

OHAT EVALUATION OF THE STATE OF THE SCIENCE FOR TRANSGENERATIONAL INHERITANCE OF HEALTH EFFECTS

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BACKGROUND

There is evidence that early life exposures can lead to disease outcomes much later in life. The traditional dogma suggests that negative effects of these exposures are reset in each generation, such that subsequent generations are unaffected by the exposure history of their parents and grandparents. However, in certain cases, these exposures appear to have far-reaching consequences, affecting multiple generations removed from the original insult. This phenomenon is known as “transgenerational inheritance.” If the effects of exposure can indeed be transmitted to subsequent generations, this would have major public health implications. It is critical to determine how widespread and robust this phenomenon is, the factors that influence it, the mechanism by which it occurs, and the range of possible phenotypic outcomes (NIEHS 2012). To assist with this effort the DNTP Office of Health Assessment and Translation (OHAT) is initiating one or more evaluations using systematic review methodology to examine the state of the science for transgenerational inheritance of health effects associated with exposure to a wide range of stressors (e.g., environmental chemicals, drugs of abuse, nutrition and diet, pharmaceuticals, infectious agents, or stress).

The specific scope of the evaluation will be determined following a phase of exploratory screening of the literature and consideration of responses to this request for information (RFI). OHAT requests information on the proposed approach for conducting the exploratory screening of the literature and the identification of scientists with knowledge or expertise relevant to this topic. Specifically, this information will help to (1) refine the proposed literature search strategy (Appendix 1) and criteria used to conduct the exploratory screening; (2) identify potential areas of focus for the systematic review(s); (3) identify unpublished, ongoing, or planned studies related to transgenerational inheritance; and (4) identify scientists with expertise or knowledge in these areas who might be consulted during the course of conducting of the systematic reviews.

Future updates on this project, will be posted at <http://ntp.niehs.nih.gov/go/38159>. Individuals interested in receiving updates on this project are encouraged to register to the NTP Listserv (<http://ntp.niehs.nih.gov/go/getnews>)

OBJECTIVES

OHAT intends to conduct one or more systematic reviews to evaluate the state-of-the-science for transgenerational inheritance of health effects associated with exposure to a wide range of stressors (e.g., environmental chemicals, drugs of abuse, nutrition and diet,

pharmaceuticals, infectious agents, or stress). The evaluation will be used to help determine how widespread and robust this phenomenon is and to identify research needs.

METHODS

Criteria for Exploratory Screening of the Literature

Types of studies

There are no restrictions based on study design.

Types of model systems

Human, whole animal, and non-mammalian (e.g., fruit fly) studies on transgenerational inheritance.

- **Gestational Exposure:** In studies of prenatal exposure (F1 generation), assessment through at least the F3 generation after the prenatal exposure. When the exposure is prenatal both the F1 (the fetus) and the F2 (the primordial germ cells developing within the F1 fetus) are directly exposed to the stressor. Thus, true transgenerational inheritance must persist at least through the F3 generation after a prenatal exposure.
- **NON-Gestational Exposure:** Assessment through at least the F2 generation for exposures occurring outside of pregnancy, where the exposed generation is considered the F0. In studies of non-gestational exposure, the timing of exposure and gender of the F0 do not matter. Exposure can occur as an infant, child, teen, or adult (as long as the individual was not pregnant).

Types of exposures and interventions

There are no restrictions based on type of exposure. Studies of selective breeding [the process of breeding for a particular trait(s)] and genetic heritability will not be considered relevant.

Types of outcomes

Studies that focused on evaluating a health outcome will be considered most relevant.

Types of publications

Publication must be a peer-reviewed, full-length article or meet the guidelines for grey literature sources described below.

We will attempt to identify all relevant studies on this topic without language restrictions.

Search Methods for Identification of Studies

Electronic searches

Search terms have been identified by: (1) reviewing relevant reviews on similar topics that are identified by members of the research staff; (2) reviewing how other relevant studies are indexed, their subject heading terms, and their keywords; and (3) reviewing MeSH indexes for relevant and appropriate terms. After their review, a combination of subject headings and keywords were identified. When available, controlled vocabulary will be used in conjunction with text word search. [Appendix 1](#) shows the search terminology for PubMed.

- **Databases to be searched**

The following database will be searched for the exploratory screening:

- MEDLINE (PubMed, from 1948 to the present)

Preliminary results from the major databases (MEDLINE, WOS and SCOPUS) are greater than 140,000 studies; therefore, we will use MEDLINE results to identify relevant classes of exposure or stressors to structure the search for non-PubMed databases (ToxNet, Scopus, EMBASE, Web of Science, LILACS, Cochrane Database of Systematic Reviews). The search strategy will be tailored for each database.

Searching other resources

- **Handsearches**

Handsearches will not be done for any specific journals.

We will scan the bibliographies of the included studies and published reviews for relevant references.

- **Grey literature¹**

We will attempt to identify unpublished and ongoing studies from the research and other stakeholder communities through a public request for information advertised in the [Federal Register](#), NIH guide, and NTP listserv. We will also consult subject matter experts and agencies represented on the NTP Executive Committee² to potentially identify data that address this

¹ Refers to written material such as reports that are difficult to find via conventional channels such as published journals and monographs because they are not published commercially or are generally inaccessible. Examples of grey literature include patents, technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, and preprints (Wikipedia, accessed October 11, 2012)

² The NTP Executive Committee provides programmatic and policy oversight to the NTP Director. The Executive Committee meets once or twice a year in closed forum. Members of this committee include the heads (or their

topic. The NTP will only consider publically available information. If a study that may be critical to the evaluation has not been peer reviewed, the NTP can have it peer reviewed through the use of experts if the owners of the data are willing to have the study made publically accessible. Any potential peer reviewers would be screened for conflict of interest prior to confirming them for service.

Grey literature, including meeting abstracts and unpublished data from personal author communication, may be included to supplement a peer-reviewed publication, but a study that is entirely unpublished or otherwise not peer-reviewed will not be considered.

Data collection and analysis

Selection of studies

Articles will be reviewed first at the title and abstract level by two members of the review team. Screeners will not be blinded to the names of the original authors, journals, or institutions. Any articles possibly meeting the inclusion criteria will be obtained for full text review. Any disagreements among the 2 screeners will be resolved by discussion, involving a third member of the review team where necessary. In cases where the title and abstract describe clearly that a study does not address the inclusion criteria, it will not be considered further.

Use of screening data to refine scope of future systematic review(s)

Studies considered relevant based on the above inclusion criteria will then be categorized as to the nature of the exposure, health outcome, and evidence stream (human, animal, non-mammalian model system, or mechanistic). The outcome of this categorization process will be used to refine the scope of any future systematic review(s) activity.

REFERENCES

NIEHS (National Institute of Environmental Health Sciences) Funding Opportunity: Transgenerational Inheritance in Mammals After Environmental Exposure (TIME) (R01)(RFA-ES-12-006). 2012. Available: <http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-12-006.html> [accessed 29 October 2012]

designees) from the following federal agencies: Consumer Product Safety Commission (CPSC), Department of Defense (DoD), US Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Cancer Institute (NCI), National Center for Environmental Health/Agency for Toxic Substances and Disease Registry (NCEH/ATSDR), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA).

APPENDIX 1: DRAFT LITERATURE SEARCH METHOD

Appendix 1. Draft Literature Search Method for PubMed	
#1	Transgeneration*[tiab] OR trans-generation*[tiab]
#2	multigeneration*[tiab] OR multi-generation*[tiab] OR intergeneration*[tiab] OR inter-generation*[tiab]
#3	(F2 OR "F 2" OR "F(2)" OR F3 OR "F 3" OR "F(3)" OR F4 OR "F 4" OR "F(4)" OR F5 OR "F 5" OR "F(5)" OR F6 OR "F 6" OR "F(6)" OR F7 OR "F 7" OR "F(7)" OR F8 OR "F 8" OR "F(8)" OR F9 OR "F 9" OR "F(9)" OR F10 OR "F 10" OR "F(10)") AND (generation*[tiab] OR offspring[tiab] OR progeny[tiab])
#4	"two generations"[tiab] OR "second generation"[tiab] OR "second generations"[tiab] OR "three generations"[tiab] OR "third generation"[tiab] OR "third generations"[tiab] OR "four generations"[tiab] OR "fourth generation"[tiab] OR "fourth generations"[tiab] OR "five generations"[tiab] OR "fifth generation"[tiab] OR "fifth generations"[tiab]
#5	Greatgrandparent*[tiab] OR "Great Grandparent"[tiab] OR "Great Grandparents"[tiab] OR "Great Grand Parent"[tiab] OR "Great Grand Parents"[tiab] OR Greatgrandfather*[tiab] OR "Great Grandfather"[tiab] OR "Great Grandfathers"[tiab] OR "Great Grand Father"[tiab] OR "Great Grand Fathers"[tiab] OR Greatgrandmother*[tiab] OR "Great Grandmother"[tiab] OR "Great Grandmothers"[tiab] OR "Great Grand Mother"[tiab] OR "Great Grand Mothers"[tiab] OR Greatgrandchild*[tiab] OR "Great Grandchild"[tiab] OR "Great Grandchildren"[tiab] OR "Great Grand Child"[tiab] OR "Great Grand Children"[tiab] OR Greatgrandson*[tiab] OR "Great Grandson"[tiab] OR "Great Grandsons"[tiab] OR "Great Grand Son"[tiab] OR "Great Grand Sons"[tiab] OR Greatgranddaughter*[tiab] OR "Great Granddaughter"[tiab] OR "Great Granddaughters"[tiab] OR "Great Grand Daughter"[tiab] OR "Great Grand Daughters"[tiab] OR Grandparent* [tiab] OR "Grand Parent"[tiab] OR "Grand Parents"[tiab] OR Grandfather* [tiab] OR "Grand Father"[tiab] OR "Grand Fathers"[tiab] OR Grandmother*[tiab] OR "Grand Mother"[tiab] OR "Grand Mothers"[tiab] OR Grandchild*[tiab] OR "Grand Child"[tiab] OR "Grand Children"[tiab] OR Granddaughter*[tiab] OR "Grand Daughter"[tiab] OR "Grand Daughters"[tiab] OR Grandson*[tiab] OR "Grand Son"[tiab] OR "Grand Sons"[tiab]

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#6	"successive generation"[tiab] OR "successive generations"[tiab] OR "later generation"[tiab] OR "later generations"[tiab] OR "subsequent generation"[tiab] OR "subsequent generations"[tiab] OR "several generations"[tiab] OR "consecutive generations"[tiab] OR "future generations"[tiab] OR "across generations"[tiab] OR "multiple generations"[tiab] OR "successive offspring"[tiab] OR "successive progeny"[tiab] OR "later offspring"[tiab] OR "later progeny"[tiab] OR "subsequent offspring"[tiab] OR "subsequent progeny"[tiab] OR "consecutive offspring"[tiab] OR "consecutive progeny"[tiab] OR "future offspring"[tiab] OR "future progeny"[tiab]
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