



NTP
National Toxicology Program

National Toxicology Program:

Evaluation of Reproductive and Developmental Hazards

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Outline

- Introduction to the National Toxicology Program
- Center for the Evaluation of Risks to Human Reproduction (CERHR)
 - Types of conclusions
 - Process for conducting evaluations
 - Examples
- Office Health Assessment and Translation (OHAT)
 - Comparison with CERHR
 - Process for conducting evaluations



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National Toxicology Program (NTP)





NTP

- Interagency program established in 1978
- Headquartered administratively at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC
- NIEHS director is NTP director
 - Director is Linda S. Birnbaum, Ph.D., DABT, ATS
 - Associate Director is John R. Bucher, Ph.D., DABT
- Mission
 - *Evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology*
- Information and/or data for meetings, workshops, reports, studies, etc. is available at <http://ntp.niehs.nih.gov>

National Toxicology Program, DHHS

Assistant Secretary for Health

Policy Oversight

NTP Executive Committee

- CPSC
- EPA
- FDA
- NCEH/ATSDR
- DoD
- NCI
- NIEHS
- NIOSH
- OSHA

Director
NIEHS and NTP

FDA

NIH
NIEHS

CDC
NIOSH

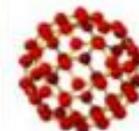
Science Oversight (External)

- NTP Board of Scientific Counselors
- Scientific Advisory Committee on Alternative Toxicological Methods

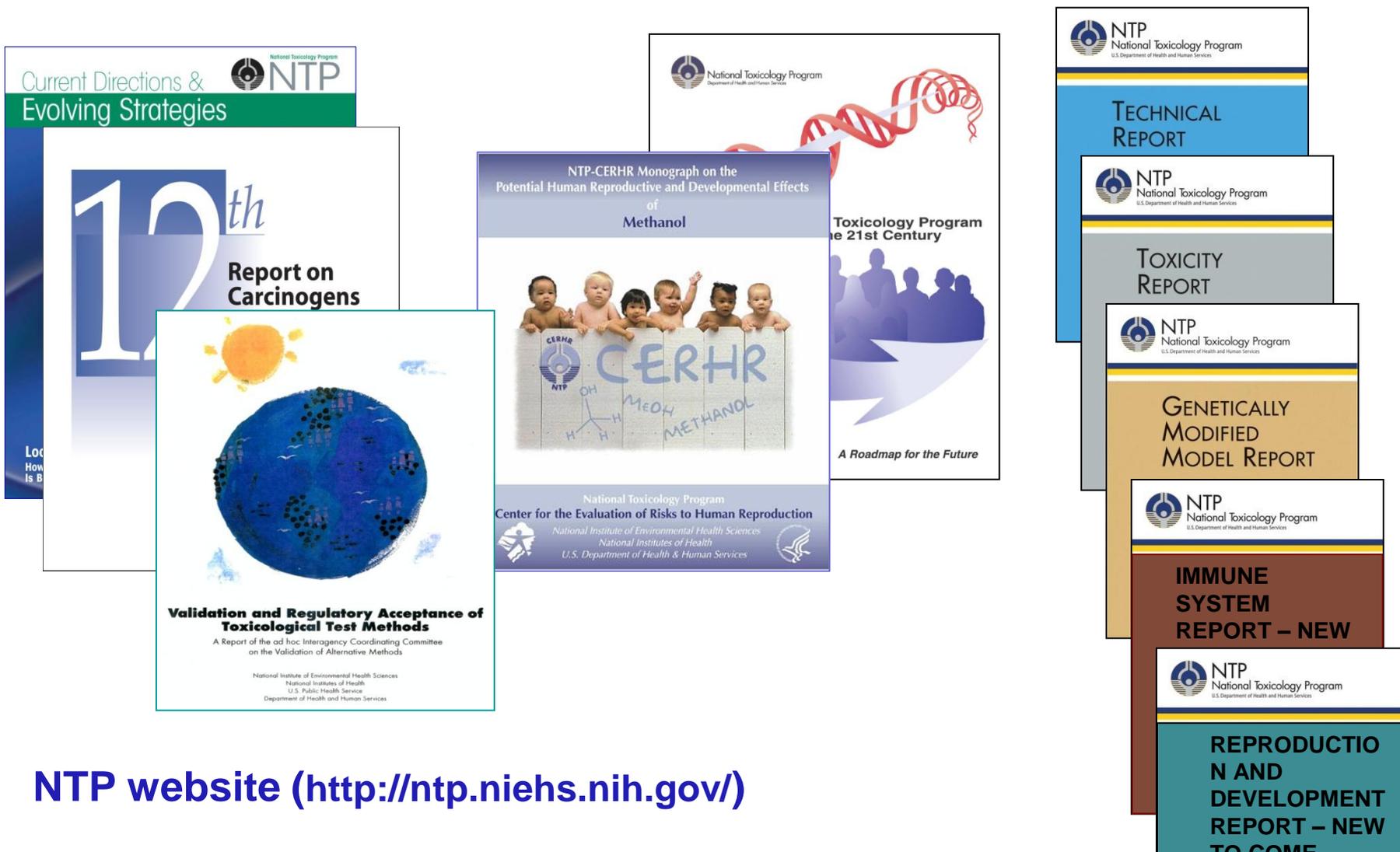


NTP carries out

- Research / testing activities
 - Thousands of substances evaluated
 - Comprehensive toxicology studies
 - High and medium throughput screening assays
 - Scope and types of studies dictated by the data needs for the specific substance
- Analysis activities
 - Report on Carcinogens
 - List of *known* and *reasonably anticipated carcinogens*
 - Non-cancer health assessments
 - Development and validation of alternative test methods



NTP communicates information through

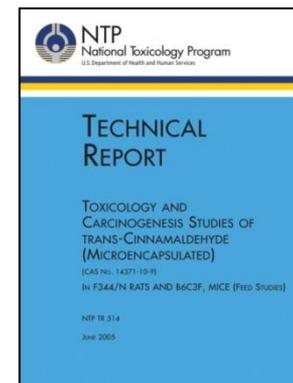


NTP website (<http://ntp.niehs.nih.gov/>)



NTP Reports for Identification of Cancer Hazards

- Report on Carcinogens
 - Congressionally mandated listing of *known* and *reasonably anticipated human carcinogens*
 - Specific criteria for listing approved by the Secretary of the Department of Health and Human Services
 - Multistep review process with public comment and peer review
- NTP Technical Reports of toxicology and carcinogenicity studies
 - Usually conducted in rats and mice, males and females
 - Five-tiered hierarchy for evaluating level of evidence of carcinogenic activity of substance
 - Draft report peer reviewed in public meeting; opportunity for public comment



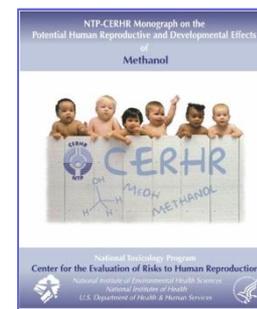
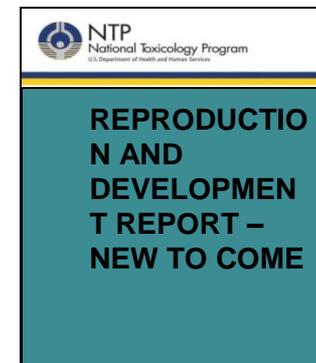


NTP Reports for Identification of Reproductive and Developmental Hazards

- New NTP technical report series planned for NTP studies of reproduction and development
 - NTP has developed a five-tiered hierarchy to classify the outcomes of its studies consistent with criteria for cancer studies [<http://ntp.niehs.nih.gov/go/33690>]
 - “Level of evidence” criteria categorize the study outcomes for
 - Reproductive toxicity
 - Developmental toxicity



- Draft reports will undergo public comment and peer review
 - Open meeting and multidiscipline experts as reviewers
- NTP-CERHR Monographs





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**Center for the Evaluation of Risks to Human
Reproduction (CERHR)
1998-2010**





CERHR

- Established in 1998; operated through 2010; name changed in 2011
- Selected chemicals, agents, mixtures, or exposure circumstances (“substances”) for evaluation based on
 - Production volume, potential for human exposure, extent of public concern, and extent of available literature with applicable data
- Published NTP-CERHR monographs that
 - Assess the evidence whether environmental substances cause adverse effects on reproduction and development [Phase 1: hazard identification]
 - Provide opinion on whether these substances may be of concern given what is known about current human exposure levels [Phase 2: level of concern]
- 19 monographs published
 - industrial chemicals, drugs, phthalates, and bisphenol A

*NTP Center for the Evaluation of
Risks to Human Reproduction*





Hazard Identification

- 7-point hazard identification scale
- Weight of evidence from human and experimental animal data considered separately
- Conclusions reached on case by case basis



CLEAR Evidence

of adverse effects



SOME Evidence

of adverse effects



LIMITED Evidence

of adverse effects



INSUFFICIENT Evidence

for a conclusion



LIMITED Evidence

of no adverse effects



SOME Evidence

of no adverse effects



CLEAR Evidence

of no adverse effects



Level of Concern Conclusions

- 5-category scale + 1 category for insufficient data
- Integration of weight of evidence for
 - Adverse developmental/reproductive effects in humans and experimental animals
 - Extent of current human exposure
 - Other factors, such as those considered in extrapolating data in animals to humans (e.g., pharmacokinetics)
- Conclusions on the potential for adverse effects on human reproduction or development
 - Evaluation can have different conclusions for different effects, life stages, or levels of exposure



SERIOUS Concern

for adverse effects



CONCERN

for adverse effects



SOME Concern

for adverse effects



MINIMAL Concern

for adverse effects



NEGLIGIBLE Concern

for adverse effects



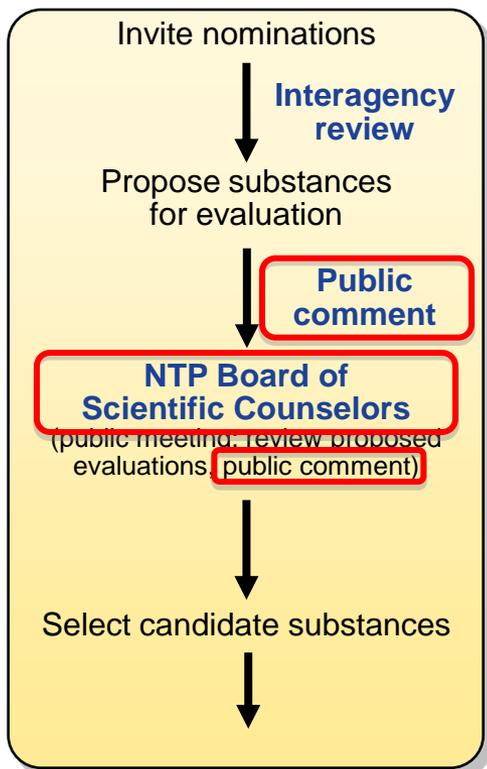
INSUFFICIENT DATA

on hazard and/or exposure

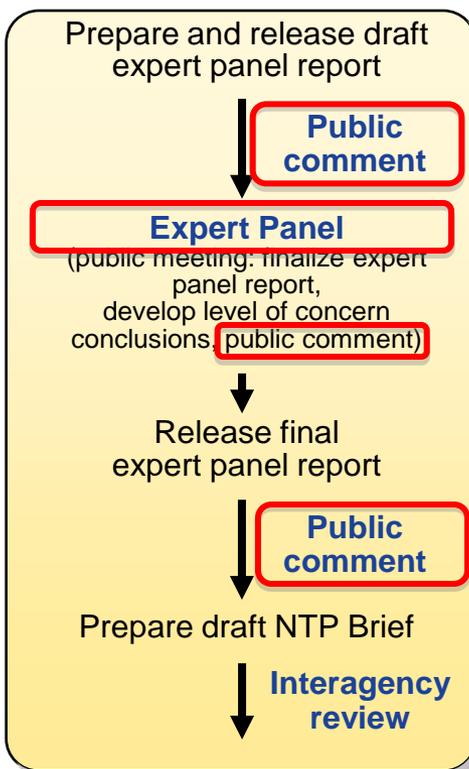


Preparation of NTP-CERHR Monographs followed an established process (external scientific input, public comments, and peer review)

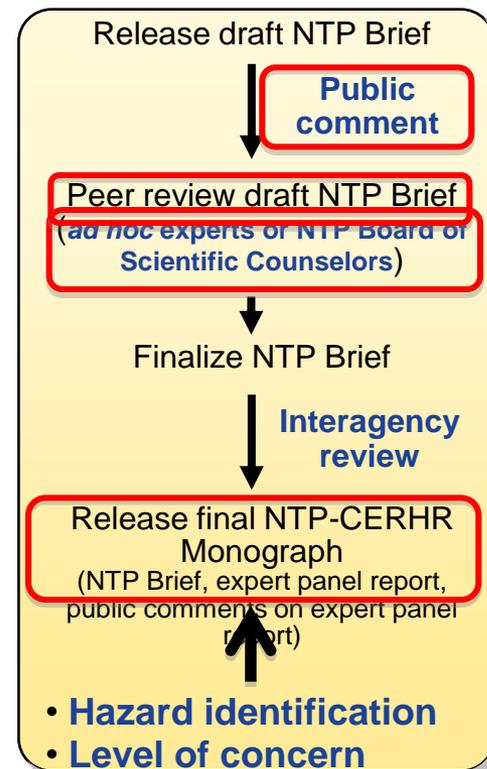
Nominations and Selection of Candidate Substances



Scientific Evaluation of Candidate Substances



Peer Review and Release of NTP Monograph



Example: Di(2-Ethylhexyl) Phthalate (2006)

Weight of evidence for developmental and reproductive toxicity

Extent of human exposure and other factors

Level of concern

Laboratory animals
(developmental effects on male reproductive tract, 14-23 mg/kg/d to dam)

Humans
(few studies)

-  **CLEAR Evidence**
of adverse effects
-  **SOME Evidence**
of adverse effects
-  **LIMITED Evidence**
of adverse effects
-  **INSUFFICIENT Evidence**
for a conclusion
-  **LIMITED Evidence**
of no adverse effects
-  **SOME Evidence**
of no adverse effects
-  **CLEAR Evidence**
of no adverse effects

+

Human exposure
Estimated up to 6 mg/kg bw/day in neonates and infants undergoing extensive medical procedures

=

Critically ill male infants

-  **SERIOUS Concern**
for adverse effects
-  **CONCERN**
for adverse effects
-  **SOME Concern**
for adverse effects
-  **MINIMAL Concern**
for adverse effects
-  **NEGLIGIBLE Concern**
for adverse effects
-  **INSUFFICIENT DATA**
on hazard and/or exposure



Clear Evidence of Hazard in CERHR Evaluations

- Chemicals with clear evidence of adverse effects in NTP-CERHR Monographs
 - Acrylamide (developmental and reproductive toxicity)
 - Bisphenol A (developmental toxicity at “high” dose)
 - 1-bromopropane (developmental and reproductive toxicity)
 - 2-bromopropane (reproductive toxicity at “high” dose)
 - Butyl benzyl phthalate (developmental toxicity)
 - Di-*n*-butyl phthalate (developmental and reproductive toxicity)
 - Di-*n*-hexyl phthalate (reproductive toxicity)
 - Di-isodecyl phthalate (developmental toxicity)
 - Genistein (developmental toxicity)
 - Methanol (developmental toxicity)



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**Office of Health Assessment and Translation
(OHAT) (2011 – present)**





CERHR

- Scope of evaluations is reproduction and development
- End product is NTP-CERHR Monograph
 - NTP Brief and expert panel report
- Set evaluation process
 - Expert panel and public comment
- Evaluation has 2 phases:
 - Hazard identification: 7-tier hierarchy for conclusions; weight of evidence of human and animal data considered separately
 - Level of concern: 5-tier hierarchy for conclusions

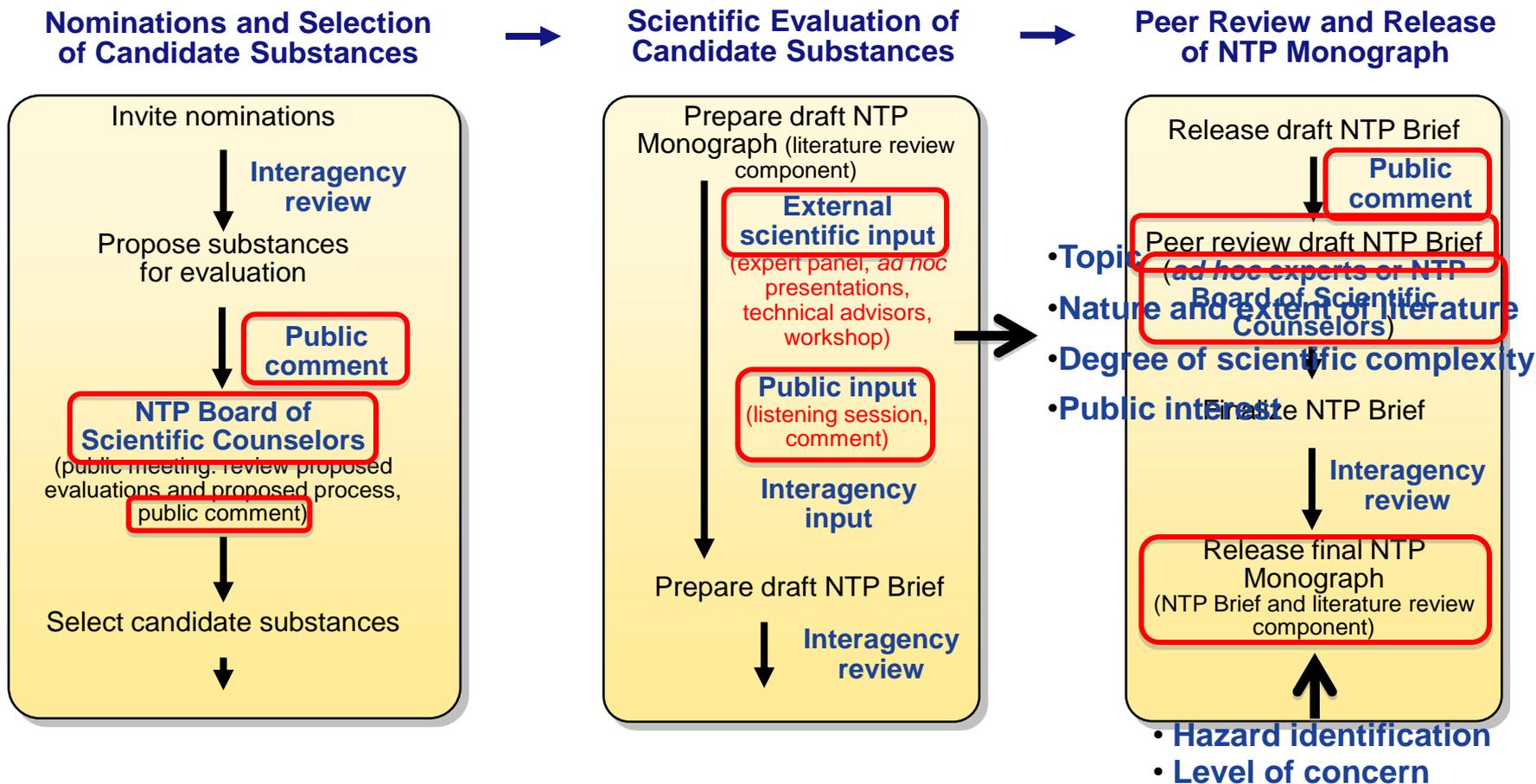
OHAT

- Expands scope of evaluations beyond just reproduction and development
- End product is NTP Monograph
 - NTP Brief and literature review component
- Set evaluation process
 - Flexibility for scientific and public inputs
- Evaluation has 2 phases:
 - Hazard identification: hierarchical descriptors being changed; weight of evidence of human and animal data considered separately
 - Level of concern: 5-tier hierarchy for conclusions



OHAT Evaluation Process

Preparation of NTP Monograph still follows an established process
(external scientific input, public comments, and peer review)





Summary

- NTP is an interagency program whose mission is to evaluate agents of public health concern
- NTP carries out a number of research/testing and analysis activities to identify chemical hazards
- NTP identifies chemical hazards using set classification schemes
- NTP produces high quality scientific reports for use in public health decision-making
- NTP follows formal processes to prepare its reports that include external peer review and opportunity for public comment