designed to assess risk of bias by domain and then determine an overall risk of bias rating for the study. The analysts piloted the tools on 2 to 3 articles to ensure a consistent approach and interpretation was applied. Further, upon completion of the dual, independent risk of bias assessments, domain-level ratings and the overall rating were compared between the two reviewers to assess inter-rater reliability. If there were differences, the reviewers discussed and determined the appropriate rating. If necessary, a third reviewer was consulted.

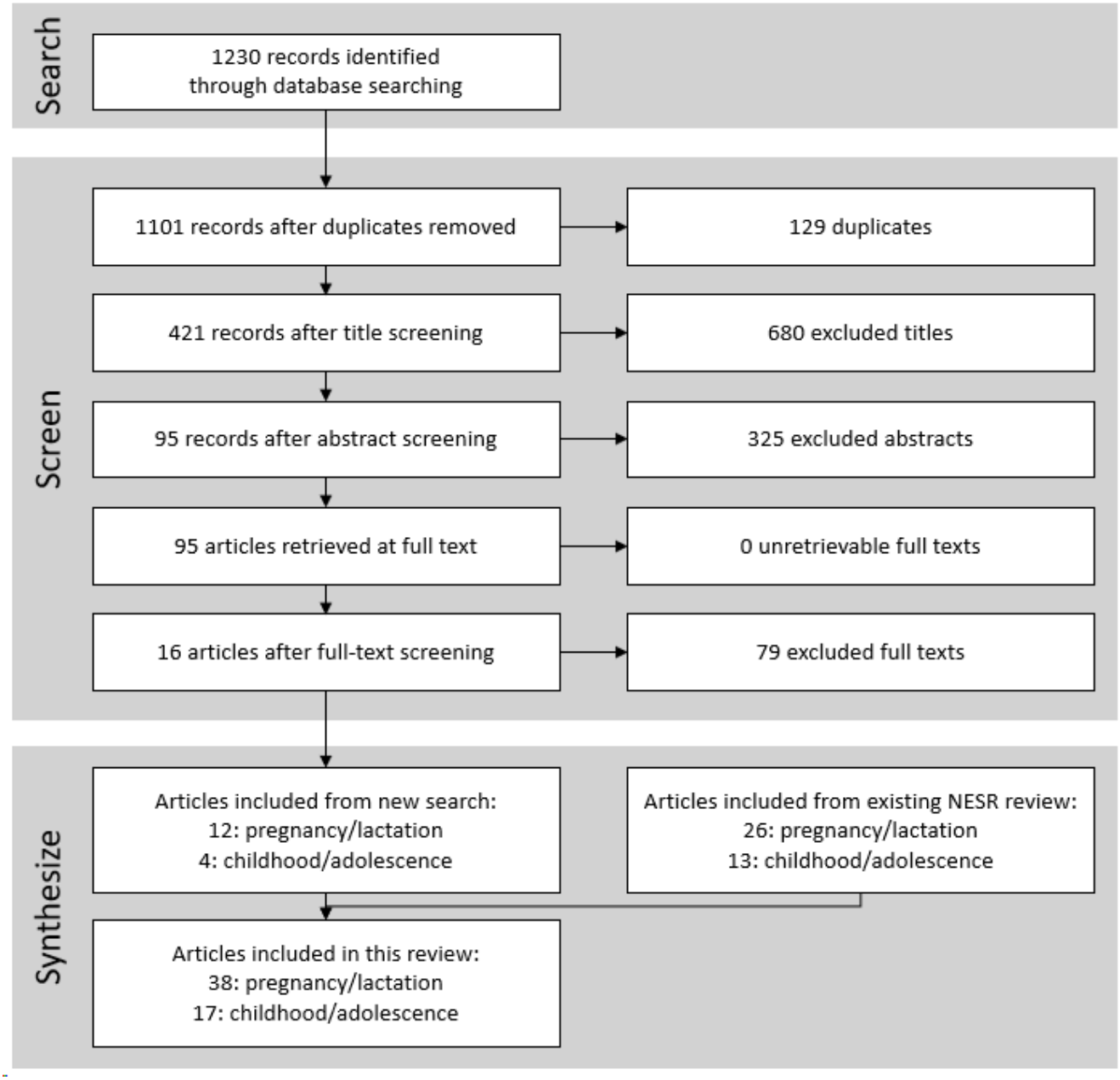
Synthesis

Synthesis was conducted by the Committee. To prepare for synthesis, a description of the evidence was drafted to provide details on the body of evidence including but not limited to, the number of included articles, the number of included studies, study designs, country of origin, participant characteristics, description of the exposure across studies, outcomes, and outcome assessment tools. A description of the evidence and data tables were sent to the Committee.

Results

PRISMA flow chart

***Figure 3-2**. PRISMA flow chart outlining the number of articles included after searching, screening and synthesis.*



Description of evidence

***Table 3-2**. Studies included in the nutrition review for children and adolescents; 17 articles included (13 from existing NESR review, 4 from update)*

Study Design	Study Name	Article (Author, year)
Randomized Controlled Trials	Fish Intervention Studies – KIDS (FINS-KIDS)	3 articles: • Hysing, 2018 • Kvestad, 2018 • Oyen, 2018
	Fish Intervention Studies - TEENS (FINS-TEENS	2 articles: • Handeland, 2017 • Skotheim, 2017
	FiSK Junior study (Fish, children, health, and cognition)	1 article: • Teisen, 2020
	Polyunsaturated fatty acids in child nutrition (PINGU)	1 article: • Kalhoff, 2019
	Unnamed trial	1 article: • Demmelmair, 2019
Longitudinal Cohort Studies	Avon Longitudinal Study of Children and Parents (ALSPAC)	2 articles: • Mesirow, 2017 • Williams, 2001
	ALLERGY 2000	1 article: • Kim, 2009
	China Jintan Child Cohort Study	1 article: • Li, 2017
	Children's Lifestyle and School Performance Study (CLASS)	1 article: • McMartin, 2012
	Community Empowerment and Care for Wellbeing and Health Longevity	1 article: • Ajmal, 2022
	Spanish Environment and Childhood Project (INMA)	1 article: • Julvez, 2020
	ROOTS Study	1 article: • Winpenny, 2018

	Unnamed cohort/study	1 article: • Aberg, 2009

Table 3-3*. Studies included in the nutrition review in children and adolescents organized by outcome; 17 articles included (13 from existing NESR review, 4 from update)*

Outcome Domain	Sub-Domain	Article (Author, year)
Developmental milestones & neurocognitive development (0-18y)	Cognition	10 articles: • Aberg, 2009 • Ajmal, 2022 • Demmelmair, 2019 • Handeland, 2017 • Kalhoff, 2019 • Kvestad, 2018 • Li, 2017 • Oyen, 2018 • Teisen, 2020 • Williams, 2001
	Language/Communication	0 articles
	Movement/physical	3 articles: • Demmelmair, 2019 • Kalhoff, 2019 • Oyen, 2018
	Social-emotional	3 articles: • Hysing, 2018 • Skotheim, 2017 • Teisen, 2020
	Academic performance	1 article: • Kim, 2009
	Attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD	1 article: • Julvez, 2020
	Anxiety	0 articles
	Depression	2 articles: • McMartin, 2012 • Winpenny, 2018

	Autism spectrum disorder (ASD)	0 articles
Neurocognitive health outcomes (19+y)		0 articles

Extracted data

Analysts extracted data that was relevant to the review question from each included article. During extraction, results were organized by the outcome domains listed in the Analytic Framework and further by the outcome assessment tool (e.g., Bayley Scale of Infant Development) and the subscale (e.g., mental development index, psychomotor development index). Therefore, when an article reported multiple domains, assessment tools, and/or subscales, data is presented in multiple rows within the extracted data file. This allows for organizing the evidence within these outcome categories. **SEE SUPPLEMENTAL FILE 3-1.**

Note that there is a large amount of data in many cells (particularly results). Data cells will need to be expanded to see all data. For results, significant findings are **bolded**, with significant findings indicating a beneficial association between seafood intake on child development in **green**, and significant findings indicating a detrimental association between seafood intake on child development in **red**.

Within the data table file, data is organized in separate tabs:

- All-sorted by author
- Cohort+Participant characteristics (results have been removed so that there is one row per article)
- All-sorted by outcome (this allows experts to scroll through results of all outcomes to look for trends)
- Each outcome domain with included articles:
  - Cognition
  - Movement/physical
  - Social-emotional
  - Academic performance
  - Attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD)
  - Depression

Risk of bias assessments

Risk of bias was assessed for each included article using Cochrane study design-specific tools: ROB 2.0-parallel arm for the randomized controlled trials and ROBINS-E for the longitudinal cohort studies. Results from the risk of bias assessments can be found in **SEE SUPPLEMENTAL FILE 3-2.**

Included articles

1. Aberg, M. A., Åberg, N., Brisman, J., Sundberg, R., Winkvist, A., & Toren, K. (2009). Fish intake of Swedish male adolescents is a predictor of cognitive performance. Acta Paediatr, 98(3), 555-560. doi: 10.1111/j.1651-2227.2008.01103.x.

2. Ajmal, A., Watanabe, K., Tanaka, E., Sawada, Y., Watanabe, T., Tomisaki, E., et al. (2022). Eating Behaviour-Consumption Frequency of Certain Foods in Early Childhood as a Predictor of Behaviour Problems: 6-year follow-up study. Sultan Qaboos Univ Med J, 22(2), 225-232. doi: 10.18295/squmj.5.2021.103

3. Demmelmair, H., Oyen, J., Pickert, T., Rauh-Pfeiffer, A., Stormark, K. M., Graff, I. E., et al. (2019). The effect of Atlantic salmon consumption on the cognitive performance of preschool children–a randomized controlled trial. Clin Nutr, 38(6), 2558-2568. doi: 10.1016/j.clnu.2018.11.031.

4. Handeland, K., Oyen, J., Skotheim, S., Graff, I. E., Baste, V., Kjellevold, M., et al. (2017). Fatty fish intake and attention performance in 14–15 year old adolescents: FINS-TEENS-a randomized controlled trial. Nutr J, 16(1), 1-10. doi: 10.1186/s12937-017-0287-9.

5. Hysing, M., Kvestad, I., Kjellevold, M., Kolden Midtbo, L., Graff, I. E., Lie, O., et al. (2018). Fatty fish intake and the effect on mental health and sleep in preschool children in FINS-KIDS, a randomized controlled trial. Nutrients, 10(10), 1478. doi: 10.3390/nu10101478.

6. Julvez, J., Fernandez-Barres, S., Gignac, F., Lopez-Vicente, M., Bustamante, M., Garcia-Esteban, R., ... et al. (2020). Maternal seafood consumption during pregnancy and child attention outcomes: a cohort study with gene effect modification by PUFA-related genes. Int J Epidemiol, 49(2), 559-571. doi: 10.1093/ije/dyz197.

7. Kalhoff, H., Mesch, C. M., Stimming, M., Israel, A., Spitzer, C., Beganovic, L., et al. (2020). Effects of LC-PUFA supply via complementary food on infant development—a food based intervention (RCT) embedded in a total diet concept. Eur J Clin Nutr, 74(5), 682-690. doi: 10.1038/s41430-019-0491-0.

8. Kim, J. L., Winkvist, A., Aberg, M. A., Aberg, N., Sundberg, R., Toren, K., et al. (2010). Fish consumption and school grades in Swedish adolescents: a study of the large general population. Acta Paediatr, 99(1), 72-77. doi: 10.1111/j.1651-2227.2009.01545.x.

9. Kvestad, I., Vabo, S., Kjellevold, M., Nostbakken, O. J., Midtbo, L. K., Hysing, M., et al. (2018). Fatty fish, hair mercury and cognitive function in Norwegian preschool children: results from the randomized controlled trial FINS-KIDS. Environ Int, 121, 1098-1105. doi: 10.1016/j.envint.2018.10.022.

10. Liu, J., Cui, Y., Li, L., Wu, L., Hanlon, A., Pinto-Martin, J., et al. (2017). The mediating role of sleep in the fish consumption–cognitive functioning relationship: a cohort study. Sci Rep, 7(1), 1-9. doi: 10.1038/s41598-017-17520-w.

11. McMartin, S. E., Kuhle, S., Colman, I., Kirk, S. F., & Veugelers, P. J. (2012). Diet quality and mental health in subsequent years among Canadian youth. Public Health Nutr, 15(12), 2253-2258. doi: 10.1017/s1368980012000535.

12. Mesirow, M. S., Cecil, C., Maughan, B., & Barker, E. D. (2017). Associations between prenatal and early childhood fish and processed food intake, conduct problems, and co-occurring difficulties. J Abnorm Child Psychol, 45(5), 1039-1049. doi:10.1007/s10802-016-0224-y.

13. Oyen, J., Kvestad, I., Midtbo, L. K., Graff, I. E., Hysing, M., Stormark, K. M., et al. (2018). Fatty fish intake and cognitive function: FINS-KIDS, a randomized controlled trial in preschool children. BMC Med, 16(1), 1-15. doi: 10.1186/s12916-018-1020-z.

14. Skotheim, S., Handeland, K., Kjellevold, M., Oyen, J., Froyland, L., Lie, O., et al. (2017). The effect of school meals with fatty fish on adolescents' self-reported symptoms for mental health: FINS-TEENS-a randomized controlled intervention trial. Food Nutr Res, 61(1), 1383818. doi: 10.1080/16546628.2017.1383818.

15. Teisen, M. N., Vuholm, S., Niclasen, J., Aristizabal-Henao, J. J., Stark, K. D., Geertsen, S. S., et al. (2020). Effects of oily fish intake on cognitive and socioemotional function in healthy 8–9-year-old children: The FiSK Junior randomized trial. Am J Clin Nutr, 112(1), 74-83. doi: 10.1093/ajcn/ nqaa050.

16. Williams, C., Birch, E. E., Emmett, P. M., Northstone, K., & Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) Study Team. (2001). Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population–based cohort study. Am J Clin Nutr, 73(2), 316-322. doi:10.1093/ajcn/73.2.316.

17. Winpenny, E. M., van Harmelen, A. L., White, M., van Sluijs, E. M., & Goodyer, I. M. (2018). Diet quality and depressive symptoms in adolescence: no cross-sectional or prospective associations following adjustment for covariates. Public Health Nutr, 21(13), 2376-2384. doi: 10.1017/s1368980018001179.

Chapter 4: Seafood toxicant exposure during pregnancy, lactation, and childhood and child growth and development: A scoping review

Introduction

Prior to conducting systematic reviews on toxicants from seafood consumed during pregnancy, lactation, childhood or adolescence on child development and health outcomes, the Evidence Center conducted a scoping review to identify: 1.) toxicant exposures with sufficient evidence to warrant a systematic review, and 2.) gaps in the evidence. This allowed the NASEM committee to prioritize exposure-outcome relationships that warranted systematic review.

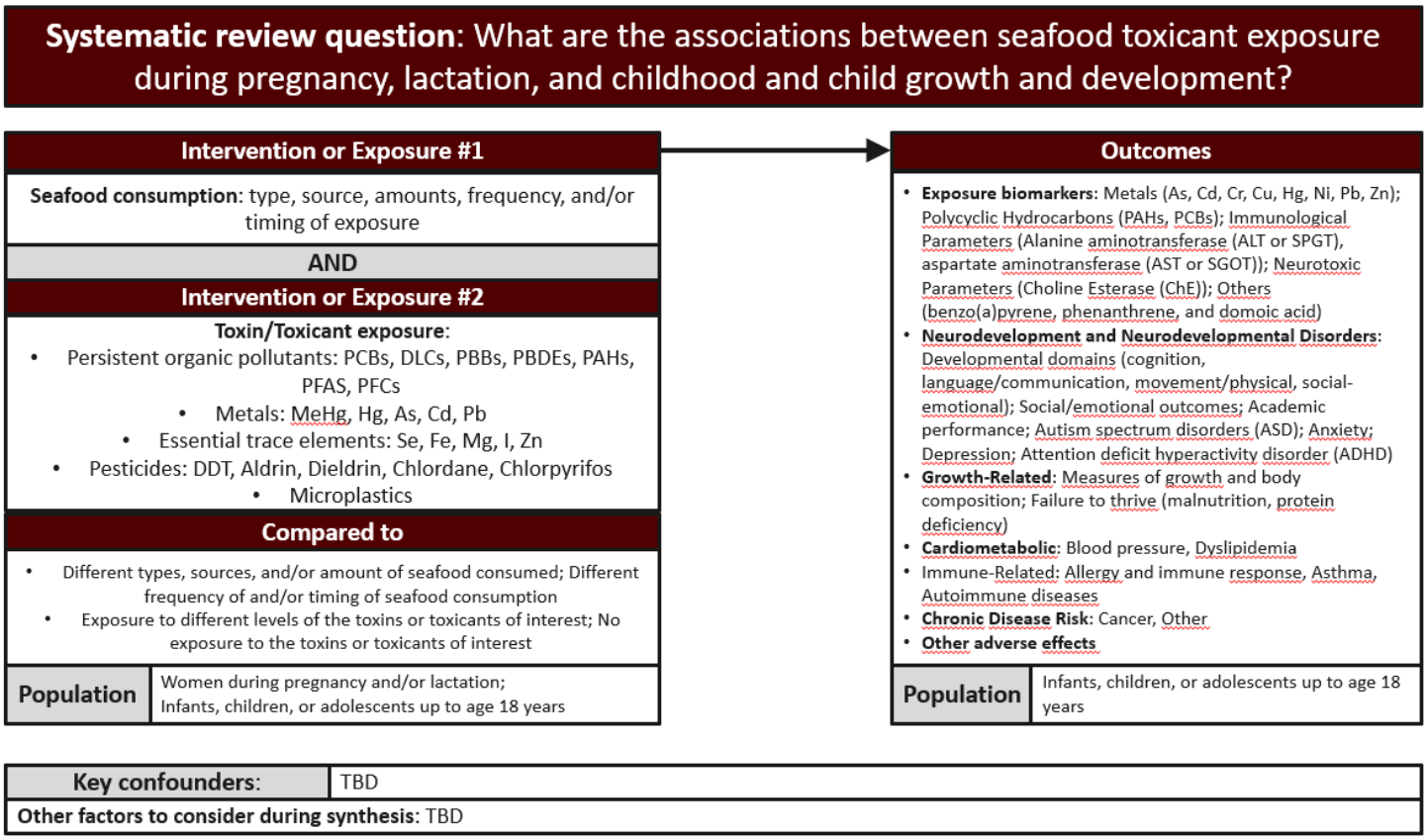
Methodology

Protocol development

Relevant data and information to create the review protocol was provided to the Evidence Center by NASEM. This information included the PECOD frameworks, inclusion/exclusion criteria, and the search strategy. The search was run by the NASEM librarian and search results were provided to the Evidence Center. The Evidence Center drafted the systematic review protocol including relevant methodology based on the provided information and registered the protocol in PROSPERO (CRD42023448200). The systematic review protocol was used to inform the scoping review methods.

Analytic framework

***Figure 4-1**. Analytic framework for examining the relationship between seafood toxicant exposure during pregnancy, lactation, and childhood and child growth and development.*



Inclusion and exclusion criteria

Table 4-1. *Inclusion and exclusion criteria for toxicology reviews*

Category	Inclusion Criteria	Exclusion Criteria
Population	Human individuals living in countries ranked as high or very high on the human development index[a] during the study ● Exposed population: Individuals in the general population who are pregnant or lactating, infants, children, or adolescents up to age 18 years. Subgroups of interest: ○ By race/ethnicity ○ By income ○ By cumulative exposure to non-chemical and environmental stressors: stress, depression, neighborhood or locale, food security) ○ By pre-existing disease burden ● Outcome population: Children and adolescents (up to age 18 years). Subgroups of interest: ○ Infants (ages 0 to 12 months) ○ Toddlers (ages 1 to 3 years) ○ Early childhood (ages 4 to 8 years) ○ Puberty (ages 9 to 13 years) ○ Adolescents (ages 14 to 18 years)	● Studies exclusively of participants with a chronic condition, hospitalized with an illness or injury. Examples include: ○ Diabetes (not including gestational diabetes) ○ Cancer ○ Cardiometabolic disorders ○ Chronic kidney disease ○ Malabsorption (any disorder that causes malabsorption from the gastrointestinal tract) ○ Asthma ● Nonhuman Primates**

Exposure	• **Must contain Exposure 1 AND Exposure 2**
	
	• **Exposure 1: Toxin or toxicants**
	  • Persistent organic pollutants:
	  ○ Polychlorinated biphenyls (PCBs), dioxin and dioxin-like compounds (DLCs)
	  ○ Polybrominated biphenyls (PBBs)
	  ○ Polybrominated diphenyl ethers (PBDEs)
	  ○ Polycyclic aromatic hydrocarbons (PAHs)
	  ○ Per- and polyfluoroalkyl substances (PFAS)
	  • Metals:
	  ○ Methylmercury
	  ○ Mercury
	  ○ Arsenic
	  ○ Cadmium
	  ○ Lead
	  • Essential trace elements:
	  ○ Selenium
	  ○ Iron
	  ○ Magnesium
	  ○ Iodine
	  ○ Zinc
	  • Pesticides
	  ○ DDT
	  ○ Aldrin
	  ○ Dieldrin
	  ○ Chlordane
	  ○ Chlorpyrifos
	  • Microplastics
	
	• **Exposure 2: Seafood consumption:**
	  ○ Types (e.g., salmon, tuna, bass)
	  ○ Sources (e.g., sea, fresh water, farmed, canned, wild)
	  ○ Amount (e.g., ounces per day, grams per meal)
	  ○ Frequency (e.g., daily, twice a week)
	  ○ Duration (e.g., length of time consuming seafood)
	  ○ Preparation (e.g., fried, baked)
	  ○ Timing (e.g., by trimester, age)
		• Studies that do not report on toxicant exposure in fish AND seafood consumption
		
		• Supplements
		• Infant formula
		
		• Toxins from algal blooms**:
		  • Cyanobacteria
		  • Ciguatera
		  • Scombroid
		  • Domoic acid (red algae)
		
		• Microorganisms (hepatitis, salmonella, e coli)**

Comparator	• Exposure to different levels of the toxins or toxicants of interest; No exposure to the toxins or toxicants of interest • Different types, sources, amounts, frequencies, durations, preparations, or timings of seafood consumption; No seafood consumption	• No comparator

Outcome	Exposure biomarkers: ○ Metals: As, Cd, Cr, Cu, Hg, Ni, Pb, Zn ○ Polycyclic Hydrocarbons: PAHs, PCBs ○ Immunological Parameters: Alanine aminotransferase (ALT or SPGT)/ aspartate aminotransferase (AST or SGOT) ○ Neurotoxic Parameters: Choline Esterase (ChE) ○ Others: benzo(a)pyrene, phenanthrene, and domoic acid Neurodevelopment and Neurodevelopmental Disorders: ○ Developmental domains: cognition, language/communication, movement/physical, social-emotional ○ Social/emotional outcomes ○ Academic performance ○ Autism spectrum disorders (ASD) ○ Anxiety ○ Depression ○ Attention deficit hyperactivity disorder (ADHD) Growth-Related ○ Measures of growth and body composition ○ Failure to thrive (malnutrition, protein deficiency) Cardiometabolic ○ Blood pressure ○ Dyslipidemia Immune-Related ○ Allergy and immune response ○ Asthma ○ Autoimmune diseases Chronic Disease Risk ○ Cancer ○ Other Other adverse effects	
Study Designs	● Randomized controlled trials ● Controlled (nonrandomized) trials ● Cohort (observational) studies, prospective or retrospective ● Case-cohort studies ● Case-control studies ● Before-after studies	● Case reports ● Studies reported in theses or conference abstracts only ● Studies not reported in English ● Studies without primary data, such as systematic reviews, narrative reviews, editorials, and commentaries ● Cross-sectional studies**

[a] https://worldpopulationreview.com/country-rankings/hdi-by-country

**Non-human primate, cross-sectional studies and studies examining algal toxin and microorganism exposure were not included in the scoping or systematic reviews. A list of non-human primate and cross-sectional studies, as well as studies with algal toxin and microorganism exposures were provided to NASEM.

Screening

All records captured in the search were screened independently by two reviewers. Screening occurred within a web-based program (DistillerSR) using screening forms developed based on the inclusion and exclusion criteria determined *a priori*. Each article was reviewed to determine if it met the inclusion criteria, in which case the article was included, or if any of the exclusion criteria were met, in which case the article was excluded. To assist with screening, a screening decision tree was created based on the inclusion-exclusion criteria (**Appendix 1**).

Screening was conducted in 3 stages or levels following the methodology of the original existing review. In the first level, the title of the article was reviewed. Title screening was used to exclude clearly irrelevant studies. Potential reasons for exclusion at the title level included wrong study population or country, as examples. If there was not a clear reason for exclusion, the article was included and moved to level 2, abstract screening. If there was no reason to exclude the article based on information in the abstract, it was included and moved to level 3, full text screening. When an article was excluded at level 2 (abstract) or level 3 (full text) the screener indicated at least one reason for exclusion. Any disagreements on whether to include or exclude an article were discussed and resolved by the two screeners. If necessary, a third party was consulted to resolve differences.

Piloting was done to ensure the screening forms were adequate and that screeners interpreted the eligibility criteria similarly. For the pilot, screeners reviewed a common set of references (25 references to start) at each screening level. The screeners discussed their responses, any questions or uncertainties they had when making their decision, and any concerns regarding the screening form. If necessary, this was repeated with another common set of references.

Manual searching (or hand-searching) was performed on all articles included after full-text screening. Manual searching is a process whereby the reference list from each included article is reviewed. If a reference is found to be relevant to the present review that was not identified in the electronic search it proceeds through the screening process as detailed above. If an article identified through manual searching

was included in the review, the librarian was notified to determine why the article was not found through the electronic search. If necessary, the search strategy would have been updated and rerun, in which case newly identified articles would go through the screening process as described above.

Data extraction

Data from all included articles were extracted by a trained analyst using a systematic approach. Only data relevant to the review was extracted. To ensure data was extracted in a consistent manner for all papers, standard data extraction forms were used. Data fields for extraction were based on guidance from NASEM and were limited to study characteristics, participant characteristics, toxicant exposure(s), outcome(s), and confounders.

Text box 4-1. *Data extraction fields for the nutrition review update*

Study characteristics:

- Author name, publication year
- Study design
- Study name, if applicable
- Country
- Sample size

Participant characteristics:

- Mother's age
- Maternal anthropometrics
- Child age
- Child sex (% female)
- Child anthropometrics
- Race/ethnicity
- Socioeconomic status
- Infant feeding practices

Exposures:

- Persistent organic pollutants
  - Polychlorinated biphenyls (PCBs) (yes/no)
  - Dioxin-like compounds (DLCs) (yes/no)
  - Polybrominated biphenyls (PBBs) (yes/no)
  - Polybrominated diphenyl ethers (PBDEs) (yes/no)
  - Polycyclic aromatic hydrocarbons (PAHs) (yes/no)
  - Per- and polyfluoroalkyl substances (PFAS and PCBs) (yes/no)
- Metals
  - Methylmercury (MeHg) (yes/no)
  - Mercury (Hg) (yes/no)
  - Arsenic (As) (yes/no)
  - Cadmium (Cd) (yes/no)
  - Lead (Pb) (yes/no)
- Essential trace elements
  - Selenium (Se) (yes/no)
  - Iron (Fe) (yes/no)
  - Magnesium (Mg) (yes/no)
  - Iodine (I) (yes/no)
  - Zinc (Zn) (yes/no)
- Pesticides
  - DDT (yes/no)
  - Aldrin (yes/no)
  - Dieldrin (yes/no)
  - Chlordane (yes/no)

- Chlorpyrifos (yes/no)
- Microplastics (yes/no)

Outcomes:

- Biomarker of exposure (yes/no)
  - Metals: As, Cd, Cr, Cu, Hg, Ni, Pb, Zn
  - Polycyclic Hydrocarbons: PAHs, PCBs
  - Immunological Parameters: Alanine aminotransferase (ALT or SPGT)/ aspartate aminotransferase (AST or SGOT)
  - Neurotoxic Parameters: Choline Esterase (ChE)
  - Others: benzo(a)pyrene, phenanthrene, and domoic acid
- Neurodevelopmental outcomes (yes/no)
  - Developmental domains: cognition, language/communication, movement/physical, social-emotional
  - Social/emotional outcomes
  - Academic performance
  - Autism spectrum disorders (ASD)
  - Anxiety
  - Depression
  - Attention deficit hyperactivity disorder (ADHD)
- Growth-related outcomes (yes/no)
  - Measures of growth and body composition
  - Failure to thrive (malnutrition, protein deficiency)
- Cardiometabolic-related outcomes (yes/no)
  - Blood pressure
  - Dyslipidemia

- Immune-related outcomes
    - Allergy and immune response
    - Asthma
    - Autoimmune diseases
- Chronic disease risk (yes/no)
    - Cancer
    - Other
- Other (yes/no)

Confounders/covariates adjusted for (list from paper)

Risk of bias assessment

Risk of bias was not conducted for this scoping review.

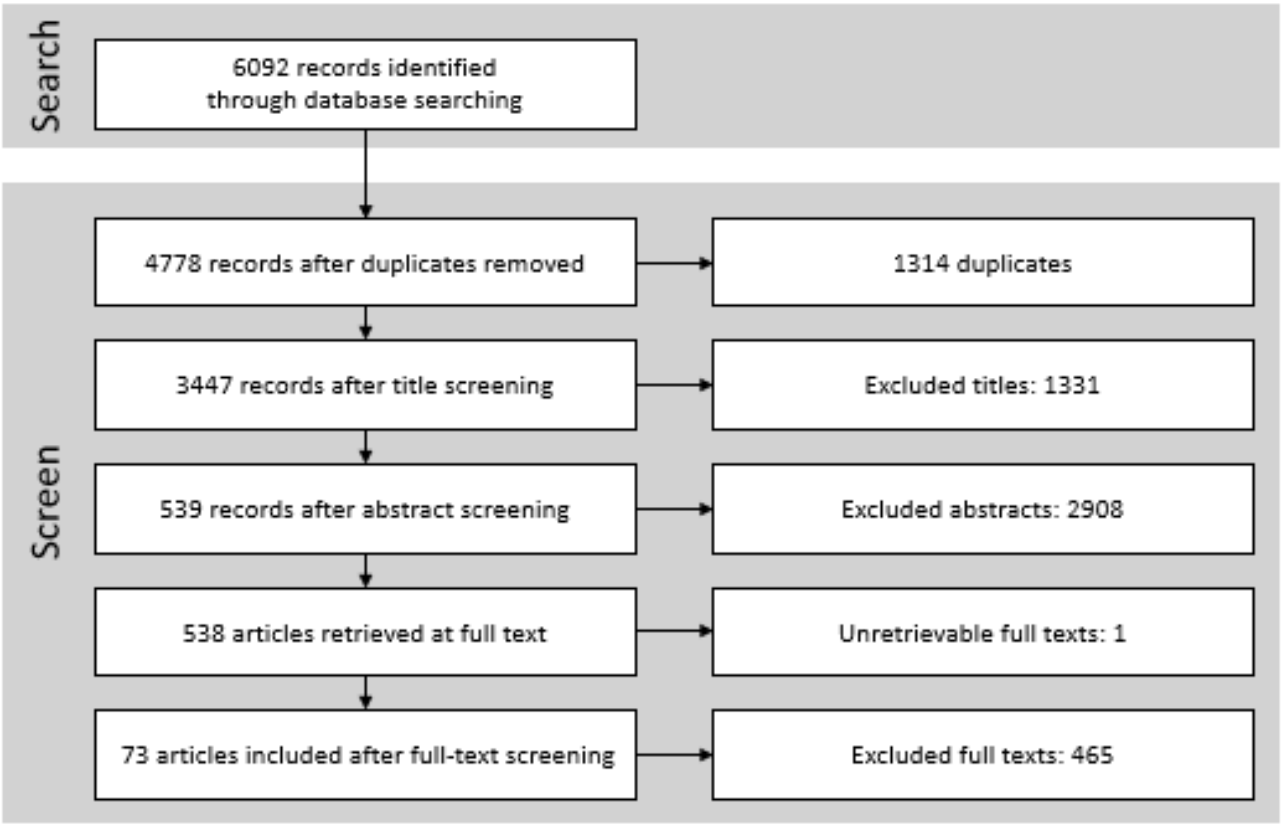
Synthesis

A description of the evidence was provided to the Committee to highlight the number of articles identified for each exposure (toxicant) and outcome.

Results

PRISMA flow chart

***Figure 4-2**. PRISMA flow chart outlining the number of articles included after electronic searching and screening.*



Description of evidence

***Table 4-2**. Number of studies included in the scoping review on seafood toxicants and child health and development outcomes*

Exposure population	**Number of articles**
Women who are pregnant or lactating	62
Children or adolescents	13
Both Women who are pregnant or lactating AND Children or adolescents	2
Total	73

***Table 4-3**. Exposures included in the scoping review on seafood toxicants and child health and development outcomes, of 73 included articles*

Exposure Category	Specific Exposure	Maternal Exposure Article (Author, year)	Child Exposure Article (Author, year)
Persistent organic pollutant	Polychlorinated biphenyls (PCBs)	11 articles: • Ballester, 2018 • Grandjean, 2001 • Halldorsson, 2008 • Julvez, 2016 • Mendez, 2009 • Miyashita, 2015 • Nakamura, 2008 • Papadopoulou, 2019 • Vizcaino, 2014 • Warembourg, 2019 • Wohlfahrt-Veje, 2014	1 article: • Warembourg, 2019
	Dioxin-like compounds (DLCs)	3 articles: • Halldorsson, 2009 • Nakamura, 2008 • Vejrup, 2016	0 articles
	Polybrominated biphenyls (PBBs)	0 articles	0 articles
	Polybrominated diphenyl ethers (PBDEs)	3 articles: • Papadopoulou, 2019 • Warembourg, 2019 • Wohlfahrt-Veje, 2014	1 article: • Warembourg, 2019
	Polycyclic aromatic hydrocarbons (PAHs)	0 articles	0 articles
	Per- and polyfluoroalkyl substances (PFAS and PFCs)	7 articles: • Beck, 2023 • Gennings, 2020 • Goudarzi, 2017 • Han, 2018 • Varsi, 2021 • Warembourg, 2019 • Yu, 2022	2 articles: • Beck, 2023 • Warembourg, 2019

Metal	Methylmercury (MeHg)	13 articles: • Barbone, 2004 • Davidson, 2008 • Deroma, 2013 • Fruh, 2021 • Geer, 2012 • Miklavcic, 2013 • Rothenberg, 2017 • Stepanova, 2018 • Tatsuta, 2017 • Trdin, 2020 • Vahter, 2000 • Valent, 2013 • Vejrup, 2016	2 articles: • Chan, 2021 • Kvestad, 2018

	Mercury (Hg)	42 articles: • Barbone, 2004 • Budtz-Jørgensen, 2007 • Cunha, 2018 • Da Cunha, 2013 • Drouillet-Pinard, 2010 • Emeny, 2019 • Garcia-Esquinas, 2013 • Golding, 2016 • Golding, 2017 • Golding, 2018 • Grandjean, 2001 • Gregory, 2016 • Hibbeln, 2018 • Hu, 2016 • Jeong, 2017 • Kim, 2016 • Kim, 2018 • Marques, 2016 • Miklavcic, 2013 • Miyashita, 2015 • Morrissette, 2003 • Muniroh, 2022 • Oken, 2005 • Oken, 2008 • Oken, 2016 • Papadopoulou, 2019 • Papadopoulou, 2021 • Rothenberg, 2017 • Rothenberg, 2021 • Sagiv, 2012 • Stratakis, 2020 • Tatsuta, 2017 • Taylor, 2016 • Trdin, 2020 • Vahter, 2000 • Vejrup, 2013 • Vejrup, 2016 • Vejrup, 2017 • Vejrup, 2022 • Warembourg, 2019 • Xu, 2016 • Xue, 2007	7 articles: • Hertz-Picciotto, 2009 • Kindgren, 2019 • Llop, 2020 • Lozano, 2021 • Qin, 2018 • Rahbar, 2013 • Warembourg, 2019

	Arsenic (As)	4 articles: • Miklavcic, 2013 • Papadopoulou, 2019 • Trdin, 2020 • Warembourg, 2019	4 articles: • Kindgren, 2019 • Rahbar, 2012 • Signes-Pastor, 2022 • Warembourg, 2019
	Cadmium (Cd)	4 articles: • Garcia-Esquinas, 2013 • Papadopoulou, 2019 • Trdin, 2020 • Warembourg, 2019	4 articles: • Kindgren, 2019 • Qin, 2018 • Rahbar, 2014 • Warembourg, 2019
	Lead (Pb)	9 articles: • Fruh, 2021 • Garcia-Esquinas, 2013 • Jeong, 2017 • Kim, 2016 • Papadopoulou, 2019 • Rothenberg, 2017 • Rothenberg, 2021 • Trdin, 2020 • Warembourg, 2019	3 articles: • Kindgren, 2019 • Qin, 2018 • Warembourg, 2019
Essential Trace Elements	Selenium (Se)	11 articles: • Drouillet-Pinard, 2010 • Fruh, 2021 • Golding, 2016 • Golding, 2017 • Gregory, 2016 • Miklavcic, 2013 • Oken, 2016 • Rothenberg, 2017 • Rothenberg, 2021 • Taylor, 2016 • Trdin, 2020	1 article: • Qin, 2018
	Iron (Fe)	2 articles: • Davidson, 2008 • Trdin, 2020	1 article: • Kindgren, 2019
	Magnesium (Mg)	1 article: • Trdin, 2020	1 article: • Kindgren, 2019
	Iodine (I)	0 articles	0 articles

	Zinc (Zn)	3 articles: • Rothenberg, 2017 • Rothenberg, 2021 • Trdin, 2020	2 articles: • Kindgren, 2019 • Qin, 2018
Pesticides	DDT	5 articles: • Halldorsson, 2008 • Mendez, 2009 • Papadopoulou, 2019 • Vizcaino, 2014 • Warembourg, 2019	1 article: • Warembourg, 2019
	Aldrin	0 articles	0 articles
	Dieldrin	0 articles	0 articles
	Chlordane	0 articles	0 articles
	Chlorpyrifos	0 articles	0 articles
Microplastics	None	0 articles	0 articles

***Table 4-4**. Outcomes included in the scoping review on seafood toxicants and child health and development outcomes, of 73 included articles*

Outcome Measurement	Maternal Exposure Article (Author, year)	Child Exposure Article (Author, year)
Exposure Biomarkers	21 articles: • Ballester, 2018 • Barbone, 2004 • Garcia-Esquinas, 2013 • Geer, 2012 • Grandjean, 2001 • Han, 2018 • Julvez, 2016 • Kim, 2016 • Kim, 2018 • Miklavcic, 2013 • Morrissette, 2003 • Nakamura, 2008 • Papadopoulou, 2019 • Stepanova, 2018 • Tatsuta, 2017 • Trdin, 2020 • Vahter, 2000 • Varsi, 2021 • Vizcaino, 2014 • Xu, 2016 • Yu, 2022	4 articles: • Kindgren, 2019 • Kvestad, 2018 • Rahbar, 2012 • Signes-Pastor, 2022

Neurodevelopment-Related Outcomes	30 articles: • Barbone, 2004 • Beck, 2023 • Budtz-Jørgensen, 2007 • Davidson, 2008 • Deroma, 2013 • Fruh, 2021 • Gennings, 2020 • Golding, 2016 • Golding, 2017 • Golding, 2018 • Halldorsson, 2009 • Hibbeln, 2018 • Hu, 2016 • Jeong, 2017 • Julvez, 2016 • Kim, 2018 • Marques, 2016 • Oken, 2005 • Oken, 2008 • Oken, 2016 • Rothenberg, 2017 • Rothenberg, 2021 • Sagiv, 2012 • Tatsuta, 2017 • Valent, 2013 • Varsi, 2021 • Vejrup, 2016 • Vejrup, 2017 • Vejrup, 2022 • Xu, 2016	9 articles: • Beck, 2023 • Hertz-Picciotto, 2009 • Kvestad, 2018 • Llop, 2020 • Lozano, 2021 • Qin, 2018 • Rahbar, 2012 • Rahbar, 2013 • Rahbar, 2014

Growth-Related Outcomes	16 articles: • Ballester, 2018 • Cunha, 2018 • Da Cunha, 2013 • Drouillet-Pinard, 2010 • Garcia-Esquinas, 2013 • Gennings, 2020 • Grandjean, 2001 • Halldorsson, 2008 • Marques, 2016 • Mendez, 2009 • Miyashita, 2015 • Muniroh, 2022 • Papadopoulou, 2021 • Taylor, 2016 • Vejrup, 2013 • Wohlfahrt-Veje, 2014	1 article: • Kvestad, 2018
Cardiometabolic Outcomes	3 articles: • Gregory, 2016 • Stratakis, 2020 • Warembourg, 2019	2 articles: • Chan, 2021 • Warembourg, 2019
Immune-Related Outcomes	1 article: • Emeny, 2019	2 articles: • Kindgren, 2019 • Signes-Pastor, 2022
Chronic Disease Risk Outcomes	2 articles: • Emeny, 2019 • Stratakis, 2020	0 articles
Other	5 articles: • Stratakis, 2020 • Garcia-Esquinas, 2013 • Goudarzi, 2017 • Xue, 2007 • Yu, 2022	O articles

Extracted data

High-level data was extracted from each included article to inform decisions regarding prioritization of exposure-outcome relationships for systematic review. The main objective of extraction was to identify the

toxicant and outcome domains within each included article. A single analyst extracted data related to the study characteristics, participant characteristics, the toxicant exposures, outcomes, and confounders. All studies included a measure of fish or seafood intake in the exposure population; therefore, seafood exposure was not extracted. **SEE SUPPLEMENTAL FILE 4-1.**

Committee decisions and next steps

The Evidence Center presented the methods and results of the scoping review to the Committee. After deliberation, the Committee decided that cord blood toxicant measures should be considered a maternal exposure, and therefore eight articles that had been excluded were included.

The scoping review included a broad number of included exposures and outcomes. To narrow the scope, the Committee prioritized the list of outcomes (**Table 4-5**). The Committee requested that the Evidence Center evaluate the scoping review results based on the newly prioritized list of outcomes to inform decisions regarding which exposure-outcome pairs have sufficient evidence to warrant a systematic review.

***Table 4-5**. Outcomes included for the seafood toxicology scoping review and the prioritized list of outcomes to determine next steps.*

Scoping Review Outcomes	**Prioritized Outcomes**
Exposure Biomarkers: • Metals: As, Cd, Cr, Cu, Hg, Ni, Pb, Zn • Polycyclic Hydrocarbons: PAHs, PCBs • Immunological Parameters: Alanine aminotransferase (ALT or SPGT)/ aspartate aminotransferase (AST or SGOT) • Neurotoxic Parameters: Choline Esterase (ChE) • Others: benzo(a)pyrene, phenanthrene, and domoic acid	**Exposure Biomarkers:** • Response biomarkers (e.g., gene expression) [1]
Neurodevelopment and Neurodevelopmental Disorders: • Developmental domains: cognition, language/communication, movement/physical, social-emotional	**Neurodevelopment and Neurodevelopmental Disorders:** • Developmental domains: cognition, language/communication, movement/physical, social-emotional

• Social/emotional outcomes • Academic performance • Autism spectrum disorders (ASD) • Anxiety • Depression • Attention deficit hyperactivity disorder (ADHD)	• Academic performance • Autism spectrum disorders (ASD) [2] • Attention deficit hyperactivity disorder (ADHD) [2] • Seizures [1,2] • Tremors, gait abnormalities [1,2]
Growth-Related: • Measures of growth and body composition • Failure to thrive (malnutrition, protein deficiency)	**Growth-Related:** • Measures of growth and body composition • Failure to thrive (malnutrition, protein deficiency)
Cardiometabolic: • Blood pressure • Dyslipidemia	**Cardiometabolic:** • Blood pressure
Immune-Related: • Allergy and immune response • Asthma • Autoimmune diseases	**Immune-Related:** • Allergy and immune response
Chronic Disease Risk: • Cancer • Other	
Other adverse effects	

[1] Not an outcome included in scoping review

[2] Grouped as "Neurological disorders"

The articles included in the scoping review were reorganized by toxicant and prioritized outcome for each of the two exposure populations (women who are pregnant or lactating and children and adolescents). Any toxicant exposure-prioritized outcome pair with 3 or more articles was determined to have sufficient data for conducting a *de novo* systematic review (**Tables 4-6 and 4-7**). Two toxicant exposure-prioritized outcome pairs were identified to proceed with de novo reviews:

- PCBs + Growth, body composition: n= 4

- Pb + Developmental domains: n= 3

Table 4-6. *Number of articles included in the scoping review on seafood toxicant exposure and child health and developmental outcomes, organized by toxicant and prioritized outcome when the exposure population was women who are pregnant or lactating.*

Exposure population: Women who are pregnant or lactating		*Prioritized Outcomes*						
Exposures		Develop Domains: cognition, language, motor	Academic	Neuro Disorders: ASD, ADHD, Seizures, Tremors, Gait abnormalities	Measures of growth, body comp	Failure to thrive: malnutrition, protein def.	Blood Pressure	Allergy & Immune response
Persistent organic pollutants	Polychlorinated biphenyls (PCBs)	2	0	1	4	0	1	0
	Dioxin-like compounds (DLCs)	2	0	0	1	0	0	0
	Polybrominated diphenyl ethers (PBDEs)	0	0	0	1	0	1	0
	Per- and polyfluoroalkyl substances (PFAS and PFCs)	2	0	0	1	0	1	0
Metals	Arsenic (As)	0	0	0	0	0	1	0
	Cadmium (Cd)	0	0	0	1	0	1	0
	Lead (Pb)	3	0	0	1	0	1	0
Essential trace elements	Selenium (Se)	2	0	0	2	0	1	0
	Iron (Fe)	2	0	0	0	0	0	0
	Magnesium (Mg)	0	0	0	0	0	0	0
	Zinc (Zn)	2	0	0	0	0	0	0
Pesticides	DDT	0	0	0	2	0	1	0
	KEY:		1 article	2 articles	≥3 articles			

Table 4-7. *Number of articles included in the scoping review on seafood toxicant exposure and child health and developmental outcomes, organized by toxicant and prioritized outcome when the exposure population was children or adolescents.*

Exposure population: Infants, children, adolescents		*Prioritized Outcomes*						
Exposures		Develop Domains: cognition, language, motor	Academic	Neuro Disorders: ASD, ADHD, Seizures, Tremors, Gait abnormalities	Measures of growth, body comp	Failure to thrive: malnutrition, protein def.	Blood Pressure	Allergy & Immune response
Persistent organic pollutants	Polychlorinated biphenyls (PCBs)	0	0	0	0	0	1	0
	Dioxin-like compounds (DLCs)	0	0	0	0	0	0	0
	Polybrominated diphenyl ethers (PBDEs)	0	0	0	0	0	1	0
	Per- and polyfluoroalkyl substances (PFAS and PFCs)	1	0	0	0	0	1	0
Metals	Arsenic (As)	0	0	1	0	0	1	1
	Cadmium (Cd)	0	0	2	0	0	1	1
	Lead (Pb)	0	0	1	0	0	1	1
Essential trace elements	Selenium (Se)	0	0	1	0	0	0	0
	Iron (Fe)	0	0	0	0	0	0	1
	Magnesium (Mg)	0	0	0	0	0	0	1
	Zinc (Zn)	0	0	1	0	0	0	1
Pesticides	DDT	0	0	0	0	0	1	0
	KEY:		1 article	2 articles	≥3 articles			

Included articles

1. Ballester, F.,Iniguez, C.,Murcia, M.,Guxens, M.,Basterretxea, M.,Rebagliato, M.,Vioque, J.,Lertxundi, A.,Fernandez-Somoano, A.,Tardon, A.,Sunyer, J.,Llop, S. (2018). Prenatal exposure to mercury and

longitudinally assessed fetal growth: Relation and effect modifiers Environmental Research, 160(#issue#), 97-106

2. Barbone, F.,Valent, F.,Pisa, F.,Daris, F.,Fajon, V.,Gibicar, D.,Logar, M.,Horvat, M. (2020). Prenatal low-level methyl mercury exposure and child development in an Italian coastal area NeuroToxicology, 81(#issue#), 376-381
3. Beck, I. H.,Bilenberg, N.,Andersen, H. R.,Trecca, F.,Bleses, D.,Jensen, T. K. (2023). Association between prenatal or early postnatal exposure to perfluoroalkyl substances and language development in 18 to 36-month-old children from the Odense Child Cohort Environmental Health: A Global Access Science Source, 22(1), 46
4. Budtz-Jorgensen, E.,Grandjean, P.,Weihe, P. (2007). Separation of risks and benefits of seafood intake Environmental Health Perspectives, 115(3), 323-327
5. Chan, P. H. Y.,Kwok, K. M.,Chan, M. H. M.,Li, A. M.,Chan, I. H. S.,Fok, T. F.,Lam, H. S. (2021). Prenatal methylmercury exposure is associated with decrease heart rate variability in children Environmental Research, 200(#issue#), 111744
6. Cunha, M. P. L.,Marques, R. C.,Dorea, J. G. (2018). Influence of maternal fish intake on the anthropometric indices of children in the western amazon Nutrients, 10(9), 1146
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8. Davidson, P. W.,Strain, J. J.,Myers, G. J.,Thurston, S. W.,Bonham, M. P.,Shamlaye, C. F.,Stokes-Riner, A.,Wallace, J. M. W.,Robson, P. J.,Duffy, E. M.,Georger, L. A.,Sloane-Reeves, J.,Cernichiari, E.,Canfield, R. L.,Cox, C.,Huang, L. S.,Janciuras, J.,Clarkson, T. W. (2008). Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy NeuroToxicology, 29(5), 767-775
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10. Drouillet-Pinard, P.,Huel, G.,Slama, R.,Forhan, A.,Sahuquillo, J.,Goua, V.,Thiébaugeorges, O.,Foliguet, B.,Magnin, G.,Kaminski, M.,Cordier, S.,Charles, M. A. (2010). Prenatal mercury contamination:

relationship with maternal seafood consumption during pregnancy and fetal growth in the 'EDEN mother-child' cohort Br J Nutr, 104(8), 1096-100

11. Emeny, R. T.,Korrick, S. A.,Li, Z.,Nadeau, K.,Madan, J.,Jackson, B.,Baker, E.,Karagas, M. R. (2019). Prenatal exposure to mercury in relation to infant infections and respiratory symptoms in the New Hampshire Birth Cohort Study Environmental Research, 171(#issue#), 523-529
12. Fruh, V.,Rifas-Shiman, S. L.,Coull, B. A.,Devick, K. L.,Amarasiriwardena, C.,Cardenas, A.,Bellinger, D. C.,Wise, L. A.,White, R. F.,Wright, R. O.,Oken, E.,Claus Henn, B. (2021). Prenatal exposure to a mixture of elements and neurobehavioral outcomes in mid-childhood: Results from Project Viva Environmental Research, 201(#issue#), 111540
13. Garcia-Esquinas, E.,Perez-Gomez, B.,Fernandez-Navarro, P.,Fernandez, M. A.,de Paz, C.,Perez-Meixeira, A. M.,Gil, E.,Iriso, A.,Sanz, J. C.,Astray, J.,Cisneros, M.,de Santos, A.,Asensio, A.,Garcia-Sagredo, J. M.,Garcia, J. F.,Vioque, J.,Lopez-Abente, G.,Pollan, M.,Gonzalez, M. J.,Martinez, M.,Aragones, N. (2013). Lead, mercury and cadmium in umbilical cord blood and its association with parental epidemiological variables and birth factors BMC public health, 13(#issue#), 841
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17. Golding, J.,Hibbeln, J. R.,Gregory, S. M.,Iles-Caven, Y.,Emond, A.,Taylor, C. M. (2017). Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: A British prebirth cohort study Int J Hyg Environ Health, 220(7), 1161-1167
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androgenic hormones in cord blood samples: The Hokkaido study Environmental Health Perspectives, 125(1), 111-118

20. Grandjean, P.,Bjerve, K. S.,Weihe, P.,Steuerwald, U. (2001). Birthweight in a fishing community: significance of essential fatty acids and marine food contaminants Int J Epidemiol, 30(6), 1272-8
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Chapter 5: Seafood and mercury exposure during pregnancy, lactation, and childhood and child growth and development: Evaluation of existing systematic reviews

Introduction

The Evidence Center conducted a scoping review to identify: 1.) toxicant exposures with sufficient evidence to warrant a systematic review, and 2.) gaps in the evidence. Based on the results of the scoping review, the Committee prioritized exposure-outcome relationships that warranted systematic review (see Chapter 4).

In addition, they also expressed an interest in capturing and evaluating the evidence related specifically to mercury exposure. The inclusion criteria applied in the scoping review required that studies report *both* fish/seafood intake as an exposure and a toxicant exposure, with demonstration of the associations between fish/seafood exposure to the toxin and/or the outcome. However, given that the primary source of mercury exposure is through fish/seafood intake, the Committee was interested in examining the association between mercury and child health outcomes using studies that did not explicitly report fish/seafood intake.

Based on the time and resources needed to screen and extract additional articles, and the knowledge that multiple systematic reviews examining the relationship between mercury and child health outcomes likely existed, recent relevant existing systematic reviews could potentially be used by the Committee to supplement or substitute for a *de novo* review.

To determine whether an existing systematic review could be used depends on its relevancy, timeliness, and quality.

- **Relevancy** is assessed by comparing PICO elements of the existing review(s) to the desired review.
- **Timeliness** is based on the time of the literature search. What is considered "timely" will depend on the topic considering the volume of research being published and advancement in research methods.
- **Quality** of a systematic review is assessed using the AMSTAR 2 tool.

If an existing review is determined to be relevant, timely, and of good quality, a *de novo* review may not be warranted. In some cases, an existing review may be identified as relevant and good quality but not timely. In that case, an update of the existing review could be considered.

Further, if more than one systematic review is identified for an outcome, a decision needs to be made regarding which review or reviews will be used. In addition to relevance, timeliness, and quality, the consistency in the evidence base (overlap of included studies) from individual reviews can help inform this decision. A duplication assessment compares the included articles across reviews identified for an outcome and identifies how many studies overlap or are unique among the reviews. When included papers from multiple reviews show little consistency/overlap, there may be differences in methodology that should be considered (e.g., comprehensiveness of search strategy) and described to clarify these differences.

Given the large amount of primary studies related to mercury exposure and child development, the Committee's desire to expand the inclusion criteria to include studies without measures of fish/seafood intake related to mercury exposure, and the likelihood of an existing relevant, recent systematic review, the decision was made to search the literature for relevant, timely, and good quality systematic reviews on mercury exposure during pregnancy, lactation, childhood, or adolescence on child health and development outcomes.

Methodology

Search

The Evidence Center's Information Scientist conducted a search to identify existing recent relevant systematic reviews that examined the relationship between mercury exposure during pregnancy, lactation, childhood, or adolescence on child health and development outcomes including dates from 2020 to present.

Screening

Two reviewers screened all results from the search at the full-text level. Conflicts were resolved by a third reviewer.

Quality assessment

The AMSTAR 2 quality assessment tool was used to assess the quality of included systematic reviews. The tool includes 16 items (**Appendix 2**), which were rated as "Yes", "Partial Yes", "No", or "No meta-analysis conducted" (recoded as "N/A"). Some items were adapted for this review to account for the observational

nature of the included studies. Two independent assessments were performed for each included review. Disagreements were discussed and resolved by the two reviewers. For the purposes of this review, an overall summary rating was determined for each systematic review by summing the item ratings (Yes= 1; Partial Yes= 0.5; No= 0; N/A= 1). Reviews that scored 8 or more (≥50%) were considered to be moderate-high quality; reviews that scored less than 8 (<50%) were considered to be lower quality.

Duplication assessment

A duplication assessment was conducted by Evidence Center analysts to compare the included articles across reviews when more than one existing systematic review was identified for an outcome. The assessment identified the included studies for each of the reviews and how many studies overlapped or were unique among the reviews.

Results

Search

A total of 53 articles were identified in the search for existing systematic reviews related to the association between mercury exposure during pregnancy, lactation, or childhood and child outcomes.

Screening

After dual full text screening, 12 systematic reviews were included. Existing systematic reviews were identified for all but 2 prioritized outcomes. For some outcomes, there was more than one systematic review identified. No articles were identified in the search related to blood pressure; however, a review from 2019 was identified through manual searching and included.

***Table 5-1**. Existing systematic reviews by prioritized outcome*

Prioritized outcome	Systematic Review (Author, year)
Neurological disorders – ASD	5 systematic reviews: • Amadi, 2022 • Ding, 2023 • Ealo Tapia, 2023 • Sulaiman, 2020 • Zhang, 2021
Developmental domains	3 systematic reviews: • Dack, 2022 • Ealo Tapia, 2023 • Saavedra, 2021
Growth – measures of growth, body composition	3 systematic reviews: • Dack, 2021 • Kumar, 2022 • Saavedra, 2021)
Biomarker - Gene expression	1 systematic review: • Paz Sabillion, 2022
Neurological disorders – ADHD	1 systematic review: • Ealo Tapia, 2023
Cardiometabolic – blood pressure	1 systematic review: • Gallego-Vinas, 2019
Immune-related – Allergy, immune response	1 systematic review: • Wang, 2022
Academic performance	0 systematic reviews
Growth – failure to thrive	0 systematic reviews

Quality assessment

The results of the AMSTAR 2 quality assessment are in **SUPPLEMENTAL FILE 5-1**. Scores ranged from 5 to 12 out of 16, with a median of 9.5 (**Table 5-2**).

***Table 5-2**. Existing reviews for mercury exposure by prioritized outcomes.*

Prioritized outcome	Existing review(s)	Overall quality assessment rating	Duplication assessment summary	Suggested action
Biomarker: Gene expression	Paz-Sabillon, 2022	9.5 (Moderate-high)	n/a	Given a moderate-high quality, can be considered
Developmental milestones	Dack, 2022 Ealo Tapia, 2023 Saavedra, 2021	12 (Moderate-high) 10 (Moderate-high) 9.5 (Moderate-high)	Reviews have some overlap but each contains unique articles	All should be considered given reviews contain unique primary studies
Neurologic Disorders: ASD	Ealo Tapia, 2023 Ding, 2023 Zhang, 2021 Amadi, 2022 Sulaiman, 2020	10 (Moderate-high) 9 (Moderate-high) 9 (Moderate-high) 9 (Moderate-high) 7 (Lower quality)	Most reviews contain unique articles	Suggest considering reviews by Ealo Tapia, Ding and Zhang. Sulaiman is lower quality but contains unique articles, so may be considered along with limitations. Amadi included few studies and no unique studies so not recommended given little added value.
Neurologic Disorders: ADHD	Ealo Tapia, 2023	10 (Moderate-high)	n/a	Given a moderate-high quality, can be considered
Growth & Body composition	Dack, 2021 Saavedra, 2021 Kumar, 2022	12 (Moderate-high) 9.5 (Moderate-high) 5 (Lower quality)	Dack, 2021 has the highest number of included articles representing all but	Given the moderate-high quality and representation of the most unique articles with near perfect overlap

			1 article from the other reviews	with other reviews, we suggest using Dack 2021
Cardiometabolic: blood pressure	Gallego-Viñas, 2019	11 (Moderate-high)	n/a	Given a moderate-high quality, can be considered
Immune-related: Allergy, Immune response	Wang, 2022	10.5 (Moderate-high)	n/a	Given a moderate-high quality, can be considered

Duplication assessment

For prioritized outcomes with more than one existing review, analysts compared the relevant included articles (i.e., articles related to mercury and the specific prioritized outcome) to assess the degree of overlap. Outcomes requiring duplication assessment included: developmental milestones, neurologic disorders (ASD), and measures of growth and body composition (Table 5-1). See **SUPPLEMENTAL FILE 5-1** tabs "DupeAssess-Developmental", "DupeAssess-ASD", and "DupeAssess-Growth" for the list of all articles and comparison of articles across reviews for a given outcome.

Developmental milestones: 3 existing systematic reviews were identified with a total of 50 articles across the reviews. The number of included articles per review were: 32 (Dack, 2022), 18 (Ealo Tapia, 2023), and 15 (Saavedra, 2021). Fifteen articles were included in more than 1 review, with 35 articles included in only 1 review. Dack, 2022 contained 18 unique articles; Ealo Tapia, 2023 contained 11 unique articles; and Saavedra, 2021 contained 6 unique articles.

- Given the number of unique articles in each systematic review and the moderate-high quality of each of these existing reviews, we suggest that the Committee considers three reviews: Dack, 2022; Ealo Tapia, 2023; Saavedra, 2021.

Neurologic Disorders: ASD: 5 existing systematic reviews were identified with a total of 58 articles across the reviews. The number of included articles per review were: 37 (Ding, 2023), 23 (Sulaiman, 2020), 12 (Zhang, 2021), 9 (Ealo Tapia, 2023), and 3 (Amadi, 2022). Twenty-two articles were included in more than 1 review, with 36 articles included in only 1 review. Ding, 2023 contained 17 unique articles; Sulaiman, 2020 contained 8 unique articles; Zhang, 2021 contained 3 unique articles; and, Amadi, 2022 did not contain any unique articles.

- Of the 5 identified systematic reviews, 4 provide unique data and we suggest these be considered by the Committee (Ding, 2023; Ealo Tapia, 2023; Sulaiman, 2020; Zhang, 2021) with the qualifier that the Sulaiman, 2020 systematic review has a lower quality score of 7 (some quality concerns: study selection not performed in duplicate, did not provide a list of excluded articles with justification, authors did not account for individual study risk of bias in meta-analysis or in interpretation of results), so should be considered with caution. The Amadi, 2022 review does not provide unique data and is therefore not necessary for consideration by the Committee.

Growth-related: measures of growth, body composition: 3 existing reviews were identified with a total of 28 articles across the reviews. The number of included articles per review were: 27 (Dack, 2021), 4 (Saavedra, 2021), and 3 (Kumar, 2022). Six articles were included in more than 1 review, with 22 articles included in only 1 review. Dack, 2021 contained 21 unique articles; Kumar, 2022 contained 1 unique article; and Saavedra, 2021 did not contain any unique articles.

- For this outcome, we suggest focusing on the Dack, 2021 systematic review, which contains all but 1 article identified among the 3 reviews and has the highest quality rating. While Saavedra, 2021 has a moderate-high quality score, it does not contain unique articles. Kumar (2022) contains 1 unique article but has a lower quality score.

Summary

Recent, relevant, moderate-high quality existing systematic reviews were identified for all prioritized outcomes except for academic performance and failure to thrive. For these two outcomes, no primary articles were identified in the scoping review, indicating insufficient evidence to warrant systematic review.

To address the evidence related to mercury exposure that includes primary evidence with and without fish/seafood exposure and considering time constraints and resource prioritization, it is suggested to proceed using the existing reviews for the available outcomes.

Included articles

1. Amadi, CN Orish, C Frazzoli, OE Orisakwe (2022). Association of autism with toxic metals: A systematic review of case-control studies. Pharmacology, biochemistry, and behavior, 212(), #Pages#
2. Dack, M Fell, CM Taylor, A Havdahl, SJ Lewis (2021). Mercury and Prenatal Growth: A Systematic Review. International journal of environmental research and public health, 18(13), #Pages#

3. Dack, M Fell, CM Taylor, A Havdahl, SJ Lewis (2022). Prenatal Mercury Exposure and Neurodevelopment up to the Age of 5 Years: A Systematic Review. International journal of environmental research and public health, 19(4), #Pages#
4. Ding, S Shi, S Qie, J Li, X Xi (2023). Association between heavy metals exposure (cadmium, lead, arsenic, mercury) and child autistic disorder: a systematic review and meta-analysis. Frontiers in pediatrics, 11()+B13+B2:B13
5. Ealo Tapia, J Torres Abad, M Madera, J Márquez Lázaro (2023). Mercury and neurodevelopmental disorders in children: A systematic review. Archivos argentinos de pediatria, 121(5), #Pages#
6. Gallego-Viñas, F Ballester, S Llop (2019). Chronic mercury exposure and blood pressure in children and adolescents: a systematic review. Environmental science and pollution research international, 26(3), #Pages#
7. Kumar, A Sharma, S Sedha (2022). Occupational and environmental mercury exposure and human reproductive health - a review. Journal of the Turkish German Gynecological Association, 23(3), #Pages#
8. Paz-Sabillón, L Torres-Sánchez, M Piña-Pozas, LM Del Razo, B Quintanilla-Vega (2023). Prenatal Exposure to Potentially Toxic Metals and Their Effects on Genetic Material in Offspring: a Systematic Review. Biological trace element research, 201(5), #Pages#
9. Saavedra, Á Fernández-Recamales, A Sayago, A Cervera-Barajas, R González-Domínguez, JD Gonzalez-Sanz (2022). Impact of dietary mercury intake during pregnancy on the health of neonates and children: a systematic review. Nutrition reviews, 80(2), #Pages#
10. Sulaiman, M Wang, X Ren (2020). Exposure to Aluminum, Cadmium, and Mercury and Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis. Chemical research in toxicology, 33(11), #Pages#
11. Wang, J Yin, X Hong, R Liu (2022). Exposure to Heavy Metals and Allergic Outcomes in Children: a Systematic Review and Meta-analysis. Biological trace element research, 200(11), #Pages#
12. .Zhang, X Li, L Shen, NU Khan, X Zhang, L Chen, H Zhao, P Luo (2021). Trace elements in children with autism spectrum disorder: A meta-analysis based on case-control studies. Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS), 67(), #Pages#

Chapter 6: Maternal seafood and lead exposure during pregnancy or lactation and child development outcomes: A systematic review

Introduction

The Evidence Center conducted a scoping review to identify: 1.) toxicant exposures with sufficient evidence to warrant a systematic review, and 2.) gaps in the evidence. Based on the results of the scoping review, the Committee prioritized exposure-outcome relationships that warranted systematic review (see Chapter 4).

Two toxicant exposure-prioritized outcome pairs were identified to proceed with de novo reviews:

- PCBs + Growth, body composition: n= 4
- Pb + Developmental domains: n= 3

This chapter provides the methods and results pertaining to the review on seafood and lead exposure on child development.

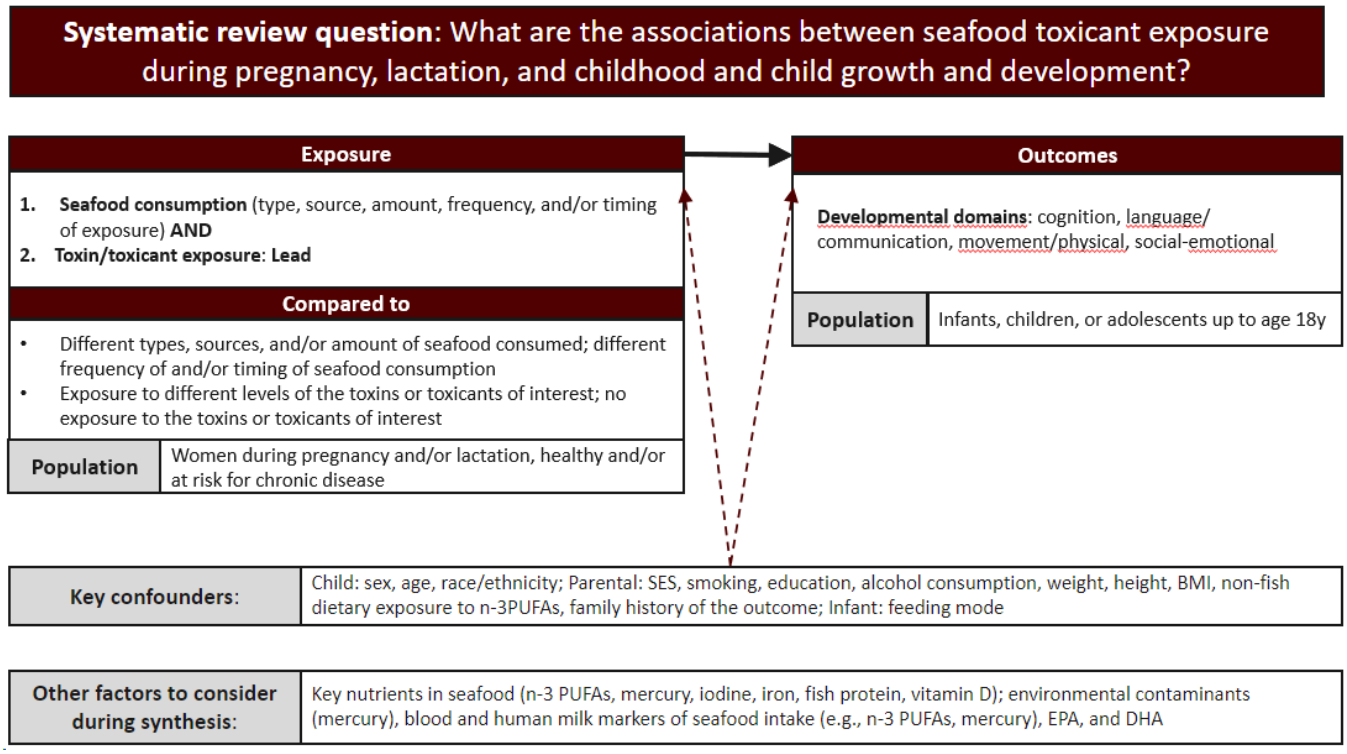
Methodology

Protocol development

Relevant data and information for the systematic review protocols were provided to the Evidence Center by NASEM. This information included the PECOD frameworks, inclusion/exclusion criteria, and the search strategy. The search was run by the NASEM librarian and search results were provided to the Evidence Center. The Evidence Center drafted the systematic review protocols including relevant methodology based on the provided information and registered the protocol in PROSPERO (CRD42023448200).

Analytic framework

***Figure 6-1**. Analytic framework for examining the relationship between seafood consumption and lead exposure during pregnancy and lactation and developmental outcomes in the child.*



Inclusion and exclusion criteria

Table 6-1. *Inclusion and exclusion criteria for toxicology reviews*

Category	Inclusion Criteria	Exclusion Criteria
Population	Human individuals living in countries ranked as high or very high on the human development index[a] during the study ● Exposed population: Individuals in the general population who are pregnant or lactating, Subgroups of interest: ○ By race/ethnicity ○ By income ○ By cumulative exposure to non-chemical and environmental stressors: stress, depression, neighborhood or locale, food security) ○ By pre-existing disease burden ● Outcome population: Children and adolescents (up to age 18 years). Subgroups of interest: ○ Infants (ages 0 to 12 months) ○ Toddlers (ages 1 to 3 years) ○ Early childhood (ages 4 to 8 years) ○ Puberty (ages 9 to 13 years) ○ Adolescents (ages 14 to 18 years)	● Studies exclusively of participants with a chronic condition, hospitalized with an illness or injury. Examples include: ○ Diabetes (not including gestational diabetes) ○ Cancer ○ Cardiometabolic disorders ○ Chronic kidney disease ○ Malabsorption (any disorder that causes malabsorption from the gastrointestinal tract) ○ Asthma ● Nonhuman Primates
Exposure	● **Must contain Exposure 1 AND Exposure 2** ● **Exposure 1: Toxin or toxicants** ● Metals: Lead ● **Exposure 2: Seafood consumption:** ○ Types (e.g., salmon, tuna, bass) ○ Sources (e.g., sea, fresh water, farmed, canned, wild) ○ Amount (e.g., ounces per day, grams per meal) ○ Frequency (e.g., daily, twice a week) ○ Duration (e.g., length of time consuming seafood) ○ Preparation (e.g., fried, baked) ○ Timing (e.g., by trimester, age)	● Studies that do not report on toxicant exposure in fish AND seafood consumption ● Supplements ● Infant formula ● Toxins from algal blooms: ● Cyanobacteria ● Ciguatera ● Scombroid ● Domoic acid (red algae) ● Microorganisms (hepatitis, salmonella, e coli)

Comparator	• Exposure to different levels of the toxins or toxicants of interest; No exposure to the toxins or toxicants of interest • Different types, sources, amounts, frequencies, durations, preparations, or timings of seafood consumption; No seafood consumption	• No comparator
Outcome	Neurodevelopmental domains: • Developmental domains: cognition, language/communication, movement/physical, social-emotional	
Study Designs	• Randomized controlled trials • Controlled (nonrandomized) trials • Cohort (observational) studies, prospective or retrospective • Case-cohort studies • Case-control studies • Before-after studies	• Case reports • Studies reported in theses or conference abstracts only • Studies not reported in English • Studies without primary data, such as systematic reviews, narrative reviews, editorials, and commentaries • Cross-sectional studies

[a] https://worldpopulationreview.com/country-rankings/hdi-by-country

Screening

All records captured in the search were screened independently by two reviewers. Screening occurred within a web-based program (DistillerSR) using screening forms developed based on the inclusion and exclusion criteria determined *a priori*. Each article was reviewed to determine if it met the inclusion criteria, in which case the article was included, or if any of the exclusion criteria were met, in which case the article was excluded. To assist with screening, a screening decision tree was created based on the inclusion-exclusion criteria (**Appendix 1**).

Screening was conducted in 3 stages or levels following the methodology of the original existing review. In the first level, the title of the article was reviewed. Title screening was used to exclude clearly irrelevant studies. Potential reasons for exclusion at the title level included wrong study population or country, as examples. If there was not a clear reason for exclusion, the article was included and moved to level 2, abstract screening. If there was no reason to exclude the article based on information in the abstract, it was included and moved to level 3, full text screening. When an article was excluded at level 2 (abstract) or level 3 (full text) the screener indicated at least one reason for exclusion. Any disagreements on whether to include or exclude an article were discussed and resolved by the two screeners. If necessary, a third party was consulted to resolve differences.

Piloting was done to ensure the screening forms were adequate and that screeners interpreted the eligibility criteria similarly. For the pilot, screeners reviewed a common set of references (25 references to start) at each screening level. The screeners discussed their responses, any questions or uncertainties they had when making their decision, and any concerns regarding the screening form. If necessary, this was repeated with another common set of references.

Manual searching (or hand-searching) was performed on all articles included after full-text screening. Manual searching is a process whereby the reference list from each included article is reviewed. If a reference is found to be relevant to the present review that was not identified in the electronic search it proceeds through the screening process as detailed above. If an article identified through manual searching was included in the review, the librarian was notified to determine why the article was not found through the electronic search. If necessary, the search strategy would have been updated and rerun, in which case newly identified articles would go through the screening process as described above.

Data extraction

Data from all included articles were extracted by a trained analyst using a systematic approach. Only data relevant to the review was extracted. To ensure data was extracted in a consistent manner for all papers, standard data extraction forms were used. Data fields for extraction were based on information outlined in the protocol and include important characteristics of the study design, methodology, results, and limitations. Forms were piloted on 2 to 3 articles (varying in study design, when appropriate) by all reviewers to ensure all relevant information was being recorded and done so in a consistent manner. A second analyst reviewed the extracted data for accuracy and completeness. Any suggested changes were discussed between the reviewers. If necessary, a third analyst was consulted.

Text box 6-1. Data extraction fields for maternal seafood and lead exposure and child developmental outcomes

Study characteristics:

- Author name, publication year
- Study design
- Study name, if applicable
- Country

- Baseline n

Participant characteristics:

- Mother's age
- Child sex (% female)
- Race/ethnicity
- Socioeconomic Status
- Maternal anthropometrics
- Gestational weight gain
- Infant feeding practices

Exposure details:

- Exposure definition/description
- Exposure assessment method

Exposure level:

- Seafood intake amount
- Maternal/infant levels of: omega-3 polyunsaturated fatty acids [PUFAs], iodine, selenium, iron, fish protein, vitamin D, mercury

Confounders:

- Key confounders accounted for
- Key confounders NOT accounted for
- Other confounders accounted for

Outcome(s) and Results:

- Outcome domain (e.g. developmental domain-cognition, developmental domain-language/communication)
- Outcome assessment tool
- Outcome assessment methods including subscale

- Child age at outcome assessment
- Results, including analytic n

Study limitations

Summary of results

Funding source

Risk of bias assessment

Risk of bias was assessed for all included studies independently by two analysts using standardized tools specific to each study's design. If a study included multiple relevant results, the analysts assessed the risk of bias pertinent to each. If there were differences in risk of bias for the different results, more than one risk of bias assessment may be reported for a paper.

For this project, Cochrane risk of bias tools specific to the included study designs were used. These include: ROB 2.0 for randomized controlled trials, ROBINS-I for non-randomized studies of interventions, and ROBINS-E for non-randomized studies of exposures. These tools are designed to assess risk of bias by domain and then determine an overall risk of bias rating for the study. The analysts piloted the tools on 2 to 3 articles to ensure a consistent approach and interpretation was applied. Further, upon completion of the dual, independent risk of bias assessments, domain-level ratings and the overall rating were compared between the two reviewers to assess inter-rater reliability. If there were differences, the reviewers discussed and determined the appropriate rating. If necessary, a third reviewer was consulted.

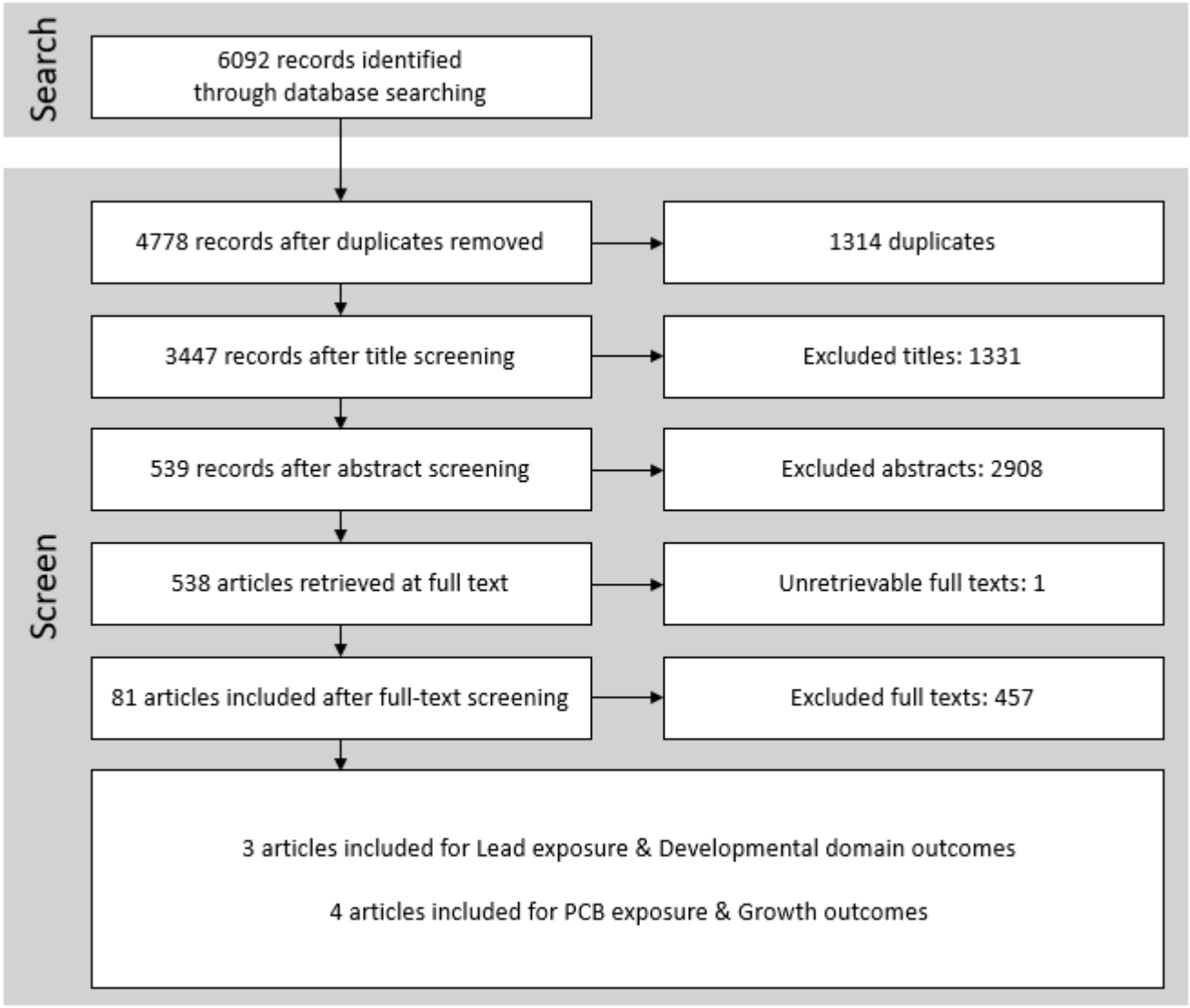
Synthesis

Synthesis was conducted by the Committee. To prepare for synthesis, a description of the evidence was drafted to provide details on the body of evidence including but not limited to, the number of included articles, the number of included studies, study designs, country of origin, participant characteristics, description of the exposure across studies, outcomes, and outcome assessment tools. A description of the evidence and data tables were sent to the Committee.

Results

PRISMA flow chart

Figure 6-2. *PRISMA flow chart outlining the number of articles included after searching and screening.*



* Note: The scoping review PRISMA flow chart included 73 articles after full-text screening (Chapter 4). Based on the Committee's decision to consider an assessment of cord blood as a maternal exposure, 8 additional full-texts were included which resulted in a total of 81 included articles.

Extracted data

Analysts extracted data that was relevant to the review question from each included article. All extracted data were reviewed by a second analyst to verify accuracy and completeness of data. Results were color-coded by the direction of the association (green = beneficial association; red = detrimental association). Significant findings are bolded. **SEE SUPPLEMENTAL FILE 6-1.**

Description of evidence

Three articles from two prospective cohort studies were included in the review examining maternal seafood and lead exposure during pregnancy and child developmental outcomes (**Table 6-2**). Two articles were from the Daxin County cohort in China (Rothenberg, 2016 and Rothenberg, 2021) and one article was from the Mothers and Children's Environmental Health cohort in Korea (Jeong, 2017).

Table 6-2. *Characteristics of studies examining the relationship of seafood and lead exposure during pregnancy and child developmental outcomes.*

STUDY CHARACTERISTICS	EXPOSURE ASSESSMENT		OUTCOMES		Results: Associations between		
Last name, Year Study design Country; Cohort Analytic n	**Fish/seafood exposure; timing**	**Pb exposure assessment; timing**	**Outcome tool & Subscales**	**Child age at outcome assessment**	**Maternal seafood/fish & Maternal Pb levels**	**Maternal seafood/fish & Child outcomes**	**Maternal Pb levels & Child outcomes**
Jeong, 2017 Prospective Cohort Study Korea; Mothers and Children's Environmental Health Analytic n= 553	Maternal fish intake; Late pregnancy	Maternal blood; Late pregnancy	Korean version of the Wechsler Preschool and Primary Scale of Intelligence (K-WPPSI); Verbal IQ, Performance IQ, Total IQ	60mo	NR	NS, beneficial	NS, direction NR
Rothenberg, 2016 Prospective Cohort Study China; Daxin County Analytic n= 270	Maternal fish and shellfish intake; Peripartum,	Maternal blood; Peripartum	Bayley Scales of Infant Development (BSID)-II; Psychomotor Developmental Index (PDI),	12mo	NS, beneficial	Sig beneficial; NS beneficial	Sig, detrimental; NS detrimental

	representing 3rd trimester		Mental Developmental Index (MDI)				
Rothenberg, 2021 Prospective Cohort Study China; Daxin County Analytic n= 190	Maternal fish and shellfish intake; Peripartum, representing 3rd trimester	Maternal blood; Peripartum	Bayley Scales of Infant Development (BSID)-II; Psychomotor Developmental Index (PDI), Mental Developmental Index (MDI)	36mo	NR	Sig beneficial; NS beneficial	NS detrimental

Abbreviations: BSID-II: Bayley Scales of Infant Development II; IQ: Intelligence Quotient; K-WPPSI: Korean version of the Wechsler Preschool and Primary Scale of Intelligence; MDI: Mental Developmental Index; NR: not reported; NS: Non-significant; PDI: Psychomotor Developmental Index; Sig: Statistically significant

Exposure assessments were similar for the three articles. Each study measured maternal fish and seafood intake in the third trimester and used maternal whole blood in late pregnancy (Jeong, 2017) or peripartum (Rothenberg, 2016; Rothenberg, 2021) to measure lead levels.

Child development was measured using the Bayley Scales of Infant Development II at 12 and 36 months in the China Daxin County cohort (Rothenberg 2016; Rothenberg, 2021). The study by Jeong et al (2017) used a Korean version of the Wechsler Preschool and Primary Scale of Intelligence tool when children were 5 years old. Analytic sample sizes ranged from 190 to 553.

To be included in the review, papers needed to report results of at least two of the following three analyses:

1.) association between maternal fish/seafood intake and PCB levels;

2.) association between maternal fish/seafood intake and child outcomes; and,

3.) association between maternal PCB levels and child outcomes.

Joeng (2017) and Rothenberg (2021) reported results for associations between maternal fish/seafood intake and child outcomes and associations between maternal PCB levels and child outcomes. Rothenberg (2016) reported results for all three associations.

Summary of findings

Associations between maternal seafood/fish intake and maternal lead levels

Rothenberg (2016) was the only article to report an analysis examining the association between maternal fish intake and PCB levels. They reported a nonsignificant negative correlation.

Associations between maternal seafood/fish intake and child growth-related outcomes

All three articles analyzed the relationship between maternal fish intake and child developmental outcomes. Results were mixed in terms of significance, but all associations were in a beneficial direction (higher levels of maternal fish intake were associated with higher child performance scores) regardless of differences in outcome test and child age.

Associations between maternal lead levels and child growth-related outcomes

All three articles analyzed the relationship between maternal lead levels and child developmental outcomes. Jeong (2017) reported no significant association but did not report the additional data to support this finding. Rothenberg (2016) reported a significant negative association between maternal lead and child's psychomotor development index (PDI) at 12 months. Other associations (PDI at 36 months, and MDI at 12 and 36 months) were non-significant but in a negative direction (Rothenberg, 2016; Rothenberg, 2021).

Risk of bias assessments

Risk of bias was assessed for each included article using ROBINS-E for longitudinal cohort studies (**Table 6-3**). All three articles were considered to have an overall risk of bias score of high, largely resulting from risk of bias due to confounding, measurement of the exposure (self-reported seafood/fish consumption), missing data, and selection of reported results.

Table 6-3. *Risk of bias assessments using ROBINS-E for studies examining associations between maternal exposure to seafood and lead and child developmental outcomes.*

Cochrane ROBINS-E: Non-randomized studies of exposures (cohort studies)								
Article	Overall risk of bias judgement	Risk of bias due to confounding	Risk of bias arising from measurement of the exposure	Risk of bias in selecting participants into the study (or analysis)	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from measurement of the outcome	Risk of bias in selection of the reported result
Jeong, 2017	High	High	High	Some Concerns	Some Concerns	High	Some Concerns	High
Rothenberg, 2021	High	High	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Rothenberg, 2016	High	High	Low	Some concerns	Some concerns	Some concerns	Low	Low

Included articles

1. Jeong, K. S., Park, H., Ha, E., Shin, J., Hong, Y. C., Ha, M., Park, H., Kim, B. N., Lee, B., Lee, S. J., Lee, K. Y., Kim, J. H., Kim, Y. (2017). High Maternal Blood Mercury Level Is Associated with Low Verbal IQ in Children J Korean Med Sci, 32(7), 1097-1104
2. Rothenberg, S. E., Korrick, S. A., Liu, J., Nong, Y., Nong, H., Hong, C., Trinh, E. P., Jiang, X., Biasini, F. J., Ouyang, F. (2021). Maternal methylmercury exposure through rice ingestion and child neurodevelopment in the first three years: a prospective cohort study in rural China Environmental Health: A Global Access Science Source, 20(1), 50
3. Rothenberg, S. E., Yu, X., Liu, J., Biasini, F. J., Hong, C., Jiang, X., Nong, Y., Cheng, Y., Korrick, S. A. (2016). Maternal methylmercury exposure through rice ingestion and offspring neurodevelopment: A prospective cohort study Int J Hyg Environ Health, 219(8), 832-842

Chapter 7: Maternal seafood and PCB exposure during pregnancy or lactation and child growth outcomes: A systematic review

Introduction

The Evidence Center conducted a scoping review to identify: 1.) toxicant exposures with sufficient evidence to warrant a systematic review, and 2.) gaps in the evidence. Based on the results of the scoping review, the Committee prioritized exposure-outcome relationships that warranted systematic review (see Chapter 4).

Two toxicant exposure-prioritized outcome pairs were identified to proceed with de novo reviews:

- PCBs + Growth, body composition: n= 4
- Pb + Developmental domains: n= 3

This chapter provides the methods and results pertaining to the review on seafood and PCB exposure on growth outcomes.

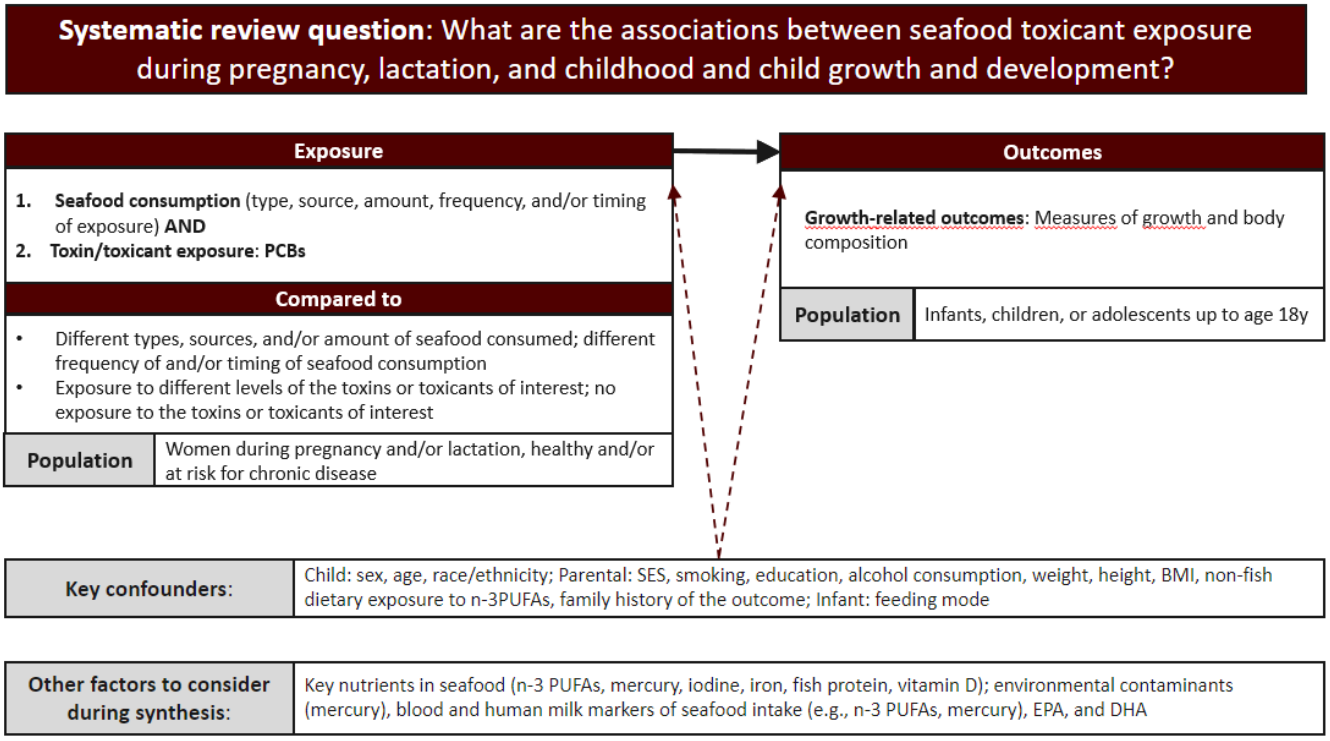
Methodology

Protocol development

Relevant data and information for the systematic review protocols were provided to the Evidence Center by NASEM. This information included the PECOD frameworks, inclusion/exclusion criteria, and the search strategy. The search was run by the NASEM librarian and search results were provided to the Evidence Center. The Evidence Center drafted the systematic review protocols including relevant methodology based on the provided information and registered the protocol in PROSPERO (CRD42023448200).

Analytic framework

***Figure 7-1**. Analytic framework for examining the relationship between seafood consumption and PCB exposure during pregnancy and lactation and growth-related outcomes in the child.*



Inclusion and exclusion criteria

***Table 7-1**. Inclusion and exclusion criteria for toxicology reviews*

Category	Inclusion Criteria	Exclusion Criteria
Population	Human individuals living in countries ranked as high or very high on the human development index[a] during the study ● Exposed population: Individuals in the general population who are pregnant or lactating. Subgroups of interest: ○ By race/ethnicity ○ By income ○ By cumulative exposure to non-chemical and environmental stressors: stress, depression, neighborhood or locale, food security) ○ By pre-existing disease burden ● Outcome population: Children and adolescents (up to age 18 years). Subgroups of interest: ○ Infants (ages 0 to 12 months) ○ Toddlers (ages 1 to 3 years) ○ Early childhood (ages 4 to 8 years) ○ Puberty (ages 9 to 13 years) ○ Adolescents (ages 14 to 18 years)	● Studies exclusively of participants with a chronic condition, hospitalized with an illness or injury. Examples include: ○ Diabetes (not including gestational diabetes) ○ Cancer ○ Cardiometabolic disorders ○ Chronic kidney disease ○ Malabsorption (any disorder that causes malabsorption from the gastrointestinal tract) ○ Asthma ● Nonhuman Primates
Exposure	● **Must contain Exposure 1 AND Exposure 2** ● **Exposure 1: Toxin or toxicants** ● Persistent organic pollutants: ○ Polychlorinated biphenyls (PCBs) ● **Exposure 2: Seafood consumption:** ○ Types (e.g., salmon, tuna, bass) ○ Sources (e.g., sea, fresh water, farmed, canned, wild) ○ Amount (e.g., ounces per day, grams per meal) ○ Frequency (e.g., daily, twice a week) ○ Duration (e.g., length of time consuming seafood) ○ Preparation (e.g., fried, baked) ○ Timing (e.g., by trimester, age)	● Studies that do not report on toxicant exposure in fish AND seafood consumption ● Supplements ● Infant formula ● Toxins from algal blooms: ● Cyanobacteria ● Ciguatera ● Scombroid ● Domoic acid (red algae) ● Microorganisms (hepatitis, salmonella, e coli)

Comparator	• Exposure to different levels of the toxins or toxicants of interest; No exposure to the toxins or toxicants of interest • Different types, sources, amounts, frequencies, durations, preparations, or timings of seafood consumption; No seafood consumption	• No comparator
Outcome	Growth-Related • Measures of growth and body composition	
Study Designs	• Randomized controlled trials • Controlled (nonrandomized) trials • Cohort (observational) studies, prospective or retrospective • Case-cohort studies • Case-control studies • Before-after studies	• Case reports • Studies reported in theses or conference abstracts only • Studies not reported in English • Studies without primary data, such as systematic reviews, narrative reviews, editorials, and commentaries • Cross-sectional studies

[a] https://worldpopulationreview.com/country-rankings/hdi-by-country

Screening

All records captured in the search were screened independently by two reviewers. Screening occurred within a web-based program (DistillerSR) using screening forms developed based on the inclusion and exclusion criteria determined *a priori*. Each article was reviewed to determine if it met the inclusion criteria, in which case the article was included, or if any of the exclusion criteria were met, in which case the article was excluded. To assist with screening, a screening decision tree was created based on the inclusion-exclusion criteria (**Appendix 1**).

Screening was conducted in 3 stages or levels following the methodology of the original existing review. In the first level, the title of the article was reviewed. Title screening was used to exclude clearly irrelevant studies. Potential reasons for exclusion at the title level included wrong study population or country, as examples. If there was not a clear reason for exclusion, the article was included and moved to level 2, abstract screening. If there was no reason to exclude the article based on information in the abstract, it was included and moved to level 3, full text screening. When an article was excluded at level 2 (abstract) or level 3 (full text) the screener indicated at least one reason for exclusion. Any disagreements on whether to include or exclude an article were discussed and resolved by the two screeners. If necessary, a third party was consulted to resolve differences.

Piloting was done to ensure the screening forms were adequate and that screeners interpreted the eligibility criteria similarly. For the pilot, screeners reviewed a common set of references (25 references to start) at each screening level. The screeners discussed their responses, any questions or uncertainties they had when making their decision, and any concerns regarding the screening form. If necessary, this was repeated with another common set of references.

Manual searching (or hand-searching) was performed on all articles included after full-text screening. Manual searching is a process whereby the reference list from each included article is reviewed. If a reference is found to be relevant to the present review that was not identified in the electronic search it proceeds through the screening process as detailed above. If an article identified through manual searching was included in the review, the librarian was notified to determine why the article was not found through the electronic search. If necessary, the search strategy would have been updated and rerun, in which case newly identified articles would go through the screening process as described above.

Data extraction

Data from all included articles were extracted by a trained analyst using a systematic approach. Only data relevant to the review was extracted. To ensure data was extracted in a consistent manner for all papers, standard data extraction forms were used. Data fields for extraction were based on information outlined in the protocol and include important characteristics of the study design, methodology, results, and limitations. Forms were piloted on 2 to 3 articles (varying in study design, when appropriate) by all reviewers to ensure all relevant information was being recorded and done so in a consistent manner. A second analyst reviewed the extracted data for accuracy and completeness. Any suggested changes were discussed between the reviewers. If necessary, a third analyst was consulted.

Text box 7-1. Data extraction fields for maternal seafood and PCB exposure and child growth outcomes

Study characteristics:

- Author name, publication year
- Study design
- Study name, if applicable
- Country
- Baseline n

Participant characteristics:

- Mother's age
- Child sex (% female)
- Race/ethnicity
- Socioeconomic Status
- Maternal anthropometrics
- Gestational weight gain
- Infant feeding practices

Exposure details:

- Exposure definition/description
- Exposure assessment method

Exposure level:

- Seafood intake amount
- Maternal/infant levels of: omega-3 polyunsaturated fatty acids [PUFAs], iodine, selenium, iron, fish protein, vitamin D, mercury

Confounders:

- Key confounders accounted for
- Key confounders NOT accounted for
- Other confounders accounted for

Outcome(s) and Results:

- Outcome
- Outcome assessment methods
- Child age at outcome assessment
- Results, including analytic n

Study limitations

Risk of bias assessment

Risk of bias was assessed for all included studies independently by two analysts using standardized tools specific to each study's design. If a study included multiple relevant results, the analysts assessed the risk of bias pertinent to each. If there were differences in risk of bias for the different results, more than one risk of bias assessment may be reported for a paper.

For this project, Cochrane risk of bias tools specific to the included study designs were used. These include: ROB 2.0 for randomized controlled trials, ROBINS-I for non-randomized studies of interventions, and ROBINS-E for non-randomized studies of exposures. These tools are designed to assess risk of bias by domain and then determine an overall risk of bias rating for the study. The analysts piloted the tools on 2 to 3 articles to ensure a consistent approach and interpretation was applied. Further, upon completion of the dual, independent risk of bias assessments, domain-level ratings and the overall rating were compared between the two reviewers to assess inter-rater reliability. If there were differences, the reviewers discussed and determined the appropriate rating. If necessary, a third reviewer was consulted.

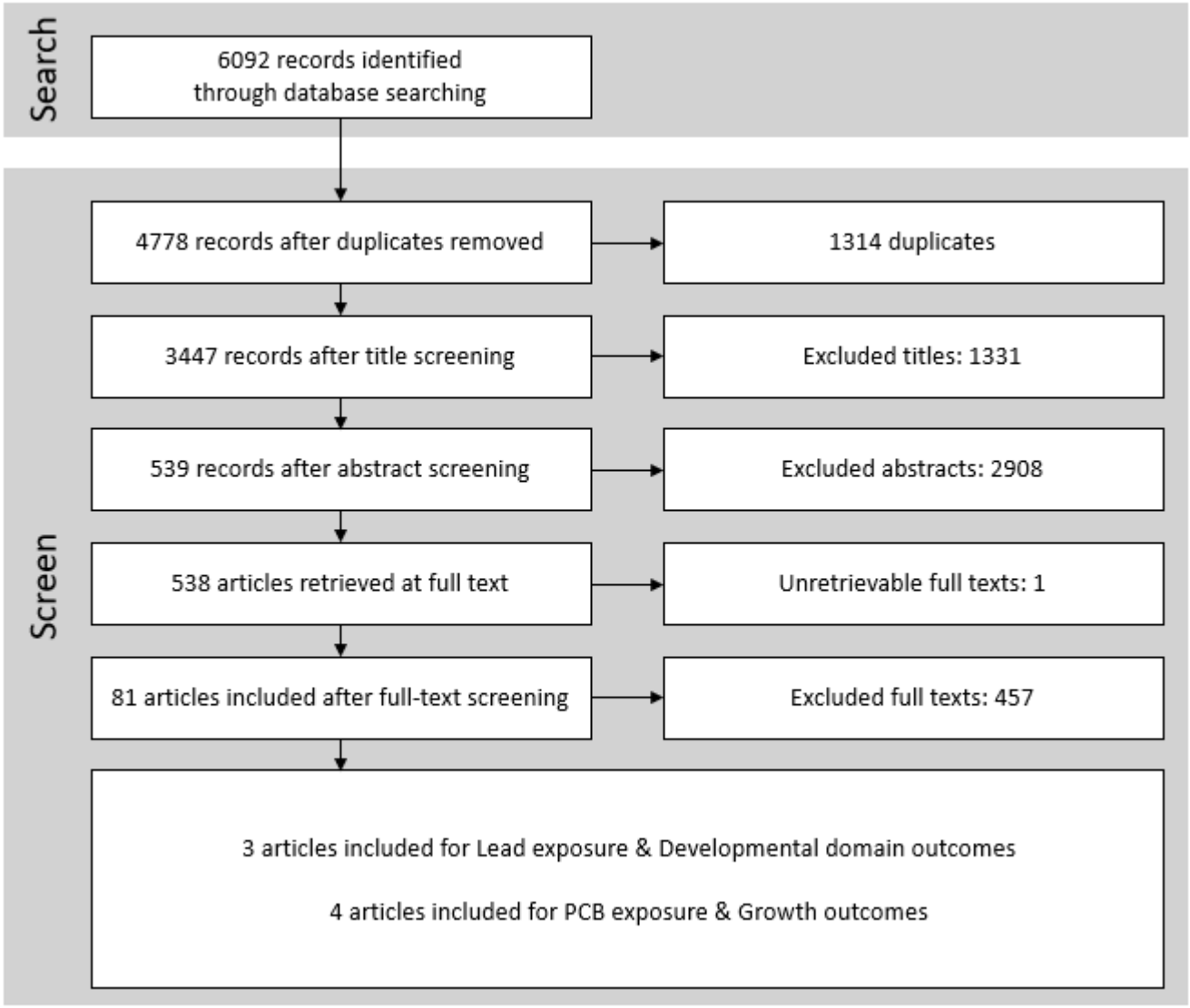
Synthesis

Synthesis was conducted by the Committee. To prepare for synthesis, a description of the evidence was drafted to provide details on the body of evidence including but not limited to, the number of included articles, the number of included studies, study designs, country of origin, participant characteristics, description of the exposure across studies, outcomes, and outcome assessment tools. A description of the evidence and data tables were sent to the Committee.

Results

PRISMA flow chart

***Figure 7-2**. PRISMA flow chart outlining the number of articles included after searching and screening.*



* Note: The scoping review PRISMA flow chart included 73 articles after full-text screening (Chapter 4). Based on the Committee's decision to consider an assessment of cord blood as a maternal exposure, 8 additional full-texts were included which resulted in a total of 81 included articles.

Extracted data

Analysts extracted data that was relevant to the review question from each included article. All extracted data was reviewed by a second analyst to verify accuracy and completeness of data. Results were color-coded by the direction of the association (green = beneficial association; red = detrimental association). Significant findings are bolded. **SEE SUPPLEMENTAL FILE 7-1.**

Description of evidence

Four articles from four prospective cohort studies were included in the review examining PCB exposure through maternal seafood consumption during pregnancy and lactation and measures of growth (**Table 7-2**). Two studies were from Denmark: one from the Danish National Birth Cohort (Halldorsson, 2008) and one from the Copenhagen Mother Child Cohort of Growth and Reproduction (Wohlfahrt-Veje, 2014). One study was from the INMA cohort in Spain (Mendez, 2009) and one study from the Hokkaido Study on Environment and Children's Health cohort in Japan (Miyashita, 2015).

Table 7-2. *Characteristics of studies examining the relationship between seafood and PCB exposure during pregnancy and child developmental outcomes*

Study characteristics	Exposure assessment		Outcomes	Results: Associations between			ROBINS-E
Last name, Year Study design Country; Cohort Analytic n	**Fish/seafood exposure; timing**	**PCB exposure assessment; timing**	**Measured outcomes; Child age**	**Maternal seafood/fish intake & maternal PCB levels**	**Maternal seafood/fish intake & Child outcome**	**Maternal PCB levels & Child outcome**	**Overall ROB rating**
Halldorsson, 2008 Prospective Cohort Study Denmark; Danish National Birth Cohort Analytic n=100	Maternal fatty fish; At 12, 25, 30 wks gestation	Maternal blood plasma; At wk 8 and 25 gestation	At birth: Weight, g Length, cm Head circumference, cm Placental weight, g	Sig, detrimental	NR	Sig, detrimental; NS, detrimental	High
Mendez, 2009 Prospective Cohort Study	Maternal seafood intake;	Maternal serum; At end of 1st	At birth: Weight, g Small size for	Sig, detrimental	Sig, detrimental;	NR	Some concerns

Spain; INfancia y Medio Ambiente (INMA) Analytic n=592	~13.5 wk gestation	trimester-beginning of 2nd trimester	gestational age (SGA) (Not clear if SGA by weight or length)		NS, mixed directions		
Miyashita, 2015 Prospective Cohort Study Japan; Hokkaido Study on Environment and Children's Health Analytic n=367	Maternal fish intake; At 3rd trimester	Maternal whole blood; At 3rd trimester (or within 5d postpartum if anemic)	At birth: Weight, g SGA by weight Length, cm Chest circumference, cm Head circumference, cm	Sig, detrimental; NS, detrimental	NS, mixed directions	NS, mixed directions	Very high
Wohlfahrt-Veje, 2014 Prospective Cohort Study Denmark; Copenhagen Mother Child Cohort of Growth and Reproduction Analytic n=417	Maternal fish intake; During pregnancy	Breast milk; Between 1-3mo post-natal	Gestational age: at birth Weight and Length: at birth, 3, 18, and 36mo	Sig, detrimental	NR	Sig, mixed direction; NS, mixed direction	High

Abbreviations: NR: not reported; NS: Non-significant; SGA: Small for gestational age; Sig: Statistically significant

The studies varied in the measurement by level of detail provided and time of maternal seafood exposure. While Halldorsson (2008) measured maternal fatty fish intake at 12-, 25-, and 30-weeks gestation, Mendez (2009) measured maternal seafood intake (along with seafood subtypes) only once early in pregnancy (at ~13.5 weeks gestation), Miyashita (2015) measured maternal fish intake in the third trimester, and Wohlfahrt-Veje (2014) did not specify when during pregnancy maternal fish intake was measured.

The studies also varied in the timing and biological specimen used for PCB assessments. Halldorsson (2008) measured PCBs in maternal blood plasma sampled at 8- and 25-weeks gestation. Mendez (2009) used maternal serum taken at the end of the first trimester or beginning of the second trimester. Miyashita (2015) used maternal whole blood samples taken in the third trimester or within 5 days postpartum from mothers

with anemia. Wohlfahrt-Vege (2014) measured PCBs in human milk, sampled between the first- and third-month post-partum.

Outcome measurement across the studies was more consistent. All studies measured birth weight. Halldorsson (2008) also reported birth length, head circumference, and placental weight. Mendez (2009) reported small for gestational age (SGA) but did not specify if they reported SGA by weight or length. Miyashita (2015) reported SGA by weight, birth length, chest circumference, and head circumference at birth. Wohlfahrt-Vege (2014) was the only study to report growth outcomes into early childhood. They reported weight and length (height) at 0, 3, 18, and 36 months. Analytic sample sizes ranged from 100 to 592.

To be included in the review, papers needed to report results of at least two of these three analyses:

1.) association between maternal fish/seafood intake and PCB levels;

2.) association between maternal fish/seafood intake and child outcomes; and,

3.) association between maternal PCB levels and child outcomes.

Halldorsson (2008) and Wohlfahrt-Vege (2014) reported results for 1.) associations between maternal fish/seafood intake and PCB levels and 3.) associations between maternal PCB levels and child outcomes. Mendez (2009) reported results for 1.) associations between maternal fish/seafood intake and PCB levels and 2.) associations between maternal fish/seafood intake and child outcomes. Miyashita (2015) reported results for all three associations.

Summary of findings

Associations between maternal seafood/fish intake and maternal PCB levels

All four studies found a significant positive association between maternal fish or seafood intake and maternal PCB levels. This was consistent regardless of indicator of PCB exposure (i.e., maternal whole blood, plasma, serum, or human milk).

Associations between maternal seafood/fish intake and child growth-related outcomes

Two of the studies examined the relationship between maternal seafood/fish exposure and child growth outcomes (Mendez, 2009; Miyashita, 2015). Mendez (2009) reported a significant association between increased prenatal crustacean consumption and increased odds of being small for gestational age. Other associations between seafood intake (by subtype) and birth weight or odds of small for gestational age were non-significant and mostly in the negative direction (i.e., greater seafood intake was associated with lower

birth weight or with greater risk of SGA). However, correlations between maternal fish intake and growth outcomes reported by Miyashita (2015) were non-significant in both directions.

Associations between maternal PCB levels and child growth-related outcomes

Three of the four studies examined an association between maternal PCB levels and child growth outcomes. The results were mixed both in terms of significance and direction. Halldorsson (2008) reported a significant negative association between maternal PCB levels and both birth weight and placental weight, while the associations between maternal PCB levels and birth length and head circumference were negative but not significant. Miyashita (2015) reported non-significant associations in both directions.

Wohlfahrt-Vege (2014) was the only study to look at growth outcomes over time. The only significant association at birth was between skinfold fat % and total toxic equivalents (TEQ) such that higher TEQ was associated with lower skinfold fat %; the associations between PCB (as TEQ) and birth weight and length were negative but not significant. The association between gestational age at birth and TEQ was not significant. Over time, there were significant positive associations between change in weight from 0-18 months with TEQ and change in height from 0-3 months, 0-18 months, and 0-36 months with TEQ suggesting a higher rate of catch-up growth.

Risk of bias assessments

Risk of bias was assessed for each included article using ROBINS-E for longitudinal cohort studies (**Table 7-3**). Mendez (2010) had an overall risk of bias rating of "some concerns," Halldorsson (2008) and Wohlfahrt-Vege (2014) were rated as high for risk of bias, and Miyashita (2015) was rated very high. The risk of bias generally stemmed from risk of bias due to confounding, measurement of the exposure (seafood/fish intake), missing data, and selection of the reported result.

Table 7-3. *Risk of bias assessments using ROBINS-E for studies on maternal exposure to seafood and PCBs and child growth-related outcomes.*

Cochrane ROBINS-E: Non-randomized studies of exposures (cohort studies)

Article	Overall risk of bias judgement	Risk of bias due to confounding	Risk of bias arising from measurement of the exposure	Risk of bias in selecting participants into the study (or analysis)	Risk of bias due to post-exposure interventions	Risk of bias due to missing data	Risk of bias arising from measurement of the outcome	Risk of bias in selection of the reported result
Halldorsson, 2008	High	Some Concerns	High	Some Concerns	Low	High	Low	High
Mendez, 2010	Some Concerns	High	Low	Low	Low	Low	Low	Low
Miyashita, 2015	Very High	High	High	Some Concerns	Low	High	Low	Very High
Wohlfahrt-Veje, 2014	High	High	Some Concerns	Some Concerns	Low	High	Low	High

Included articles

1. Halldorsson, T. I., Thorsdottir, I., Meltzer, H. M., Nielsen, F., Olsen, S. F. (2008). Linking exposure to polychlorinated biphenyls with fatty fish consumption and reduced fetal growth among Danish pregnant women: A cause for concern? American Journal of Epidemiology, 168(8), 958-965
2. Mendez, M. A., Plana, E., Guxens, M., Foradada Morillo, C. M., Albareda, R. M., Garcia-Esteban, R., Goni, F., Kogevinas, M., Sunyer, J. (2010). Seafood consumption in pregnancy and infant size at birth: Results from a prospective Spanish cohort Journal of Epidemiology and Community Health, 64(3), 216-222
3. Miyashita, C., Sasaki, S., Ikeno, T., Araki, A., Ito, S., Kajiwara, J., Todaka, T., Hachiya, N., Yasutake, A., Murata, K., Nakajima, T., Kishi, R. (2015). Effects of in utero exposure to polychlorinated biphenyls, methylmercury, and polyunsaturated fatty acids on birth size Science of the Total Environment, 533(#issue#), 256-265
4. Wohlfahrt-Veje, C., Audouze, K., Brunak, S., Antignac, J. P., Le Bizec, B., Juul, A., Skakkebaek, N. E.,Main, K. M. (2014). Polychlorinated dibenzo-p-dioxins, furans, and biphenyls (PCDDs/PCDFs and PCBs) in breast milk and early childhood growth and IGF1 Reproduction, 147(4), 391-399

Appendix

Appendix 1. Toxicology review: Screening decision tree

1. EXPOSURE/POPULATION:
What exposure is *measured* in…

Pregnant/lactating women:
Seafood/fish exposure: (list)
Toxicant exposure: (list)

Children:
Seafood/fish exposure: (list)
Toxicant exposure: (list)

Note: requires seafood **AND** toxicant exposures in 1 population group

→ Exposures not measured in pregnant/lactating women OR children → **EXCLUDE**: Population of exposure or species

→ No measurement of seafood/fish intake → **EXCLUDE**: Exposure – no seafood measure

→ No measurement of toxicant → **EXCLUDE**: Exposure – no toxicant measure

2. OUTCOME/POPULATION:
What outcome is *measured* in children: (list)

→ No outcome measurement in children → **EXCLUDE**: Population of outcome

3. ASSESSMENT TIMING:
Are the exposure and outcomes measured at or around the same time

→ Yes, measured at/around same time → **EXCLUDE**: Study design/Cross-sectional

4. ANALYSES OF EXPOSURES:

a.) Association between fish/seafood exposure and toxicant exposure, *and* (Association between fish/seafood exposure and outcome
and/or
Association between toxicant exposure and outcome)

OR

b.) Association between fish/seafood exposure and outcome
and
Association between toxicant exposure and outcome

→ **INCLUDE**

Fish/seafood exposure measured, but fish/seafood was not considered when assessing associations with toxicant exposure or outcome measure (e.g., reported as descriptive data; controlled for in analysis between toxicant exposure and outcome)

→ **EXCLUDE**: Exposure-seafood or toxicant; Outcome

Appendix 2. AMSTAR 2 tool

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)
- ☐ Timeframe for follow-up

- ☐ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, *and*
- ☐ a plan for investigating causes of heterogeneity
- ☐ justification for any deviations from the protocol

- ☐ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
- ☐ *Explanation for* including only RCTs
- ☐ OR *Explanation for* including only NRSI
- ☐ OR *Explanation for* including both RCTs and NRSI

- ☐ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):
- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):
- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:
- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☐ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

☐ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:

- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:

- ☐ from confounding, *and*
- ☐ from selection bias

For Yes, must also have assessed RoB:

- ☐ methods used to ascertain exposures and outcomes, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

- ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

☐ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  - ☐ AND investigated the causes of any heterogeneity

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
  - ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  - ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  - ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Supplemental file list

Supplemental file 2-1. Seafood consumption during pregnancy and lactation and neurocognitive development in the child – A systematic review: Data files

Supplemental file 2-2. Seafood consumption during pregnancy and lactation and neurocognitive development in the child – A systematic review: Risk of bias assessment results

Supplemental file 2-3. Seafood consumption during pregnancy, lactation, childhood and adolescents and neurocognitive development in the child – Full text excluded articles with rationale

Supplemental file 3-1. Seafood consumption during childhood and adolescence and neurocognitive development in the child – A systematic review: Data files

Supplemental file 3-2. Seafood consumption during childhood and adolescence and neurocognitive development in the child – A systematic review: Risk of bias assessment results

Supplemental file 4-1. Seafood toxicant exposure during pregnancy, lactation, and childhood and child growth and development – A preliminary scoping review: Data files

Supplemental file 4-2. Seafood toxicity during pregnancy, lactation, childhood and adolescents and child health and development outcomes – Special categories of excluded articles

Supplemental file 4-3. Seafood toxicity during pregnancy, lactation, childhood and adolescents and child health and development outcomes – Full text excluded articles with rationale

Supplemental file 5-1. Seafood and mercury exposure during pregnancy, lactation, and childhood and child growth and development – Identifying existing systematic reviews: Data files

Supplemental file 6-1. Maternal seafood and lead exposure during pregnancy or lactation and child development outcomes – A systematic review: Data files

Supplemental file 7-1. Maternal seafood and PCB exposure during pregnancy or lactation and child growth outcomes – A systematic review: Data files