

## **Transgenerational Inheritance of Health Effects: A State-of-the-Science Evaluation**

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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 consequences affecting multiple generations removed from the original insult. This phenomenon is termed “transgenerational inheritance.”

The Office of Health Assessment and Translation (OHAT) conducted a state-of-the-science evaluation to examine the extent of the evidence 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) in humans or non-human animals. Transgenerational inheritance of health effects is a long-standing topic of interest for NIEHS and also overlaps with the institute’s interest in epigenetics. Epigenetics emerged as a key theme in the NIEHS strategic plan (<http://www.niehs.nih.gov/about/strategicplan/>) and OHAT is currently preparing a scoping review of the epigenetics literature. The transgenerational inheritance and epigenetics projects are intended to be complementary, and together address the general phenomenon of transgenerational inheritance by focusing separately on the evidence for potential health effects and the mechanisms.

This state-of-the-science review was developed using the OHAT approach for conducting literature-based health assessments, to examine the evidence for transgenerational inheritance of health effects associated with exposure to a wide range of stressors in humans and animals. This review systematically collected and categorized the literature to develop a systematic evidence map for transgenerational inheritance by broad health effect categories, exposures, types of evidence, and identified areas of consistency, uncertainty, data gaps and research needs. In addition, a subset of studies were assessed for risk of bias (internal validity) to examine general bias and study quality issues for the transgenerational study design. The evaluation protocol is available on the Transgenerational Inheritance of Health Effects page on the NTP website<sup>1</sup>.

We identified 49 human and 232 animal studies with a transgenerational study design and developed summary tables. Data extraction was managed with structured forms and stored in a database format using the Health Assessment Workspace Collaborative (HAWC, <https://hawcproject.org>) tool, an open source and freely available web-based interface application. Most exposures were to environmental chemicals; however, exposures ranged from non-chemical stressors such as food availability and the experience of the Holocaust to drugs of abuse, pharmaceuticals and radiation.

Many studies reported transgenerational effects; however, datasets are limited for reaching conclusions on consistency of the findings given the heterogeneity of the data (i.e., there are few bodies of evidence or groups of studies for which the same exposure and health effect were studied). In addition, the example datasets examined for risk of bias suggest issues in study design and conduct (e.g., failure to consider the litter as the unit of analysis) that would present limitations in the body of evidence to support conclusions on potential transgenerational health effects.

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<sup>1</sup> State of the Science Evaluation for Transgenerational Inheritance of Health Effects:  
<https://ntp.niehs.nih.gov/pubhealth/hat/noms/trans/index.html>

This state of the science review provides a summary of the current literature base and indicates potential areas that would benefit from further study. Rather than additional studies on a wide range of exposures, targeted research addressing inconsistencies identified in this review using study design and conduct practices to minimize bias would help to establish bodies of evidence needed to critically assess transgenerational effects.

Data extracted from the individual studies in this evaluation are available in HAWC and provides researchers open access to the included studies. In addition, future studies should consider changes to study design, conduct, and reporting to minimize the risk of bias issues that were common in the subset of studies examined. Specifically, future transgenerational studies should control for litter effects, standardize the age at outcome assessment, randomize treatment, and blind the outcome assessors to treatment groups.