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
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
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:

- IMMUNE SYSTEM REPORT – NEW TO COME
- TECHNICAL REPORT
- TOXICITY REPORT
- GENETICALLY MODIFIED MODEL REPORT
- IMMUNE SYSTEM REPORT – NEW TO COME
- 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
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
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
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
Preparation of NTP-CERHR Monographs followed an established process (external scientific input, public comments, and peer review)

Nominations and Selection of Candidate Substances

- Invite nominations
  - Interagency review
  - Propose substances for evaluation
  - Public comment
  - NTP Board of Scientific Counselors (public meeting: review proposed evaluations, public comment)
- Select candidate substances

Scientific Evaluation of Candidate Substances

- Prepare and release draft expert panel report
  - Public comment
  - Expert Panel (public meeting: finalize expert panel report, develop level of concern conclusions, public comment)
- Release final expert panel report
  - Public comment
- Prepare draft NTP Brief
  - Interagency review

Peer Review and Release of NTP Monograph

- Release draft NTP Brief
  - Public comment
- Peer review draft NTP Brief (ad hoc experts or NTP Board of Scientific Counselors)
  - Finalize NTP Brief
  - Interagency review
- Release final NTP-CERHR Monograph
  - Public comment
  - Interagency review
  - Release final NTP-CERHR Monograph
    - NTP Brief, expert panel report, public comments on expert panel report
  - Hazard identification
  - Level of concern
Example: Di(2-Ethylhexyl) Phthalate (2006)

Weight of evidence for developmental and reproductive toxicity

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

Extent of human exposure and other factors

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

Level of concern

- **Critically ill male infants**
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)
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)

Nominations and Selection of Candidate Substances
- Invite nominations
- Interagency review
- Propose substances for evaluation
- Public comment
- NTP Board of Scientific Counselors (public meeting, review proposed evaluations and proposed process, public comment)
- Select candidate substances

Scientific Evaluation of Candidate Substances
- Prepare draft NTP Monograph (literature review component)
- External scientific input (expert panel, ad hoc presentations, technical advisors, workshop)
- Public input (listening session, comment)
- Interagency input
- Prepare draft NTP Brief
- Interagency review

Peer Review and Release of NTP Monograph
- Release draft NTP Brief
- Peer review draft NTP Brief (ad hoc experts or NTP Board of Scientific Counselors)
- Finalize NTP Brief
- Interagency review
- Release final NTP Monograph (NTP Brief and literature review component)

- Public comment
- Interagency review
- Hazard identification
- Level of concern

- Topic
- Nature and extent of literature
- Degree of scientific complexity
- Public interest
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