NTP
National Toxicology Program

Draft Report on Carcinogens Concept: Di- and Tri-Haloacetic Acids Found as Water Disinfection By-Products

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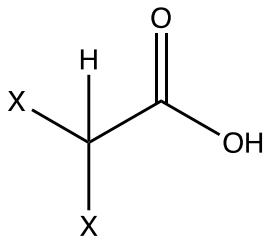
Water disinfection by-products

- What are water disinfection by-products?
  - Formed by reaction of vegetative material or other organic materials, such as chemical pollutants, in water with antimicrobial oxidizing agents such as chlorine, chloramine, chlorine dioxide, or with naturally occurring halides.
  - Composition varies with water source, method of disinfection, season of the year.
  - Found in public water supply, including swimming pools and spas.
- Over 500 chemicals have been identified.
  - Trihalomethanes: 58% by weight of halogenated by-products.
  - Haloacetic acids: 36% by weight of halogenated by-products.

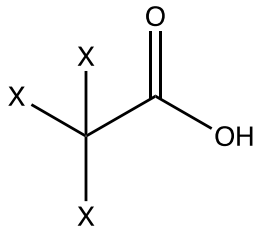
Exposure

- Over 48,000 U.S. public water systems provide disinfected water to more than 250 million people.
- 98% of U.S. water treatment systems use some type of chlorine disinfection process.
- Water chlorination is also widely used in Canada and Europe.
- Ingestion is major exposure route for haloacetic acids (HAAs) followed by inhalation and dermal exposures.
  - Low vapor pressure and low pKa of HAAs.
  - HAAs are in ionized form at pH of drinking water and have low dermal permeability.

Di- and tri- haloacetic acids identified in water



- Dichloroacetic acid
- Dibromoacetic acid
- Bromochloroacetic acid
- Diiodoacetic acid
- Bromoiodoacetic acid
- Chloroiodoacetic acid



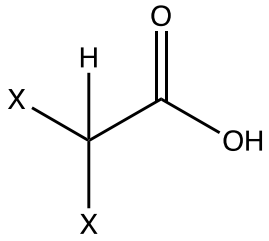
X = halogen

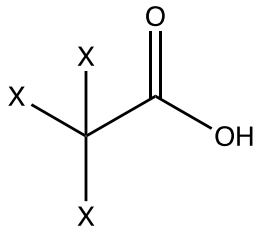
- Trichloroacetic acid
- Tribromoacetic acid
- Bromodichloroacetic acid
- Dibromochloroacetic acid

Regulations

- EPA Disinfectants and Disinfection Byproducts Rules (Stage 1, 1998; Stage 2, 2006)
  - Maximum contaminant level (MCL) for each location within the water distribution system as a running annual average of 60 µg/L or 60 ppb for HAA5.
  - HAA5 = dibromo-, dichloro-, monobromo-, monochloro-, trichloroacetic acids
- Proposed monitoring under EPA Fourth Unregulated Contaminant Monitoring Rule will add four additional HAAs to include the entire HAA9 class.
  - Four additional HAAs: bromochloro-, bromodichloro-, dibromochloro-, tribromoacetic acids

Di- and tri- haloacetic acids identified in water





X = halogen

- **Dichloroacetic acid**
- **Dibromoacetic acid**
- **Bromochloroacetic acid**
- Diiodoacetic acid
- Bromoiodoacetic acid
- Chloroiodoacetic acid

- **Trichloroacetic acid**
- **Tribromoacetic acid**
- **Bromodichloroacetic acid**
- **Dibromochloroacetic acid**

Evaluation Sources

- NTP
  - Technical reports and nomination documents
  - RoC background documents and profiles
- IARC monographs
- ATSDR toxicological profiles
- EPA IRIS toxicological reviews

Water chlorination by-products and reports

Tri-halomethanes & Haloacetic Acids	IARC volume	NTP TR #	Listed RoC/IARC	Other Reviews
Tri-halomethanes				
Chloroform		TR-000 gav	RAHC	ATSDR
Chlorodibromomethane	52	TR-282 gav	Group 3	ATSDR
Bromoform	52	TR-350 gav	Group 3	ATSDR
Bromodichloromethane	52	TR-321 gav TR-53 dw	RAHC	ATSDR
Mono-HAAs				
Chloroacetic acid		TR-396 gav		
Bromoacetic acid				
Di-HAAs				
Dichloroacetic acid	84, 106		Group 2B	IRIS
Dibromoacetic acid	101	TR-537 dw	Group 2B	
Bromochloroacetic acid	101	TR-549 dw	Group 2B	
Tri-HAAs				
Trichloroacetic acid	84, 106		Group 2B	IRIS
Tribromoacetic acid				
Bromodichloroacetic acid		TR-583 dw		
Dibromochloroacetic acid				

gav = gavage, dw = dosed water; Roc, RAHC = reasonably anticipated to be a human carcinogen, IARC, Group 3 = not classifiable; 2B= possibly a carcinogen.

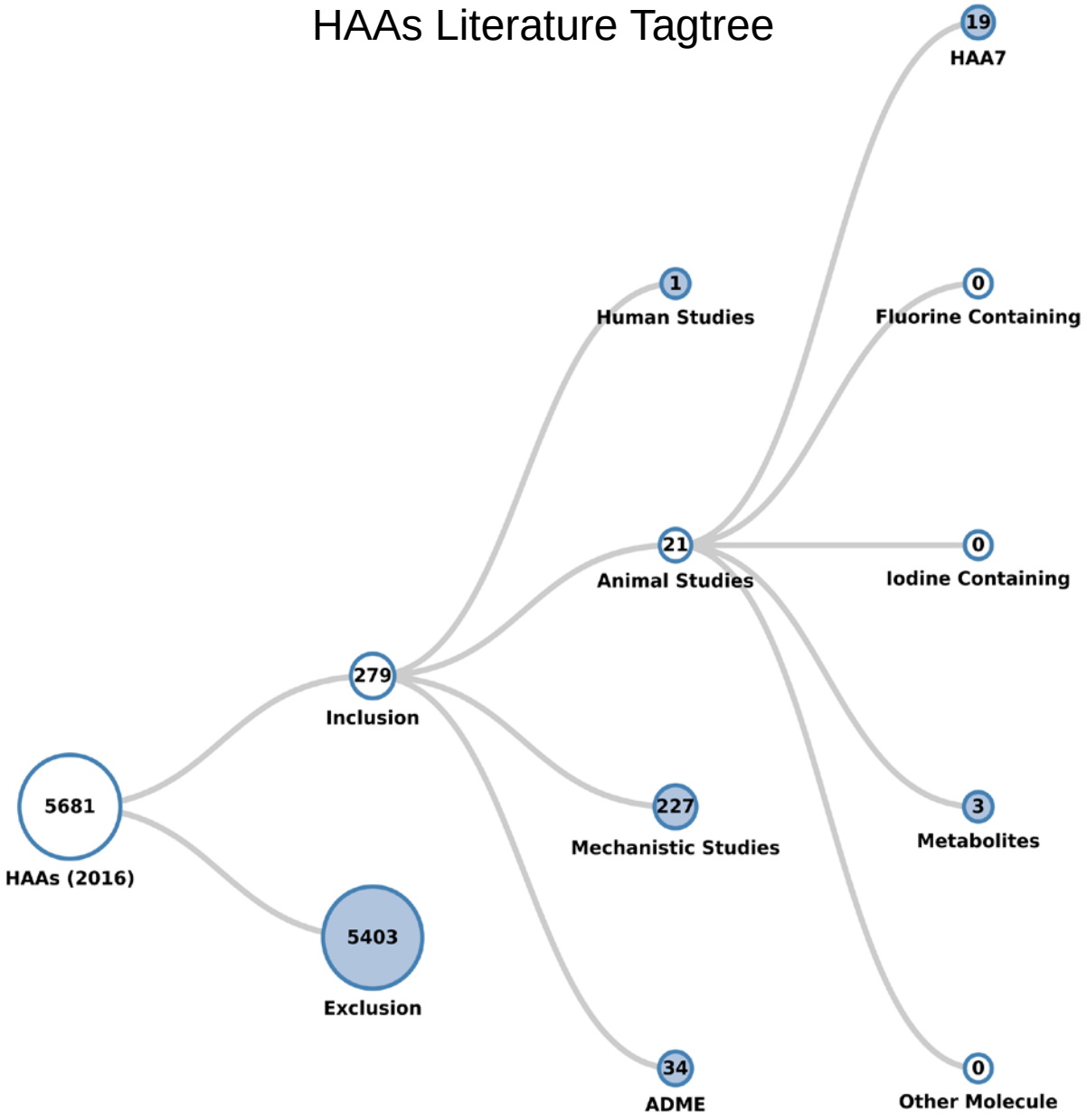
Scoping activities

Preliminary Literature Review

- Initial PubMed search covered chemical class terms, the di- and tri-substituted chloro- or bromoacetic acids, other di- and tri- HAAs (iodo- or fluoro-substituted), and metabolites.
- These searches were crossed with search terms for animal cancer studies and ten characteristics of carcinogens, and uploaded into Health Assessment Workplace Collaborative (HAWC) system of report management.
- Studies were excluded from consideration if they did not relate directly to an individual chemical or chemical class (for example, the chemical is a component of another chemical), or do not measure cancer endpoints or potential mechanisms of carcinogenicity.

Cancer studies in experimental animals

HAAs Literature Tagtree



Cancer studies in experimental animals

Drinking water exposure to haloacetic acids

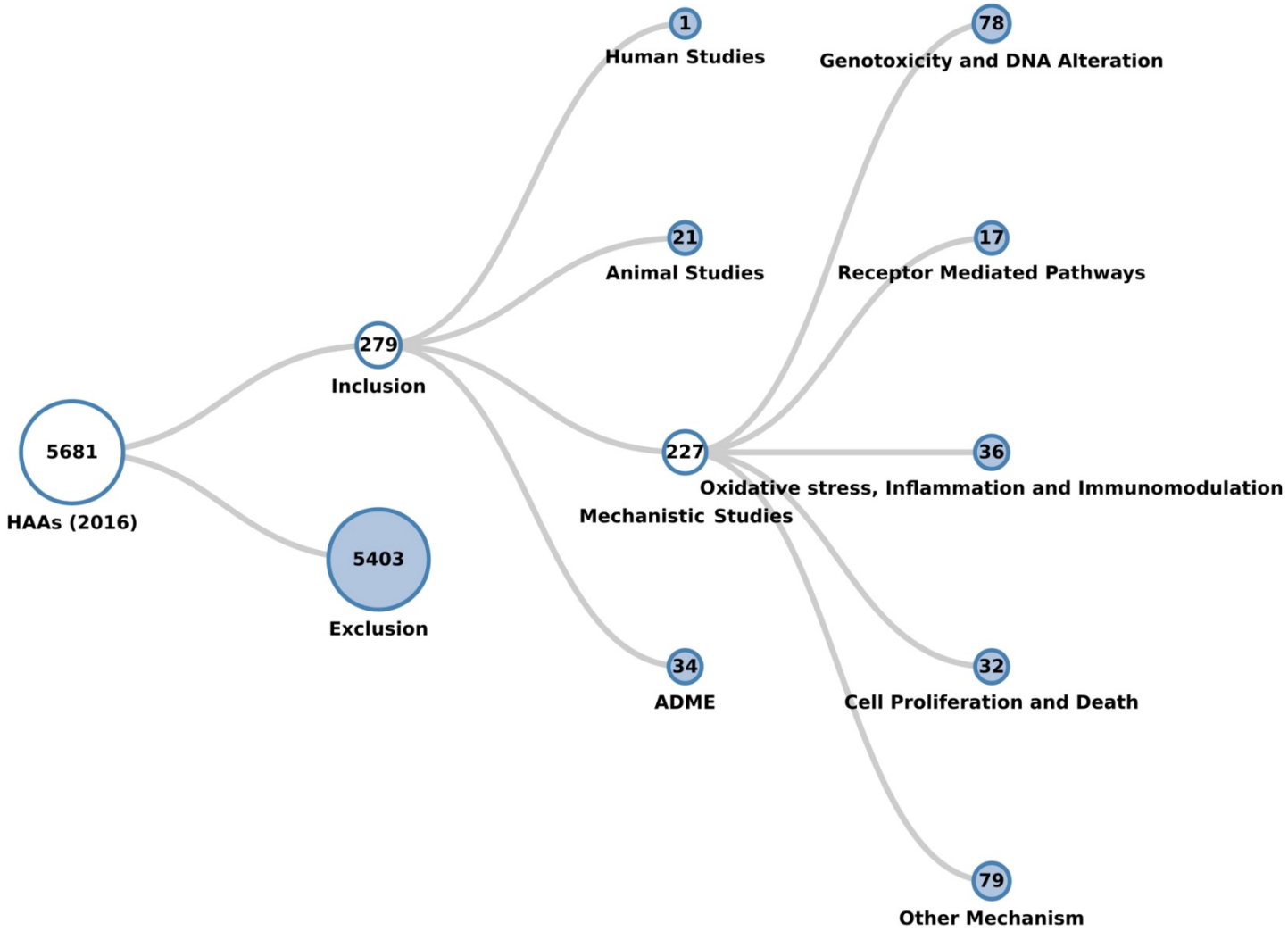
Species	Dichloro-acetic acid	Dibromo-acetic acid	Bromochloro-acetic acid
Rat	3 studies	1 study	1 study
Mouse	9 studies	1 study	1 study 1study^{dermal}

Species	Trichloro-acetic acid	Bromodichloro-acetic acid	Tribromo-acetic acid	Chlorodibromo-acetic acid
Rat	2 studies	1 study	0	0
Mouse	4 studies	1 study	0	0

Cancer studies were not located for diiodoacetic acid, bromoiodoacetic acid, or chloroiodoacetic acid.

Characteristics of Carcinogens

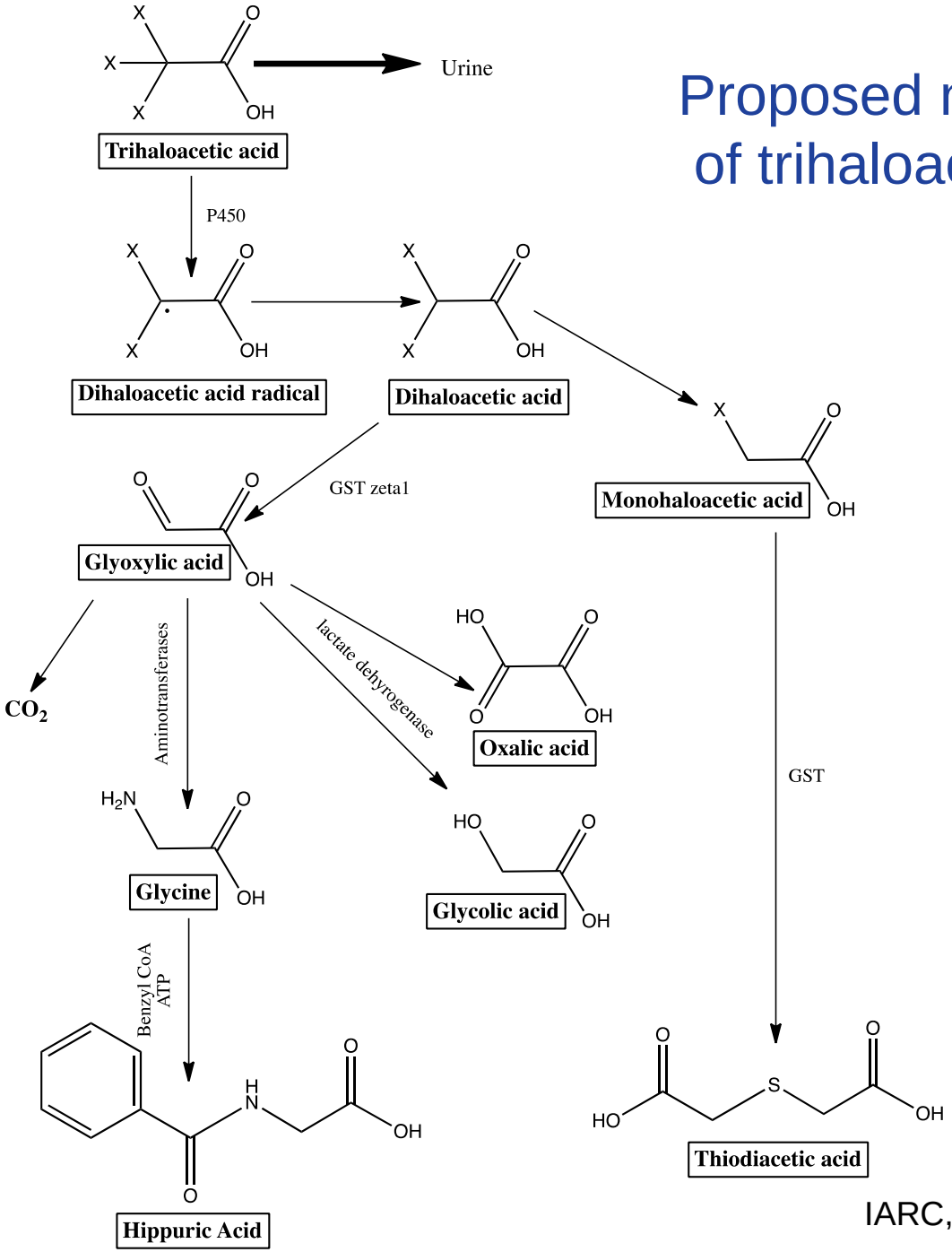
HAAs Literature Tagtree



Mechanisms for potential carcinogenicity

- A preliminary review of the body of literature shows that although this group of chemicals has structural similarities, there are some apparent similarities and differences in metabolism and disposition.
- Thus, a **key issue** is whether some di- and tri-haloacetic acids found in drinking water should be evaluated individually, some as a chemical class, or all as a chemical class.

Proposed metabolism of trihaloacetic acids



IARC, 2014

Approach for cancer hazard evaluation

ORoC will establish an information group

- Develop an approach and rationale to evaluate some or all of di- and tri-HAAs as potential class that considers the following questions:
  - What cancer endpoints do di- and tri-HAAs have in common?
  - What properties of carcinogens and related metabolic pathways do di- and tri-HAAs have in common?
  - How do chemical properties of halogen substitution affect metabolism, mechanisms of carcinogenesis, and cancer endpoints?
- Input from the information group will be used to develop a protocol that outlines methods for the cancer evaluation.
  - Post on RoC website to increase transparency of review.

Rationale and public health significance

- Adequate human exposure to haloacetic acids found as water disinfection by-products.
- Adequate cancer database.
  - Cancer studies in experimental animals.
  - Studies on mechanisms of carcinogenicity.
- To identify chemicals that may pose a cancer hazard to people living in the United States and help inform public health decisions on water distribution systems and disinfection processes.

Review questions and comments

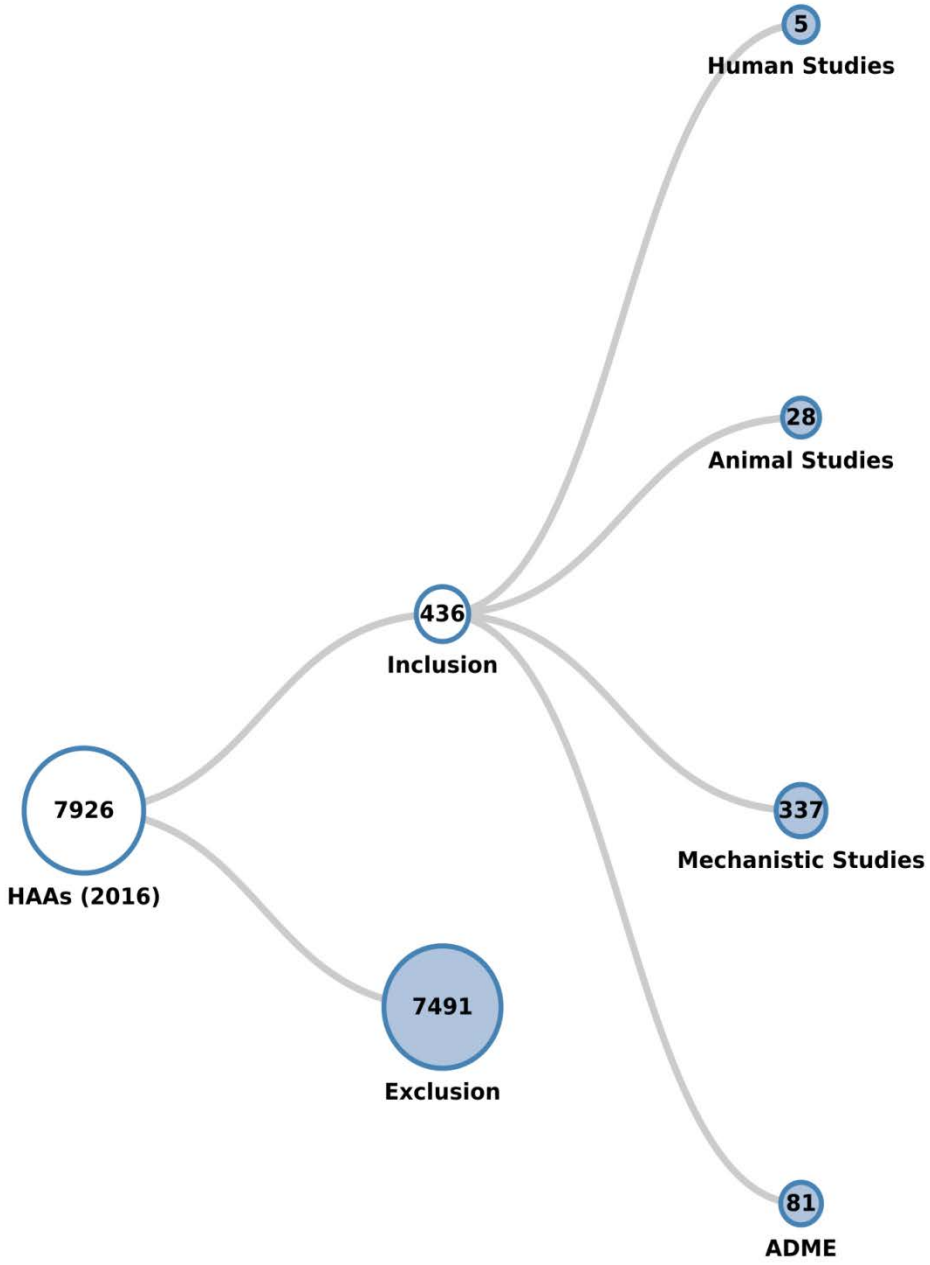
1. Comment on the merit of the proposed project relative to the mission and goals of the NTP. The NTP's stated goals are to: *Provide information on potentially hazardous substances to all stakeholders; develop and validate improved testing methods; strengthen the science base in toxicology; coordinate toxicology testing programs across DHHS* http://ntp.niehs.nih.gov/go/about.

2. Comment on the clarity and validity of the rationale for the proposed evaluation.

3. Comment on the strategy and approach proposed to meet the stated objectives of the evaluation. Are the objective and approach for the cancer evaluation reasonable and clearly articulated? Are you aware of other scientific issues that need to be considered?

4. Rate the overall significance and public health impact of this evaluation as low, moderate, or high.

5. Provide any other comments you feel NTP staff should consider in developing this evaluation.


5
Human Studies
28
Animal Studies
436
Inclusion
7926
HAAs (2016)
337
Mechanistic Studies
7491
Exclusion
81
ADME