National Toxicology Program
U.S. Department of Health and Human Services

LITERATURE SEARCH RESULTS FOR THE

SYSTEMATIC REVIEW OF FLUORIDE EXPOSURE AND NEURODEVELOPMENTAL AND COGNITIVE HEALTH EFFECTS

September 16, 2020

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Division of the National Toxicology Program
National Institute of Environmental Health Sciences

NOTICE:

This document contains the literature search and selection results for the systematic review of fluoride exposure and neurodevelopmental and cognitive health effects following the protocol[1]. It does not represent and should not be construed to represent any NTP determination or policy.

[1] https://ntp.niehs.nih.gov/go/785076

LITERATURE SEARCH RESULTS

Literature Search

Search terms were developed to identify all relevant published evidence on developmental neurobehavioral toxicity or thyroid-related health effects potentially associated with exposure to fluoride by reviewing Medical Subject Headings for relevant and appropriate neurobehavioral and thyroid-related terms, and by extracting key neurological and thyroid-related health effects and developmental neurobehavioral terminology from reviews and a sample of relevant primary data studies. A combination of relevant subject headings and keywords were subsequently identified. A test set of relevant studies was used to ensure the search terms retrieve 100% of the test set. Six electronic databases were searched (see) using a search strategy tailored for each database (specific search terms used for the PubMed search are presented in **Appendix 1**; the search strategy for other databases are available in the protocol (https://ntp.niehs.nih.gov/go/785076). A search of PubChem indicated that sodium fluoride was not found in either the Tox21 or ToxCast databases; therefore, these databases were not included in the search. No language restrictions or publication year limits were imposed, and databases were searched in December 2016, with several updated searches and a final updated search on April 1, 2019.

Following the peer review of the September 6, 2019 draft monograph in November 2019 by a committee convened by the National Academies of Sciences, Engineering and Medicine (NASEM) (NASEM 2020), an additional search was conducted on May 1, 2020, where only primary human epidemiology studies were prioritized during screening. The review of the 2020 search results focused on the human studies because they formed the basis of the conclusions in the September 6, 2019 draft. A supplemental literature search of Chinese-language databases (described below) was also conducted.

Literature searches for this systematic review were conducted independent of the literature search conducted for the NTP (2016) systematic review of animal studies. The current literature search strategy was based on the search terms used for NTP (2016) and refined for the current evaluation, including the addition of search terms to identify human studies. Although the review process identified studies prior to 2015, the current assessment did not evaluate the studies published prior to 2015 and relied on the NTP (2016) assessment. The focus of the literature searches for this systematic review was to identify and evaluate relevant animal studies that were published since completion of the literature searches for the NTP (2016) assessment in addition to the human and mechanistic data that were not previously evaluated.

Supplemental Chinese Database Literature Search

Following NASEM committee peer review in November 2019 (NASEM 2020), additional searches were developed for non-English-language databases to systematically search for studies that were previously identified from other resources (e.g., Chinese-language studies from the Fluoride Action Network website) and select non-English-language databases with the most potential to contain additional relevant non-English publications that were not previously identified. Multiple non-English language databases were explored before finding two databases (CNKI and Wanfang) that covered studies previously identified from other sources. These two Chinese electronic databases were searched in May 2020 with no language restrictions or publication year limits. Search terms from the main literature search were refined to focus on human epidemiology studies. The CNKI and Wanfang databases have character limits in the search strings; therefore, key terms were prioritized using text analytics to identify the most prevalent terms from neurodevelopmental or cognitive human epidemiology studies

previously identified as relevant. Search strings were designed to capture known relevant studies that were previously identified from searching other resources without identifying large numbers of non-relevant studies [the search strategy for both databases are available in the protocol (https://ntp.niehs.nih.gov/go/785076)]. New animal and mechanistic references retrieved were scanned for evidence that might extend the information currently in the September 6, 2019 draft. Although additional studies were identified, data that would materially advance the animal and mechanistic findings were not identified; therefore, these studies were not extracted nor were they added to the draft. Newly-retrieved human references were reviewed to identify studies that might impact conclusions with priority given to identifying and translating null studies that may have been missed using previous approaches. Null studies that were identified were translated and included.

Databases Searched

Main Literature Database Search

- BIOSIS (Thomson Reuters)
- EMBASE
- PsycINFO (APA PsycNet)
- PubMed (NLM)
- Scopus (Elsevier)
- Web of Science (Thomson Reuters, Web of Science indexes the journal Fluoride)

Supplemental Chinese Database Literature Search

- CNKI
- Wanfang

Searching Other Resources

The reference lists of all included studies; relevant reviews, editorials and commentaries; and the Fluoride Action Network website (http://fluoridealert.org/) were manually searched for additional relevant publications. Following NASEM committee peer review in November 2019 (NASEM 2020), the Fluoride Action Network website was again searched for relevant references and contacted to identify null or no effect studies.

Tracking Study Eligibility and Reporting the Flow of Information

The main reason for exclusion at the full-text-review stage was annotated and reported in the study selection flow diagram (**Figure 1**) [using reporting practices outlined in Moher *et al.* (2009) The first reason for exclusion that the reviewers noted was documented, although studies may have multiple reasons for exclusion (e.g., both exposure and outcome not relevant). The following reasons for exclusion were documented (see **References Excluded After Full-Text Review**): (1) population not relevant; (2) exposure not relevant; (3) comparator not relevant; (4) outcome not relevant; (5) supporting information only (e.g., exposure assessment; absorption, distribution, metabolism, and excretion [ADME] study; review); (6) study retracted; (7) other (e.g., abstract, commentary, or editorial only); (8) animal in vivo and/or mechanistic-only studies from the 2020 searches; (9) human studies with secondary neurological outcomes only (anxiety, aggression, motor activity, or biochemical changes) from the 2020 searches; or (10) foreign language human studies with primary neurological outcomes (learning, memory, intelligence) not translated from the supplemental Chinese database literature search.

Literature Search Results

Literature Search Results Counts and Title and Abstract Screening

The electronic database searches retrieved 25,524 unique references in total (20,883 references during the initial search conducted in December 2016, 3,733 references during the literature search updates [including the final updated search conducted for the primary epidemiology studies on May 1, 2020], and 908 references from the supplemental Chinese database searches); 15 additional references were identified by technical advisors or from reviewing reference lists in published reviews and included studies. As a result of title and abstract screening, 1,038 references were moved to full-text review, 11,478 were excluded during manual title and abstract screening for not satisfying the PECO criteria, and an additional 13,023 were not screened and excluded based on the SWIFT algorithm.

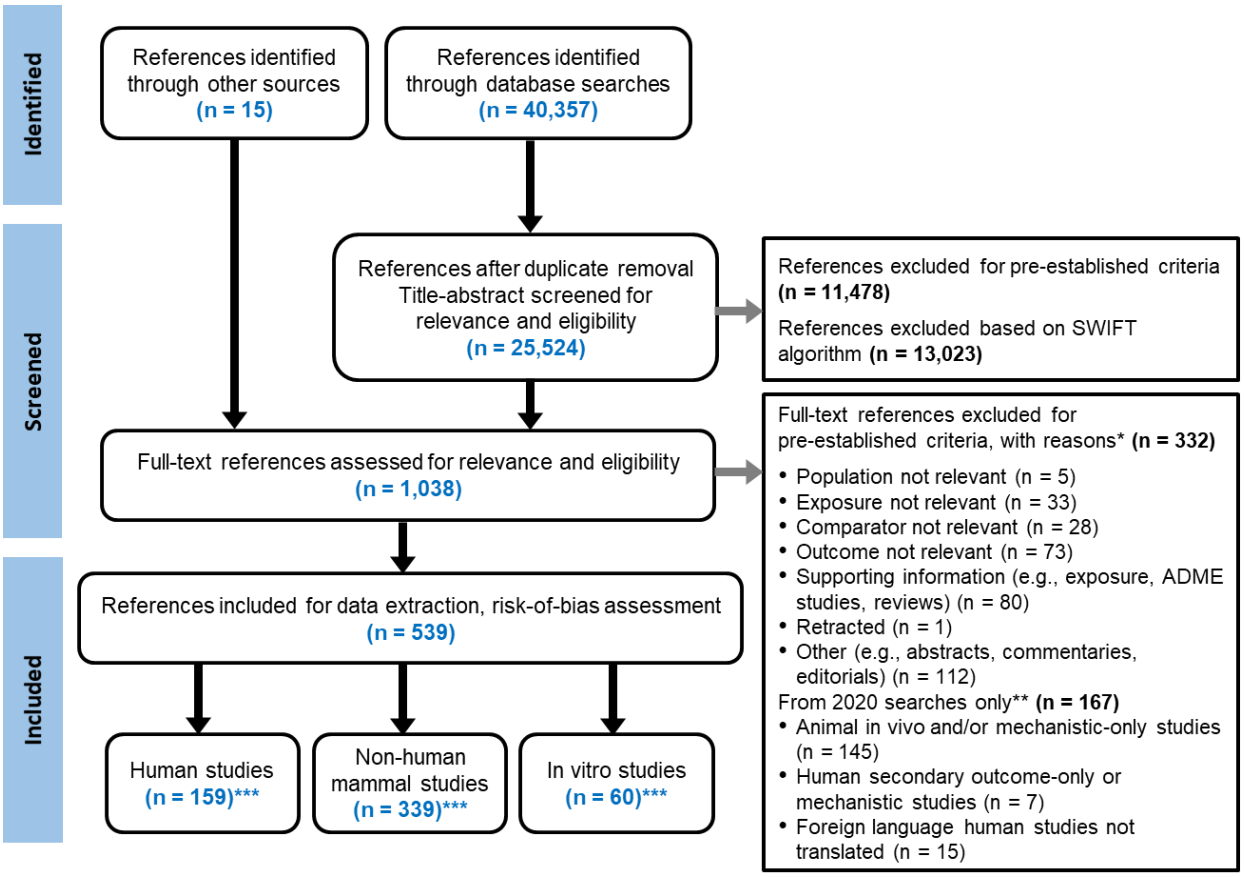
Full-text Review

Among the 1,038 references that underwent full-text review, 499 references were excluded during the full-text review with reasons for exclusion documented at this stage; 332 references were excluded for not satisfying the PECO criteria; and 167 references from the May 2020 searches (main literature search update and supplemental Chinese database searches) were excluded for not including information that would materially advance the human, animal in vivo, or mechanistic findings (see the Literature Search Section for a description of the methodology). These screening results are outlined in a study selection diagram that reports numbers of studies excluded for each reason at the full text review stage (see **Figure 1**) [using reporting practices outlined in Moher *et al.* (2009)]. After full-text review, 539 studies were considered relevant with primary neurological outcomes, secondary neurological outcomes, and/or outcomes related to thyroid function (see **References Included After Full-Text Review**). A few studies assessed data for more than one evidence stream (human, non-human mammal, and/or in vitro), and several human and animal studies assessed more than one type of outcome (e.g., primary and secondary outcomes). The number of included studies is summarized below.

- 159 human studies (78 primary only; 13 secondary only; 5 primary and secondary; 6 primary and thyroid; 2 secondary and thyroid; and 55 thyroid only);
- 339 non-human mammal studies (7 primary only; 186 secondary only; 67 primary and secondary; 6 primary, secondary, and thyroid; 4 secondary and thyroid; and 69 thyroid only); and
- 60 in vitro/mechanistic studies (48 neurological and 12 thyroid).

One publication contained human, experimental non-human mammal, and in vitro data. Three publications contained both human and experimental non-human mammal data. Fourteen publications contained data relevant to both experimental non-human mammal studies and in vitro studies. The lists of included and excluded references are provided in the subsequent sections.

Figure 1. Study Selection Diagram



* Studies may have been excluded for more than one reason; the first reason identified by the screener was recorded.

** Animal in vivo, human secondary outcome-only, and human and animal mechanistic references from the 2020 database searches were scanned for evidence that might strengthen the information in the September 6, 2019 draft monograph. Although 145 additional animal in vivo and/or mechanistic studies and 7 additional human secondary outcome-only or mechanistic-only studies were identified, information that would materially advance the human, animal in vivo, and mechanistic findings was not identified; therefore, these studies were not included. Additionally, 15 human primary outcome studies from the 2020 Chinese database search were excluded based on English abstracts and google translations because information that would materially advance the human findings was not identified; 1 null publication from the 2020 Chinese database search (Kang *et al.* 2011) as identified, translated, and included.

*** One publication contained human, experimental non-human mammal, and in vitro data. Three publications contained both human and experimental non-human mammal data. Fourteen publications contained data relevant to both experimental non-human mammal studies and in vitro studies.

REFERENCES INCLUDED AFTER FULL-TEXT REVIEW

List of Included Studies

Studies in Humans

As described in **Figure 1**, 159 human studies were included; however, full data extraction was only conducted on studies with neurological outcomes or thyroid hormone data. Data extraction was completed using the Health Assessment Workspace Collaborative (HAWC), an open source and freely available web-based interface application.[2] Data were extracted from a subset of included studies in humans (n = 116) and are available in HAWC based on outcome. The following lists of references are organized as studies that are available in HAWC followed by studies that are not available in HAWC. Specifically, data for primary neurodevelopmental or cognitive outcomes (learning, memory, and intelligence) and secondary neurobehavioral outcomes (anxiety, aggression, motor activity, or biochemical changes), as well as thyroid hormone level data, were extracted from included human studies and are available in HAWC. Data for included studies identified through the 2020 literature search update were only extracted for primary neurodevelopmental or cognitive outcomes; a subset of these studies (n = 5) also included secondary neurobehavioral outcomes and/or thyroid hormone level data that were not extracted because those data would not materially advance the human or mechanistic findings. Included human studies that only evaluated other thyroid-related effects including goiters or thyroid size (n = 43) were not extracted and are not available in HAWC.

Studies Available in HAWC

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[2] HAWC (Health Assessment Workspace Collaborative): A Modular Web-based Interface to Facilitate Development of Human Health Assessments of Chemicals (https://hawcproject.org/portal/).

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Studies in Non-human Animals

As described in **Figure 1**, 339 non-human animal studies were included; however, full data extraction was only conducted on studies with primary neurological outcomes and/or secondary functional neurological outcomes (e.g., motor activity). Data extraction was completed using HAWC. Data were extracted from a subset of included studies in animals (n = 123) and are available in HAWC based on outcome. The following lists of references are organized as studies that are available in HAWC followed by studies that are not available in HAWC. Specifically, all primary outcomes and functional neurological secondary outcomes (e.g., motor activity) were extracted from animal studies and are available in HAWC, including studies from the NTP (2016) assessment. Studies are also available in HAWC that evaluated mechanistic effects related to oral fluoride exposure at or below 20 ppm fluoride drinking water equivalents for categories of mechanistic endpoints with the largest amount of available data (i.e., biochemistry of the brain or neurons, neurotransmission, oxidative stress, and histopathology [n = 70]); however, these mechanistic data were generally not extracted. Several animal studies assessed primary neurological outcomes and/or functional neurological secondary outcomes and mechanistic effects in the four mechanistic categories listed above (n = 56). In total, 140 animal studies are available in HAWC (70 with primary neurological outcomes and/or secondary functional neurological outcomes without relevant mechanistic data; 15 with relevant mechanistic data only; and 55 with primary/or secondary functional neurological outcomes with relevant mechanistic data). Studies that evaluated other mechanistic endpoints, as well as studies that only assessed mechanistic effects at fluoride levels above 20 ppm fluoride drinking water equivalents, are not available in HAWC (n = 199).

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In Vitro Experimental Studies

As described in **Figure 1**, 60 in vitro experimental studies were included; however, data extraction was not conducted on in vitro studies. Therefore, in vitro experimental studies are not available in HAWC with the exception of in vitro studies that also reported in vivo non-human animal data that meet the relevant criteria for being made available in HAWC. The following lists of references are organized as studies that are available in HAWC (n = 6) followed by studies that are not available in HAWC (n = 54).

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List of Excluded Studies by Main Reasons[3]

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APPENDICES

Appendix 1. Literature Search Strategy

The strategy for this search is broad for the consideration of neurodevelopmental or cognitive endpoints and comprehensive for fluoride as an exposure or treatment in order to ensure inclusion of relevant papers. The search terms for PubMed are provided below. The specific search strategies for other databases are available in the protocol (https://ntp.niehs.nih.gov/go/785076).

Database	Search Terms
PUBMED	((Fluorides[mh:noexp] OR fluorides, topical[mh] OR sodium fluoride[mh] OR Fluorosis, Dental[mh] OR fluorosis[tiab] OR fluorid*[tiab] OR flurid*[tiab] OR fluorin*[tiab] OR florin*[tiab]) NOT (18F[tiab] OR f-18[tiab] OR 19F[tiab] OR f-19[tiab] OR f-labeled[tiab] OR "fluorine-18"[tiab] OR "fluorine-19"[tiab] OR pet-scan[tiab] OR radioligand*[tiab])) AND ((Aryl Hydrocarbon Hydroxylases[mh] OR Aryl Hydrocarbon Receptor Nuclear Translocator[mh] OR Behavior and Behavior Mechanisms[mh] OR Gene Expression Regulation[mh] OR Glucuronosyltransferase[mh] OR Intelligence tests[mh] OR Malate Dehydrogenase[mh] OR Mediator Complex Subunit 1[mh] OR Mental disorders[mh] OR Mental processes[mh] OR Monocarboxylic Acid Transporters[mh] OR Myelin Basic Protein[mh] OR nervous system[mh] OR nervous system diseases[mh] OR nervous system physiological phenomena[mh] OR Neurogranin[mh] OR Oligodendroglia[mh] OR Peroxisome Proliferator-Activated Receptors[mh] OR Psychological Phenomena and Processes[mh] OR Receptors, thyroid hormone[mh] OR Receptors, thyrotropin[mh] OR Retinoid X Receptors[mh] OR thyroid diseases[mh] OR thyroid hormones[mh] OR Thyrotropin-releasing hormone[mh] OR Thyroxine-Binding Proteins[mh] OR Pregnane X Receptor[supplementary concept] OR thyroid-hormone-receptor interacting protein[supplementary concept] OR Constitutive androstane receptor[supplementary concept] OR Academic performance[tiab] OR auditory[tiab] OR cortical[tiab] OR delayed development[tiab] OR developmental impairment[tiab] OR developmental-delay*[tiab] OR developmental-disorder*[tiab] OR euthyroid[tiab] OR gait[tiab] OR glia*[tiab] OR gliogenesis[tiab] OR hyperactiv*[tiab] OR impulse-control[tiab] OR iodide peroxidase[tiab] OR IQ[tiab] OR ischemi*[tiab] OR locomotor[tiab] OR mental deficiency[tiab] OR mental development[tiab] OR mental illness[tiab] OR mental-deficit[tiab] OR mobility[tiab] OR mood[tiab] OR morris-maze[tiab] OR morris-water[tiab] OR motor abilit*[tiab] OR Motor activities[tiab] OR motor performance[tiab] OR nerve[tiab] OR neural[tiab] OR neurobehav*[tiab] OR Neurocognitive impairment[tiab] OR neurodegenerat*[tiab] OR Neurodevelopment*[tiab] OR neurodisease*[tiab] OR neurologic*[tiab] OR neuromuscular[tiab] OR neuron*[tiab] OR neuropath*[tiab] OR obsessive compulsive[tiab] OR OCD[tiab] OR olfaction[tiab] OR olfactory[tiab] OR open-field-test[tiab] OR passive avoidance[tiab] OR plasticity[tiab] OR senil*[tiab] OR sociab*[tiab] OR speech*[tiab] OR spelling[tiab] OR stereotypic-movement*[tiab] OR synap*[tiab] OR tauopath*[tiab] OR Thyroglobulin[tiab] OR Thyroid disease*[tiab] OR thyroid gland[tiab] OR thyroid hormone*[tiab] OR thyronine*[tiab] OR visual motor[tiab] OR Visuospatial processing[tiab] OR water maze[tiab]) OR ((active-avoidance[tiab] OR ADHD[tiab] OR alzheimer*[tiab] OR amygdala[tiab] OR antisocial[tiab] OR anxiety[tiab] OR anxious[tiab] OR asperger*[tiab] OR attention deficit[tiab] OR autism[tiab] OR autistic[tiab] OR behavioral[tiab] OR behaviors[tiab] OR behavioural[tiab] OR behaviours[tiab] OR bipolar[tiab] OR cerebellum[tiab] OR cognition[tiab] OR cognitive[tiab] OR communication-disorder*[tiab] OR comprehension[tiab] OR cranial[tiab] OR dementia[tiab] OR dendrit*[tiab] OR dentate-gyrus[tiab] OR depression[tiab] OR dextrothyroxine[tiab] OR diiodothyronine*[tiab] OR diiodotyrosine[tiab] OR down syndrome[tiab] OR dyslexia[tiab] OR entorhinal cortex[tiab] OR epilep*[tiab] OR gangli*[tiab] OR goiter[tiab] OR graves-disease[tiab] OR hearing[tiab] OR hippocamp*[tiab] OR human development[tiab] OR hyperthyroid*[tiab] OR hypothalam*[tiab] OR hypothyroid*[tiab] OR impulsiv*[tiab] OR Intellectual disability[tiab] OR intelligence[tiab] OR language[tiab] OR learning[tiab] OR lewy bod*[tiab] OR

Database	Search Terms
	long-term potentiation[tiab] OR long-term synaptic depression[tiab] OR memory[tiab] OR mental disorder*[tiab] OR mental recall[tiab] OR monoiodotyrosine[tiab] OR Motor activity[tiab] OR motor skill*[tiab] OR multiple sclerosis[tiab] OR myxedema[tiab] OR Nervous system[tiab] OR nervous-system[tiab] OR neurit*[tiab] OR optic[tiab] OR palsy[tiab] OR panic[tiab] OR parahippocamp*[tiab] OR paranoia[tiab] OR paranoid[tiab] OR parkinson*[tiab] OR perception[tiab] OR perforant*[tiab] OR personality[tiab] OR phobia[tiab] OR problem solving[tiab] OR proprioception[tiab] OR psychomotor[tiab] OR reflex[tiab] OR risk taking[tiab] OR schizophrenia[tiab] OR seizure*[tiab] OR sensation*[tiab] OR sleep[tiab] OR smell[tiab] OR spatial behavior[tiab] OR stroke[tiab] OR substantia-nigra[tiab] OR taste[tiab] OR thyroiditis[tiab] OR thyrotoxicosis[tiab] OR Thyrotropin[tiab] OR thyroxine[tiab] OR triiodothyronine[tiab] OR vision[tiab]) NOT medline[sb]))

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