INPLASY PROTOCOL

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None declared.

A systematic review of epidemiological studies on the association between organophosphate flame retardants and neurotoxicity

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Review question / Objective: **This study aims to collect published or unpublished related studies systematically and comprehensively, and screen out the articles that meets the quality standards for qualitative combination, so as to draw a relatively reliable comprehensive conclusion on the relationship of organophosphate flame retardants (OPFRs) with neurodevelopmental toxicity.**
Eligibility criteria: **In brief, epidemiological studies including cohort study, case-control study and cross-sectional survey were screened. Studies regarding relationships between human exposure to organophosphate esters and neurotoxicity were possible eligible for the present systematic review. The adverse neurodevelopmental outcomes included development of cognition, behavior, motor, brain change, emotion, etc. Studies that did not meet the above criteria were not included in this systematic review.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 May 2022 and was last updated on 13 May 2022 (registration number INPLASY202250083).

INTRODUCTION

Review question / Objective: **This study aims to collect published or unpublished related studies systematically and comprehensively, and screen out the articles that meets the quality standards for qualitative combination, so as to draw a relatively reliable comprehensive conclusion on the relationship of organophosphate flame retardants (OPFRs) with neurodevelopmental toxicity.**

Condition being studied: **Association between organophosphate flame retardants and neurotoxicity. We conducted the systematic literature search using databases including MEDLINE (accessed**

through PubMed), Web of Science, and CNKI (Chinese National Knowledge Infrastructure) on February 16, 2022.

METHODS

Search strategy: The word "organophosphate ester" and their variants combined with "neurobehavioral", "neurodevelopment", "cognitive", "cognition", "behavior", "attention deficit", "autism", "motor", "neuroimaging", "brain imaging", "anxiety", and "depression" were used for literature search.

Participant or population: Human.

Intervention: OPFR exposure.

Comparator: A comparison population exposed to lower levels or no exposure/ exposure below detection levels, or with different levels of target outcome group, or no target disease control group.

Study designs to be included: All observational studies including cohort study, case-control study, case-cohort study and cross-sectional survey.

Eligibility criteria: In brief, epidemiological studies including cohort study, case-control study and cross-sectional survey were screened. Studies regarding relationships between human exposure to organophosphate esters and neurotoxicity were possible eligible for the present systematic review. The adverse neurodevelopmental outcomes included development of cognition, behavior, motor, brain change, emotion, etc. Studies that did not meet the above criteria were not included in this systematic review.

Information sources: We conducted the systematic literature search using databases including MEDLINE (accessed through PubMed), Web of Science, and CNKI (Chinese National Knowledge Infrastructure) on February 16, 2022. The word "organophosphate ester" and their variants combined with "neurobehavioral", "neurodevelopment", "cognitive", "cognition", "behavior", "attention deficit", "autism", "motor", "neuroimaging", "brain imaging", "anxiety", and "depression" were used for literature search. According to a prespecified spreadsheet, two authors (Jing-yi Zhao and Zi-yang Zhan) abstracted information on first author, year of publication, country, study design, sample size, population source, species of organophosphate flame retardants and their metabolites, biological metrics of exposure measurement, concentrations of organophosphate esters, outcomes of interested, scales of outcome measurement, confounders, and primary findings, respectively. When the extraction content was inconsistent, it is decided by the other two authors (Meng-juan Lu and Hui Gao) after discussion. Two authors (Hui Gao and Meng-juan Lu) independently assessed the risk of bias of the original included study, using a modified instrument (Supplemental Material, Table S3) on basis of the Cochrane Collaboration's "Risk of Bias" tool. Jing-yi Zhao and Zi-xiang Zhan worked equally to this work and assigned as the first authors. Meng-Juan was assigned as one of co-authors. Lu Fang-biao Tao, De Wu and Hui Gao worked equally to this work and assigned as the corresponding authors.

Main outcome(s): The present systematic review suggested that OPFR exposure were negatively associated with childhood cognition including a decrease in intelligence quotient, working memory, fine motor, psychomotor and mental development; OPFR exposure increased the risk of externalizing problems including attention deficiency, hyperactivity and withdrawal), but decreased the risk of internalizing problems and anxiety.

Quality assessment / Risk of bias analysis: Two authors (Hui Gao and Meng-juan Lu) independently assessed the risk of bias of the original included study, using a modified instrument (Supplemental Material, Table S3) on basis of the Cochrane Collaboration's "Risk of Bias" tool. According to the prespecified criteria, selection bias, exposure assessment, outcome assessment, confounding, incomplete outcome data, selective

outcome reporting outcome, and other sources of bias were evaluated. The rating for the risk of bias in each domain was "low", "probably low", "probably high", "high" or "unknown". Any discrepancy was resolved by discussion between the two authors.

Strategy of data synthesis: A narrative synthesis of the results, with thematic analysis, was provided to identify key themes. A conceptual frame-work was constructed to guide the organization and presentation of results based on the content analysis for the identified themes.

Subgroup analysis: Stratified by different outcomes, including childhood cognition and behavior.

Sensitivity analysis: Stratified by different outcomes, including childhood cognition and behavior.

Language: English.

Country(ies) involved: China.

Keywords: organophosphate flame retardants; cognition; behavior; neurotoxicity; childhood.

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