



IRIS PUBLIC SCIENCE MEETING

November 9, 2021



Welcome and Logistics

- Keep your phone **muted** throughout the Zoom Meeting.
- **To ask a question or provide a comment**, use the “Chat” pod of Zoom Meeting to inform the meeting host of your question. Questions and comments (webinar) will be posed at the end of each issue discussion.
- **To report technical difficulties or webinar issues to the meeting host**, use the “Chat” pod of the Zoom Meeting.



INTRODUCTION AND ROLE OF ASSESSMENT PLANS IN THE IRIS PROCESS

Kris Thayer

Director, Chemical & Pollutant Assessment Division (CPAD)
Center for Public Health and Environmental Assessment (CPHEA)
Office of Research and Development
U.S. Environmental Protection Agency

- **IRIS assessments contribute to decisions across EPA and other health agencies.**
- **Toxicity values**
 - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
 - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS assessments have no direct regulatory impact until they are combined with**
 - Extent of exposure to people, cost of cleanup, available technology, etc.
 - Regulatory options.
 - Both of these are the purview of EPA's program offices.

Integrated Risk Information System

CONTACT US SHARE

IRIS Assessments in Development

- [Vanadium and Compounds \(Oral\) - IRIS Assessment Plan \(IAP\)](#) **NEW**
- [Update to the Systematic Review Protocol for the PFAS IRIS Assessments](#)
- [PBP Modeling for Chloroprene and a Supplemental Analysis of Metabolite Clearance \(Draft Report\)](#)

[See the Full List of Assessments in Development](#)

Staying Connected

- [How IRIS connects with you](#)
- [How you can connect with IRIS](#)

Get email alerts

sign up

EPA's mission is to protect human health and the environment. EPA's IRIS Program supports this mission by identifying and characterizing the health hazards of chemicals found in the environment. Each IRIS assessment can cover a chemical, a group of related chemicals, or a complex mixture.

Basic Information

- [Learn About IRIS](#)
- [Guidance & Tools](#)
- [IRIS Process](#)
- [History of IRIS](#)

IRIS Assessments

- [Browse A to Z List of Chemicals](#)
- [Browse by Organ/System](#)
- [Assessments in Development](#)

Program Materials

- [Developments in the IRIS Program](#)
- [IRIS Program Outlook](#)
- [IRIS Agenda](#)
- [IRIS Dockets](#)
- [Other Program Materials](#)

Recent Additions

- 08/19: [IRIS Public Science Meeting \(Webinar\) for Vanadium \(Oral\)](#)
- 07/28: [Update to the Systematic Review Protocol for the PFAS IRIS Assessments](#)
- 07/24: [IRIS Assessment Plan for Vanadium and Compounds \(Oral\)](#)

Search IRIS

By Chemical, CASRN, or Keyword

Search the IRIS database of final assessr

Search

IRIS Calendar

- [Public meetings & workshops - list view](#)
- [Public meetings & workshops - month view](#)
- [Stakeholder requested meetings - list view](#)

IRIS Program Outlook

Program Outlook

Agendas

UPDATE: EPA released an update to the Program Outlook Document in June 2020.

To maintain transparency, the IRIS Program is providing an updated outlook of program activities. The following document describes assessments that are in development and projected public milestone dates. Updates to the IRIS Outlook document will occur at least three times a year (February, June, October).

See the current [list of assessments in development](#).

Table 1. IRIS Program Outlook – June 2020

Current Status	Assessment	Next Anticipated Public Step(s)	Projected Fiscal Year Quarter
Post-Peer Review	Ethyl tertiary butyl ether (ETBE) ¹	Step 7: Final	FY20 – Q4
	tert-Butyl Alcohol ¹	Step 7: Final	FY20 – Q4
Draft Development	Arsenic, Inorganic	Step 1: Systematic Review Protocol	Released May 28, 2019, NAS review meeting July 16, 2019.
		Step 4: Public Comment Draft	FY22 – Q2
		Step 4: External Peer Review	FY22 – Q4
	Chromium VI	Step 1: Systematic Review Protocol	Released March 15, 2019, Public Science Meeting April 24, 2019.
		Step 4: Public Comment Draft	FY21 – Q4
		Step 4: External Peer Review	FY22 – Q1
Chloroform (Inhalation)		Step 1: IRIS Assessment Plan	Released September 18, 2017, Public Meeting on September 27, 2017.
		Step 1: Systematic Review Protocol	Released January 31, 2018.
		Step 4: Public Comment Draft	FY21 – Q3
		Step 4: External Peer Review	FY21 – Q4
Methylmercury		Step 1: IRIS Assessment Plan	Released April 4, 2019, Public Science Meeting May 15, 2019.
		Step 1: Systematic Review Protocol	Released May 26, 2020
		Step 4: Public Comment Draft	FY23 – Q3
		Step 4: External Peer Review	FY24 – Q1



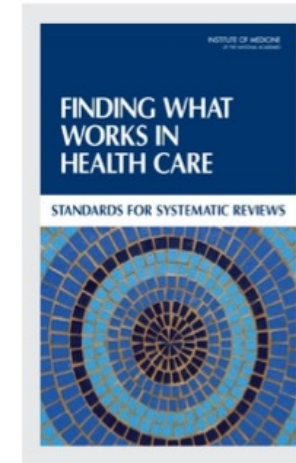
IRIS Program Outlook

- To maintain transparency, ORD has developed a public IRIS Program Outlook.
- Describes assessments that are in development and projected public milestone dates.
- Updates to the IRIS Outlook document occurs at least three times a year (February, June, October).
- **Naphthalene added to the IRIS Program Outlook in 2021. EPA has resumed assessment development following its suspension in 2018.**

Table 1. IRIS Assessment Products – October 2021

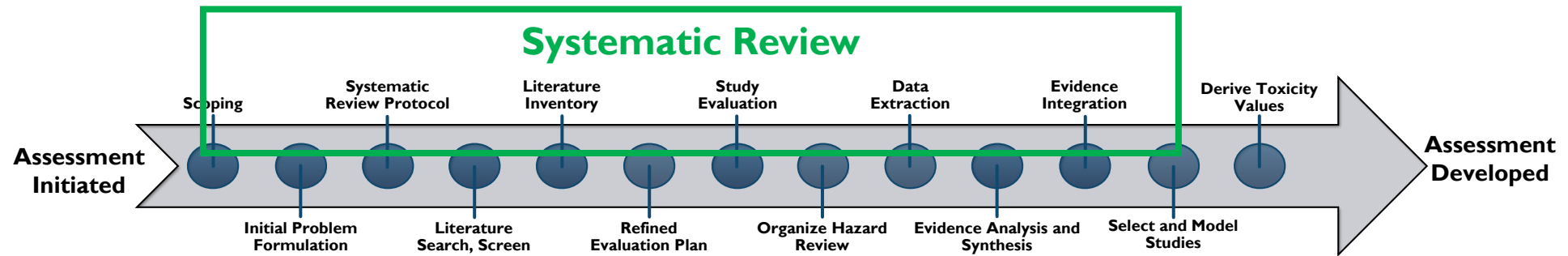
Assessment	Public Product(s)	Projected Deliverable Date
Arsenic, Inorganic	Systematic Review Protocol	Released on May 28, 2019. NAS review meeting July 16, 2019
	Public Comment Draft	
	External Peer Review	
Chloroform (Inhalation)	IRIS Assessment Plan	
	Systematic Review Protocol	
	Public Comment Draft	FY23
	External Peer Review	FY24
Chromium VI	Systematic Review Protocol	
	Public Comment Draft	
	External Peer Review	
Ethylbenzene	IRIS Assessment Plan	
	Systematic Review Protocol	
	Public Comment Draft	
	External Peer Review	
Formaldehyde	Public Comment Draft	
	External Peer Review	
	External Peer Review	
Inorganic Mercury salts	IRIS Assessment Plan	
	Systematic Review Protocol	
	Public Comment Draft	
	External Peer Review	
Methylmercury	IRIS Assessment Plan	Released on April 4, 2019. Public Science Meeting on May 15, 2019
	Systematic Review Protocol	Released on May 26, 2020
	Public Comment Draft	
Naphthalene	IRIS Assessment Plan	Released on July 5, 2018. Public Science Meeting on November 9, 2021
	Systematic Review Protocol	FY22 Q3
	Public Comment Draft	TBD
Perfluorobutyrate (PFBA) ¹	Systematic Review Protocol	Released on November 8, 2019
	Public Comment Draft	Released on August 18, 2021
	External Peer Review	FY22 Q1
Perfluorodecanoate (PFDA) ¹	Systematic Review Protocol	Released on November 8, 2019
	Public Comment Draft	FY22 Q4
	External Peer Review	FY22 Q4
Perfluorohexanoic acid (PFHxA) ¹	Systematic Review Protocol	Released on November 8, 2019
	Public Comment Draft	FY22 Q2
	External Peer Review	FY22 Q2
Perfluorohexane Sulfonic Acid (PFHxS) ¹	Systematic Review Protocol	Released on November 8, 2019
	Public Comment Draft	FY22 Q4
	External Peer Review	FY22 Q4
Perfluorononanoate (PFNA) ¹	Systematic Review Protocol	Released on November 8, 2019

A structured and documented process for transparent literature review

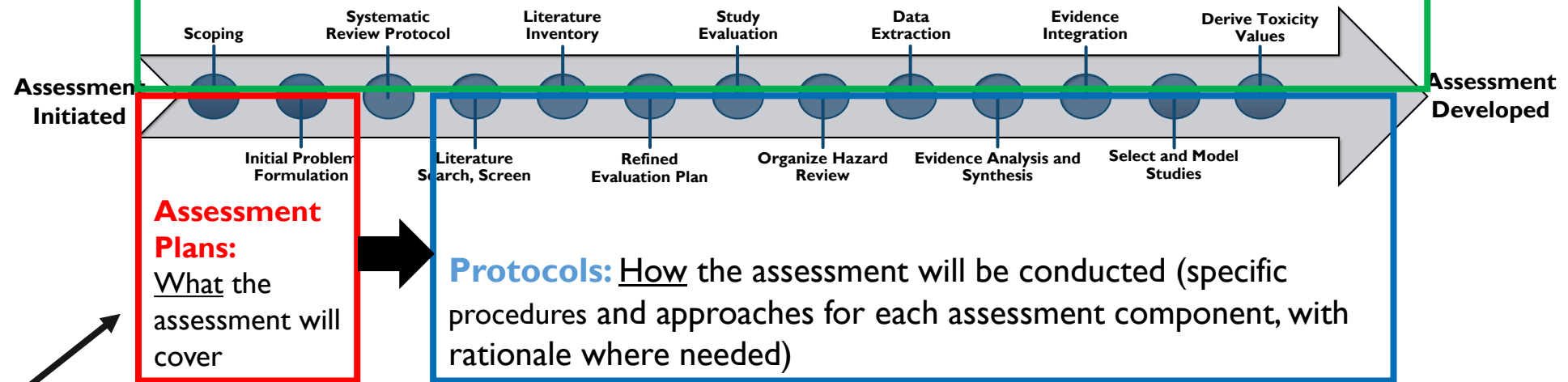


“As defined by IOM [Institute of Medicine]¹, systematic review ‘is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies.’”

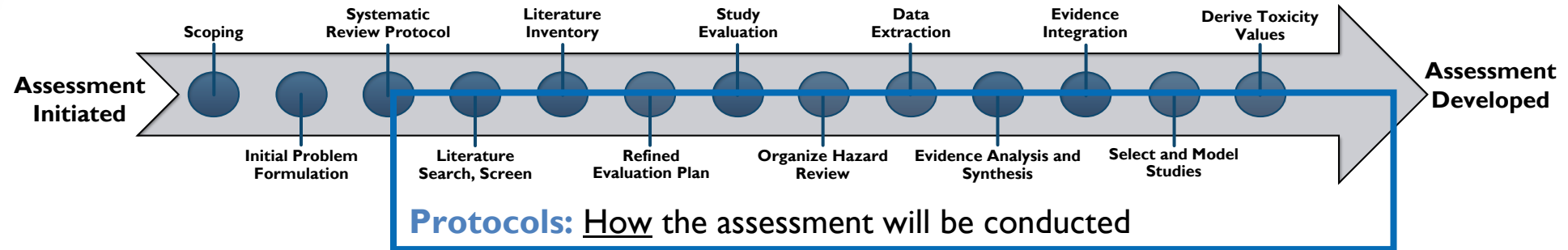
¹ Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011



IRIS Handbook: Approaches and considerations for applying principles of systematic review to IRIS assessments, general frameworks, and examples.



What we are presenting today



- In IRIS, comments received on IAP are considered when preparing the protocol (updated IAP text is included in the protocol) and protocols are released for 30-day public comment period
- Protocol is iterative – Public comment and knowledge gained during implementation may result in revisions to the protocol to focus on the best available evidence. Major revisions are documented via updates, e.g., changes to specific aims or PECO
- List of included, excluded, and studies tagged as supplemental are disseminated through protocols (either during initial release or as an update)



IRIS Assessment Plan for Naphthalene

Presentation for the
EPA IRIS Public Meeting
November 9, 2021

Ingrid L. Druwe, PhD & Erin Yost, PhD
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

The purpose of this IRIS Public Science Meeting is to discuss the science that informs the Public Comment Draft of the Naphthalene Assessment Plan. The draft plan and this presentation do not represent and should not be construed to represent any Agency determination or policy.

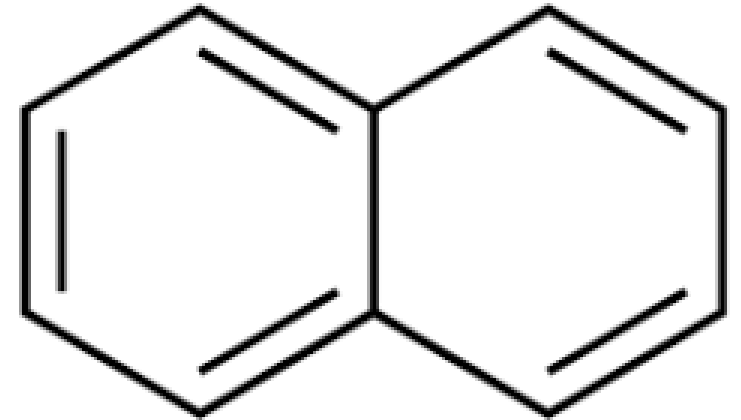
- Naphthalene is a polycyclic aromatic hydrocarbon, and is a white crystalline solid with a distinct odor
- Production: 100-250 million lbs/yr in the U.S.

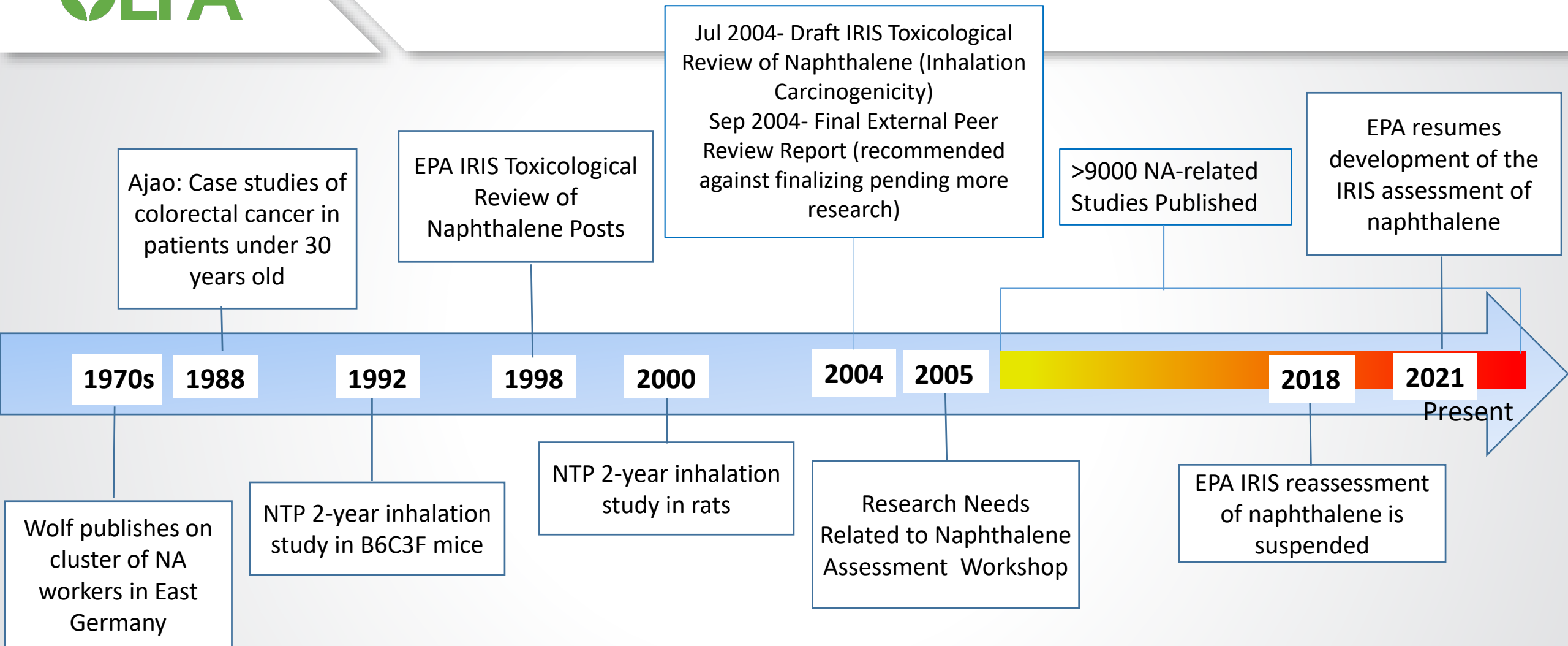
Uses:

- Manufacture of industrial products
- Major consumer products
- Also used as an inert ingredient and fragrance in non-food use pesticide products regulated by EPA

Exposure:

- Inhalation, ingestion, dermal and occupational







Program Office Interest

- Office of Land and Emergency Management (OLEM) needs:
 - Oral and inhalation toxicity values
- Statutes, regulations, policies:
 - Comprehensive Environmental Response, Compensation and Liability Act (CERCLA);
 - Emergency Planning and Community Right-to-Know Act (EPCRA);
 - RCRA Subtitle I (Underground Storage Tanks)
- Naphthalene IRIS assessment may be used to:
 - Make risk determinations for response actions (e.g., short-term removals, long-term remedial response actions) under CERCLA and RCRA including Subtitle I leaking underground storage tanks.



Scope of Assessment

- Focus will be on inhalation, oral and dermal exposure
- Based on initial literature survey*, the assessment will evaluate the potential for NA exposure to cause:
 - Respiratory system effects
 - Hematological effects
 - Immune system effects
 - Reproductive system effects
 - Developmental system effects
 - Cancers

*Updated literature survey is available in Yost et al., 2021, “Health Effects of Naphthalene Exposure: A Systematic Evidence Map and Analysis of Potential Considerations for Dose-Response Evaluation”. *Environ Health Perspect.* 129(7): 76002. doi: 10.1289/EHP7381



Specific Aims

- Literature searches to identify pertinent epidemiology and experimental studies for each health outcome
- Study evaluations (risk of bias and sensitivity)
- Data extraction
- For each health outcome, synthesize the human and animal evidence separately, then integrate the evidence overall. Biological support from mechanistic studies and nonmammalian model systems will be considered.
- Derive toxicity values (e.g., reference doses [RfDs], reference concentrations [RfCs], cancer risk estimates, considering both nonlinear and linear extrapolation) as supported by the available data.
- Characterize strengths and limitations of the databases, uncertainties and identify key data.

	Evidence
Populations	<p><u>Human</u>: Any population and lifestage (occupational or general population, including children and other sensitive populations). Note: Case reports and case series will be tracked during study screening but are not the primary focus of this assessment.</p> <p><u>Animal</u>: Nonhuman mammalian animal species (whole organism) of any lifestage.</p>
Exposures	<p><u>Human</u>: Any exposure to naphthalene (CASRN 91-20-3), including occupational exposures, via oral, inhalation, or dermal route[s]. Exposures quantified by either biomonitoring or occupational exposure history are preferred.</p> <p><u>Animal</u>: Any exposure to naphthalene (CASRN 91-20-3) via oral, inhalation, or dermal route[s]. Studies employing chronic exposures or short-term, developmental-only exposures will be considered the most informative. Studies involving exposures to mixtures will be included only if they include an arm with exposure to naphthalene alone.</p> <p>Studies describing physiologically-based pharmacokinetic (PBPK) models for naphthalene will be included.</p>
Comparators	<p><u>Human</u>: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of naphthalene, or exposure to naphthalene for shorter periods of time.</p> <p><u>Animal</u>: A concurrent control group exposed to vehicle-only treatment.</p>
Outcomes	<p>All health outcomes (both cancer and noncancer). Based on preliminary screening work, EPA anticipates that a systematic review for health effect categories other than those identified (i.e., hematological, immune system, respiratory system, reproductive/developmental system, and cancer) will not be undertaken unless a significant amount of new evidence is found upon review of references during the comprehensive literature search.</p>



Literature Survey

Human Studies					Animal Studies					
	Occupational Epidemiological Studies	General Population Epidemiological Studies	Controlled Exposure Studies	Case Reports/Case Series	Chronic	Subchronic	Short-term	Acute	Multigenerational	Gestational
Inhalation Exposure										
Cardiovascular					2	1				
Dermal					2					
Developmental				3						
Endocrine/Exocrine					2	1				
Gastrointestinal	1			4	2					
Hematological				6	2					
Hepatic				4	2	1		1		
Immunological	1	3			2	1				
Nasal					3	1	2	4		
Neurological				3	2	1				
Pulmonary	1	1		1	3			4		
Renal				1	2	1				
Reproductive				2	2	1				
Ocular				4	2					
Other effects ^a					3	1	2			

^aOther effects include body weight, clinical signs, and other observations

NOTE: The numbers represent the numbers of studies that investigated a particular health effect, not the number of studies that identified a positive association with exposure to naphthalene. If a journal article or report included, for example, a study in both rats and mice, it was counted as two studies. Blanks indicate that no studies were identified in the systematic literature search and screening for that specific effect category.

Human Studies					Animal Studies					
	Occupational Epidemiological Studies	General Population Epidemiological Studies	Controlled Exposure Studies	Case Reports/Case Series	Chronic	Subchronic	Short-term	Acute	Multigenerational	Gestational
Oral Exposure										
Cardiovascular				9		3				
Dermal										
Developmental				1						
Endocrine/Exocrine						2				
Gastrointestinal				17		2				
Hematological				31		4	1	1		
Hepatic				22		7	6	1		
Immunological						3	1	1		
Nasal										
Neurological				5		4	1			
Pulmonary				9		4	1			
Renal				29		6	2			
Reproductive				1		3	1			
Ocular				4		29	20	1		
Other effects ^a				27		15	5	9		

^aOther effects include body weight, clinical signs, and other observations

NOTE: The numbers represent the numbers of studies that investigated a particular health effect, not the number of studies that identified a positive association with exposure to naphthalene. If a journal article or report included, for example, a study in both rats and mice, it was counted as two studies. Blanks indicate that no studies were identified in the systematic literature search and screening for that specific effect category.

Human Studies					Animal Studies					
	Occupational Epidemiological Studies	General Population Epidemiological Studies	Controlled Exposure Studies	Case Reports/Case Series	Chronic	Subchronic	Short-term	Acute	Multigenerational	Gestational
Dermal or Multiple/Unknown (Biomarker) Routes of Exposure										
Cardiovascular		2		3						
Dermal				2			2	2		
Developmental		1		2						
Endocrine/Exocrine		3					1			
Gastrointestinal	1			2						
Hematological		2		12		1	1			
Hepatic		3		11			1			
Immunological		3				1				
Nasal										
Neurological	1	1		4						
Pulmonary				3						
Renal				8			1			
Reproductive		7		1		1	1			
Ocular	1			2		1	1	1 ^b		
Other effects ^a	2	2		9		1	1			

^aOther effects include body weight, clinical signs, and other observations. ^bOne animal study that evaluated ocular exposure is recorded here; all other animal studies in this table evaluated dermal exposure.



Key Science Issues



Science Topic I: Species Differences in Toxicokinetics

- Differences in metabolism and toxicokinetics:
 - Toxicokinetic differences in rate and extent of metabolism of naphthalene in various tissues
 - Catalytic rate differences between mouse, rat and human CYP2F enzyme homologs
 - eg., CYP2F: CYP2F1 (human) vs CYP2F2 (mouse) vs CYP2F4 (rat)
 - Anatomical differences in nasal turbinates
- PBPK:
 - Evaluation of the current and available naphthalene PBPK models for reliable route-to-route, interspecies, and/or intraspecies extrapolation

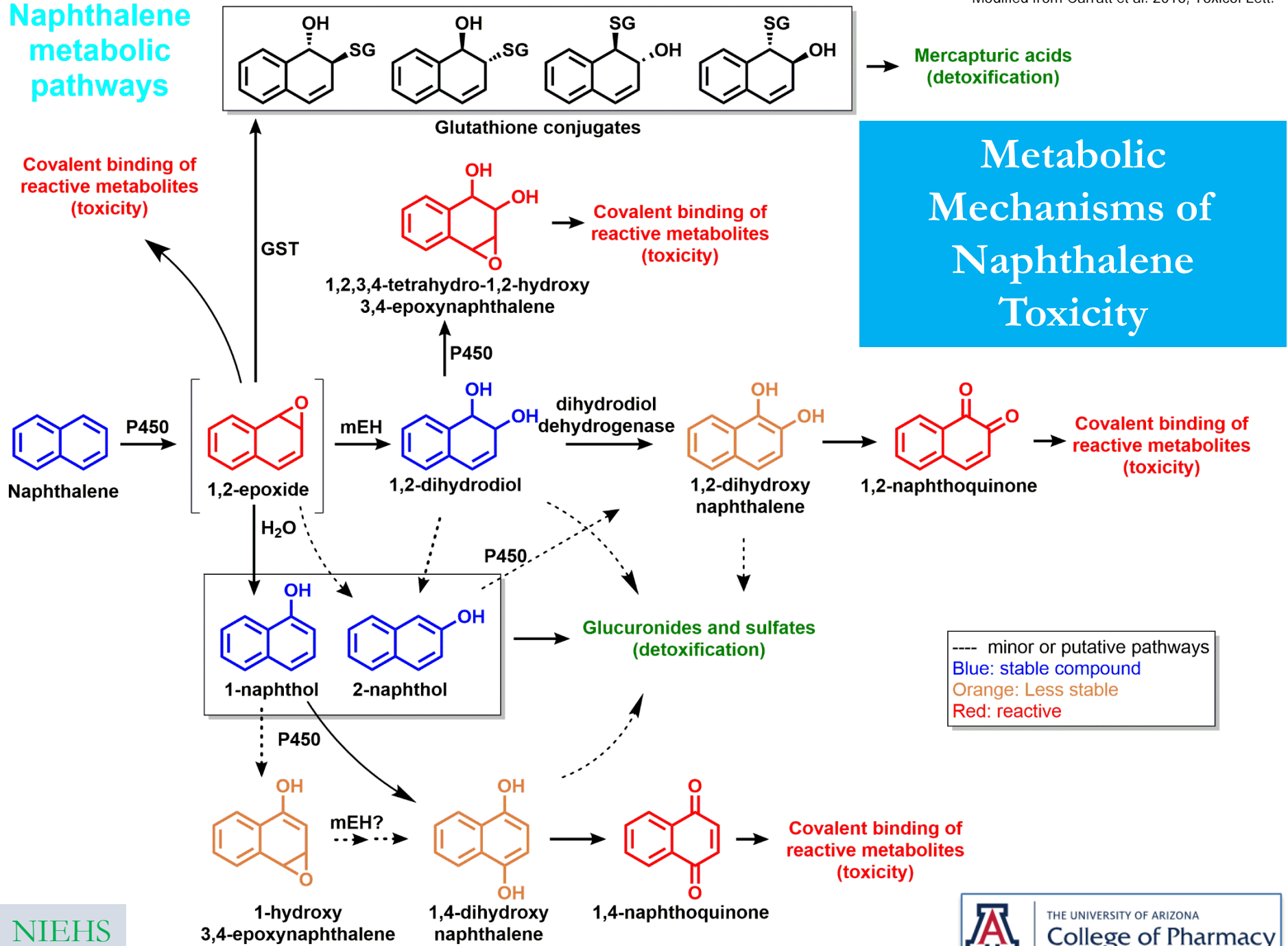


Dr. Xinxin Ding

NAS-Identified Expert

University of Arizona

Naphthalene metabolic pathways



Metabolic Mechanisms of Naphthalene Toxicity

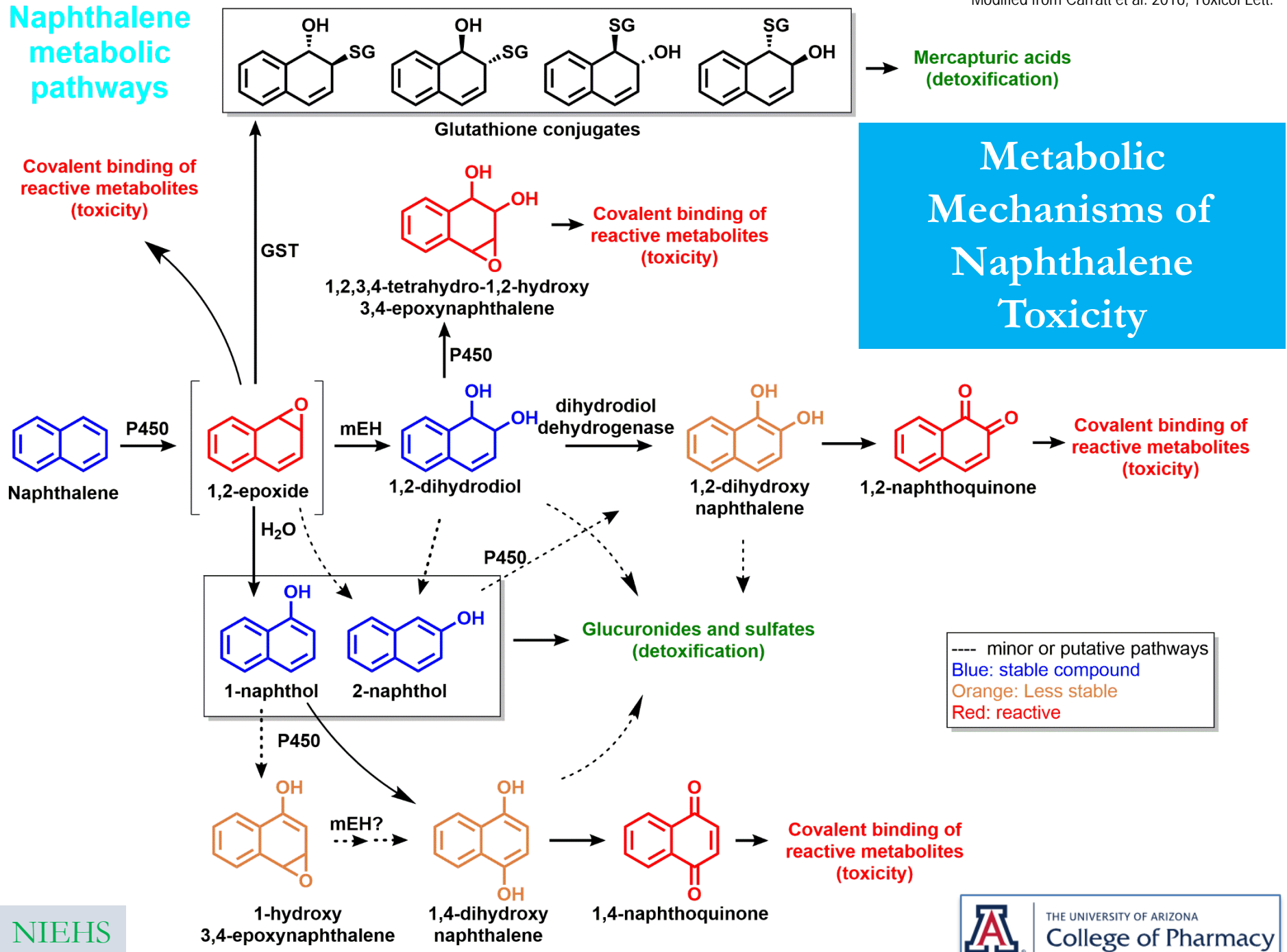


Dr. Laura Van Winkle

NAS-Identified Expert

University of California, Davis

Naphthalene metabolic pathways



Metabolic Mechanisms of Naphthalene Toxicity



Science Topic 2: Mode of action for carcinogenicity

- Proposed processes involved in naphthalene-induced tumor formation:
 - Genotoxicity
 - Cytotoxicity & Sustained regenerative cell proliferation
 - Other contributing processes (e.g., adduct formation; oxidative stress)
- Other considerations:
 - Potential differences in enzyme activation (e.g., bioactivation by CYPs) across species

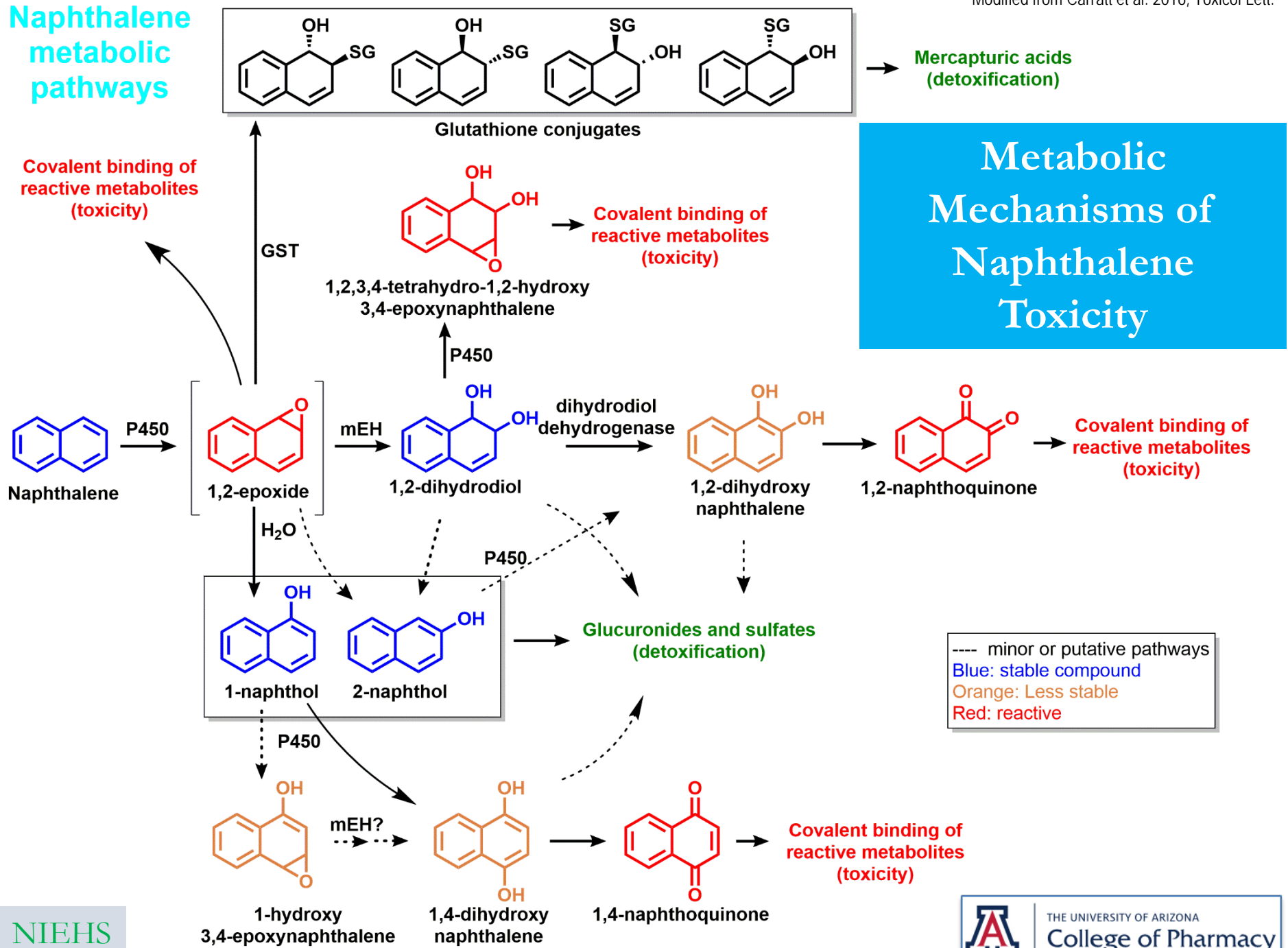


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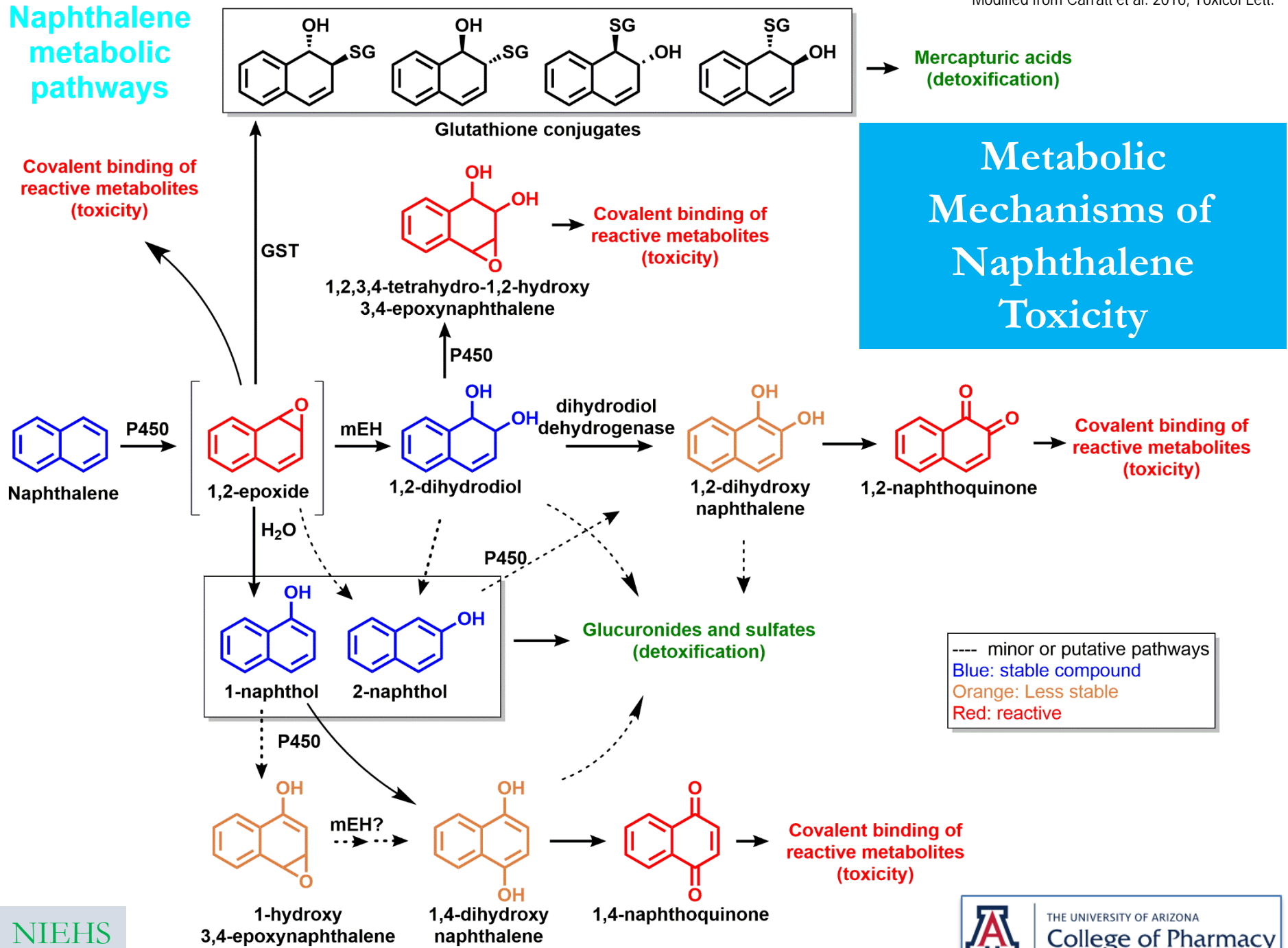


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Metabolic Mechanisms of Naphthalene Toxicity



Public Commenters



Dr. Jessica Rymann-Rasmussen

Public Commenter

American Petroleum Institute (API)

Oral Comments



Thank you!