

CROSS-SPECIES MODE OF ACTION INFORMATION ASSESSMENT FOR BISPHENOL A (BPA)



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What is Integrated Ecological and Human Health Risk Assessment?

- ❖ "A science-based approach that combines the processes of risk estimation for humans, biota, and natural resources in one assessment" (WHO/UNEP/ILO IPCS Integrated Risk Report)
- ❖ The advantages are efficiency (2 in 1), coherent expression of assessment results, and recognition of species interdependence

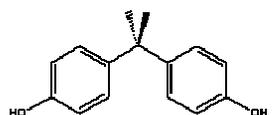
Mode of Action (MOA): The key step in the toxic response after chemical interaction at the target site that is responsible for the physiological outcome or pathology (IPCS, 1999).

How May Cross-Species Mode of Action Information Assessment Aid Integrated Risk Assessment?

- ❖ Identification of sensitive species
- ❖ Determination of relationship between a chemical's mode of action for each species and species relatedness (i.e., evolutionary relationship), provides a method to predict effects in untested but related species
- ❖ Application of mode of action information to risk assessment

Approach:

- ❖ Cross-species mode of action information for developmental and reproductive effects of BPA was gathered from the literature
- ❖ The relationship between mode of action and species relatedness was assessed
- ❖ Limited to animal species



Case Study Chemical Selection:

- Bisphenol A (2,2-bis(4-hydroxyphenyl) propane; BPA)**
- ❖ High production volume chemical
 - Component of polycarbonate plastics, epoxy resins, and polyester resins
 - Production has increased and is predicted to increase further
 - Sources of exposure: oil, gas, chemical, plastic, and electronics production
 - BPA detected in tissue of some wildlife species and human newborn serum
 - ❖ Effects data for some vertebrate and invertebrate species
 - ❖ Well-described estrogen agonist mode of action for a number of vertebrate species (see purple box for definition of estrogen agonist)

Case Study Findings:

What is the representation of species with effects data after BPA treatment across the animal kingdom?

BPA *in vivo* effects data identified for 17 animal species representing 7 animal classes in 3 phyla.

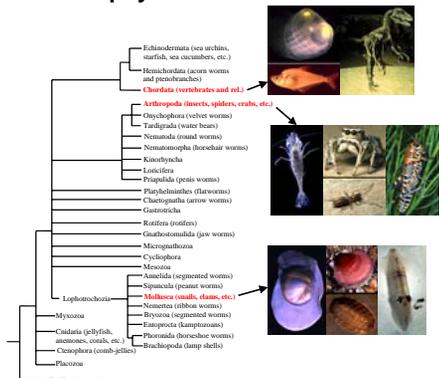


Figure 1: Phyla of the animal kingdom with BPA effects data, indicated in red.

What are the Mode of Action Data for BPA across species?

INVERTEBRATES:

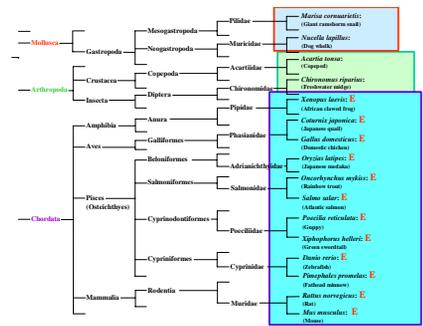
- ❖ Small number of tested species (5) clumped within two groups of species, molluscs and arthropods (i.e., patchy coverage of invertebrate species)
- ❖ Small number of studies
- ❖ Feminization effects after BPA treatment in snails
- ❖ Unknown mode of action for BPA in tested invertebrate species
- ❖ Species sensitive to BPA exposure: Snails and the freshwater midge (aquatic insect)

VERTEBRATES:

- ❖ Reptiles:
 - Insufficient data to determine mode of action; very small number of studies
- ❖ Amphibians:
 - Insufficient data to determine mode of action; small number of studies
 - Possible effects on thyroid hormone activity
- ❖ Birds:
 - Data consistent with estrogen agonist mode of action
 - Small number of studies
 - Estrogen receptor binding data
 - Known role for estrogens in bird sexual differentiation
- ❖ Fish:
 - Data consistent with estrogen agonist mode of action
 - Large number of studies
 - Known role for estrogens in fish sexual differentiation
 - Some effects may be explained by other (non-estrogen agonist) modes of action
- ❖ Mammals:
 - Data support estrogen agonist mode of action; some results suggest additional MOAs
 - Largest number of studies
 - Small number of tested species (2) and both rodents (i.e., patchy coverage of among mammals)
 - Known roles for estrogens during female development and sexual differentiation
 - Some study findings and interpretations differ
- ❖ Sensitive groups of species: Amphibians and fish
- ❖ Sensitive mammalian endpoint: Mammary gland development

What are the relationships between BPA MOA and species relatedness?

Relationship between relatedness and estrogen agonist MOA in mammals and fish. No other strong patterns (given the limited data) were identified.



E = Estrogen Agonist MOA; Mimicking estrogens in the body by binding to and activating the estrogen receptor (ER)

Figure 2. Weight of evidence for BPA cross-species mode of action information within the animal kingdom (shown in a phylogenetic tree).

What Did We Learn?

- ❖ Cross-species mode of action assessment is a promising method for applying mode of action information to integrated risk assessment
- ❖ Cross-species effects assessment is an excellent method for assessing relative sensitivities among species w/data.
- ❖ Cross-species mode of action assessment and other integrated assessment approaches have potential for chemical screening and testing programs that consider wildlife, such as EPA's Endocrine Disruptor Screening and Testing Program
- ❖ Recommended criteria for chemical selection for a future case study:
 - Mode of action data for many species
 - Mode of action data for multiple species within 1 phyla
 - High potency chemical (e.g., ethinyl estradiol, vinclozolin)

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