Systematic Evidence Map (SEM) to Characterize Available Evidence for 9000 PFAS

Kristina Thayer
CPHEA/CPAD
Office of Research and Development

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Goals

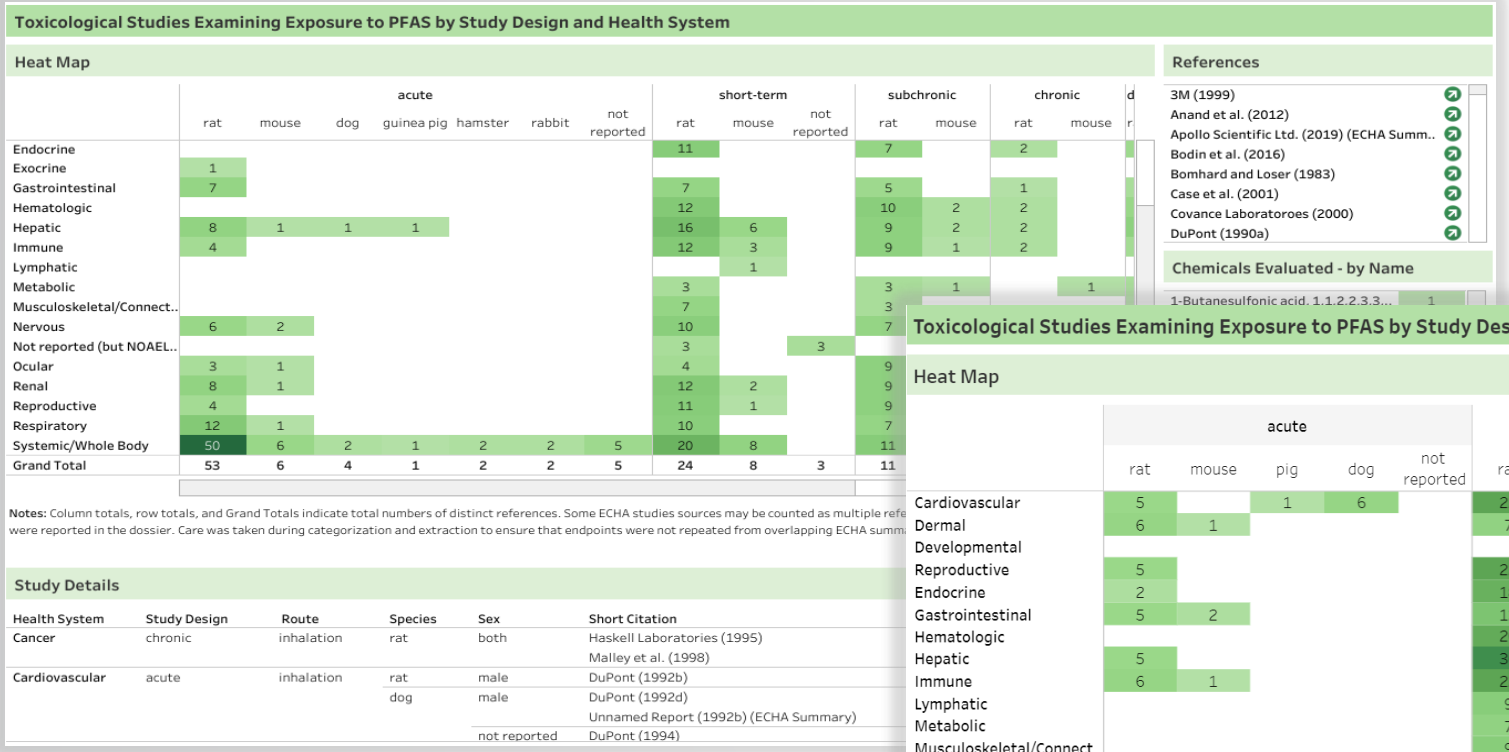
- Use systematic review methods to identify and summarize animal bioassay and epidemiological evidence for ~9000 PFAS
  - Create a repository that is easily updated, web-based, and shareable
  - Focused on PFAS structures and substances listed in EPA CompTox Chemicals Dashboard
- Specific uses:
  - Identify *in vivo* evidence to inform CCTE efforts to characterize PFAS library
  - Characterize data gaps and key research needs
  - Be positioned to quickly address new PFAS assessment needs

Approach

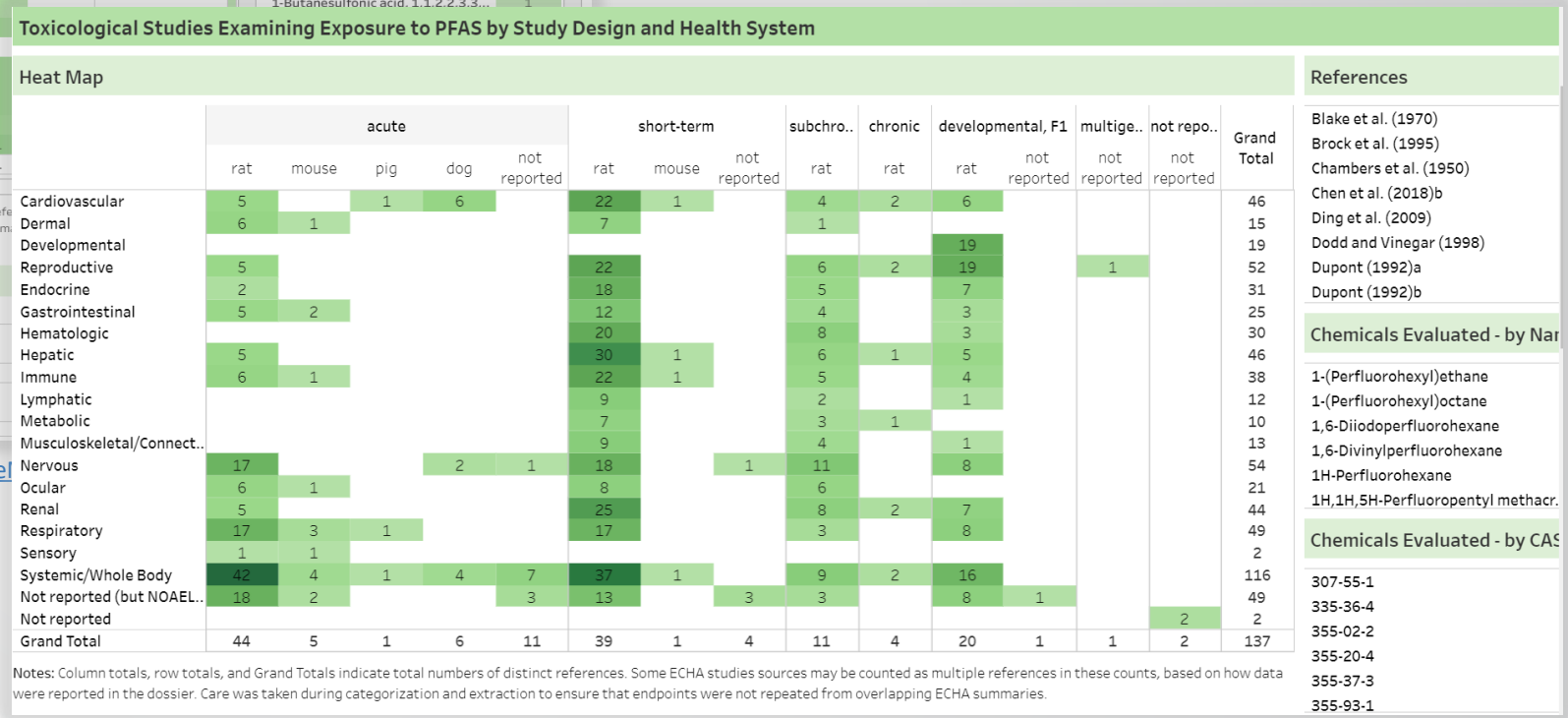
- Systematic review methods used to search for, screen, and evaluate the relevant literature
  - Use machine-learning and automated approaches to develop search strategies
- Searches initiated in batches as they were identified of interest ("PFAS 150", "PFAS 430", "PFAS 9000")
  - List of 9,000 PFAS substances and structures includes most of the chemicals in the EPA CompTox chemicals dashboard (https://comptox.epa.gov/dashboard/chemical_lists/PFASSTRUCT)
- Study methods and findings summarized ("data extraction") and the results made available online as downloadable and interactive visual formats
- ADME studies*, PBPK models*, *in vitro* studies, and exposure-only human studies being tracked as supplemental material
- Cross-checked reference lists with other resources (e.g., ATSDR drafts)

*ADME = absorption, distribution, metabolism, and elimination; PBPK model = physiologically based pharmacokinetic model

Interactive Displays: Inventory



https://public.tableau.com/app/profile/literature.inventory/viz/PFAS-150Evidence



https://public.tableau.com/app/profile/laura.carlson/viz/BDRP2021posterLMC/AnimalStudies

Interactive Displays: Extraction

Chemical	Endpoint	Study	Animal Description	Route	Exposure Duration
6:2 Fluorotelomer alcohol	Liver Weight, Absolute	Mukerji et al. 2015	P0 Mouse, Crl:CD-1(ICR)BR (♀)	oral gavage	14d pre-mating, 14d mating, gestation, lactation
			P0 Mouse, Crl:CD-1(ICR)BR (♂)	oral gavage	109 d (premating-sacrifice)
		Serex T et al. 2014	Rat, Crl:CD(SD) (♀)	oral gavage	90 d
			Rat, Crl:CD(SD) (♂)	oral gavage	90 d
		Unnamed report (2005a) (ECHA summary)	Rat, Crl:CD(SD) (♂♀)	oral gavage	28 d
	Liver Weight, Relative	Mukerji et al. 2015	P0 Mouse, Crl:CD-1(ICR)BR (♀)	oral gavage	14d pre-mating, 14d mating, gestation, lactation
			P0 Mouse, Crl:CD-1(ICR)BR (♂)	oral gavage	109 d (premating-sacrifice)
		ECHA, 2007, 5701160	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
		Serex T et al. 2014	Rat, Crl:CD(SD) (♀)	oral gavage	90 d
		ECHA, 2007, 5701160	Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
		Serex T et al. 2014	Rat, Crl:CD(SD) (♂)	oral gavage	90 d
6:2 Fluorotelomer methacrylate	Liver Weight, Absolute	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
	Liver Weight, Absolute, Recovery	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
	Liver Weight, Relative	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
	Liver Weight, Relative, Recovery	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
Trifluoroacetic acid	Liver Weight, Absolute	Unnamed Report (2010a) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	GD 6-19
		Unnamed Report (2012b) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	up to 57 d (premating-lactation)
			P0 Rat, Crl:CD(SD)IGS BR (♂)	oral gavage	38 d (premating-termination)
		Saillenfait et al. 1997	P0 Rat, Sprague-Dawley (♀)	oral gavage	GD 10-20
			F1 Rat, Sprague–Dawley (♂♀)	oral gavage	GD 10-20
		Unnamed Report (2016a) (ECHA Summary)	Rat, Wistar Rj:Wi (Iops Han) (♀)	oral diet	90 d
			Rat, Wistar Rj:Wi (Iops Han) (♂)	oral diet	90 d
	Liver Weight, Relative	Unnamed Report (2012b) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	up to 57 d (premating-lactation)
			P0 Rat, Crl:CD(SD)IGS BR (♂)	oral gavage	38 d (premating-termination)
		Saillenfait et al. 1997	P0 Rat, Sprague-Dawley (♀)	oral gavage	GD 10-20
			F1 Rat, Sprague–Dawley (♂♀)	oral gavage	GD 10-20
		Unnamed Report (2016a) (ECHA Summary)	Rat, Wistar Rj:Wi (Iops Han) (♀)	oral diet	90 d
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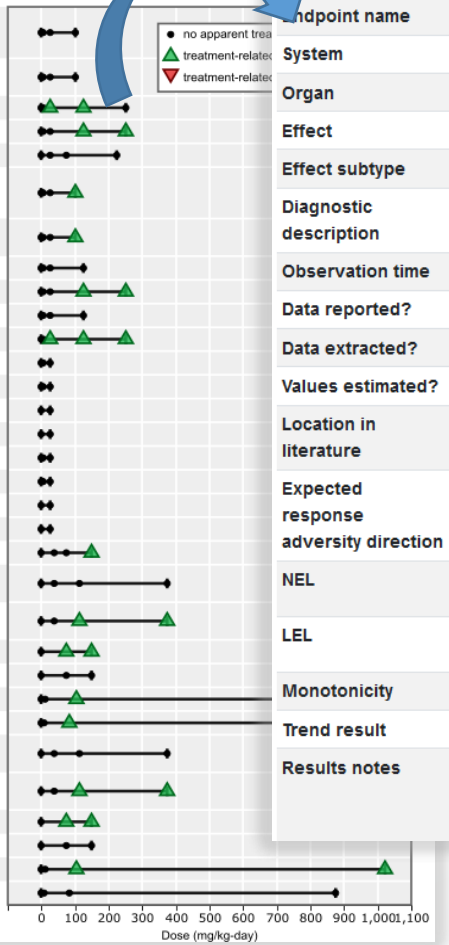


Liver Weight, Absolute

Endpoint Details

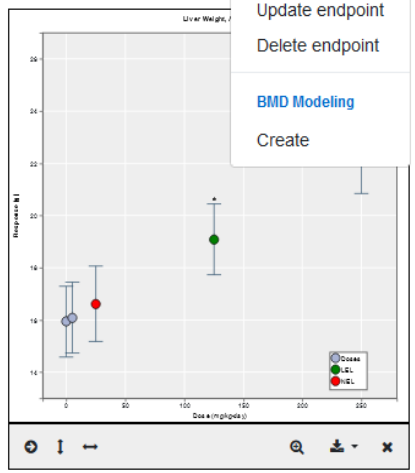
Endpoint name	Liver Weight, Absolute
System	Hepatic
Organ	Liver
Effect	Clinical Observation
Effect subtype	Organ Weight
Diagnostic description	Liver, Weight
Observation time	90 d
Data reported?	✔
Data extracted?	✔
Values estimated?	–
Location in literature	Table 5
Expected response adversity direction	---
NEL	25 mg/kg-day
LEL	125 mg/kg-day
Monotonicity	--
Trend result	not reported
Results notes	"Following 90 days of dosing, effects on organ weights were present in the testes, liver and kidney of males (Table 5) and in livers and kidneys

Actions

Endpoint Editing
Update endpoint
Delete endpoint

BMD Modeling
Create

Plot

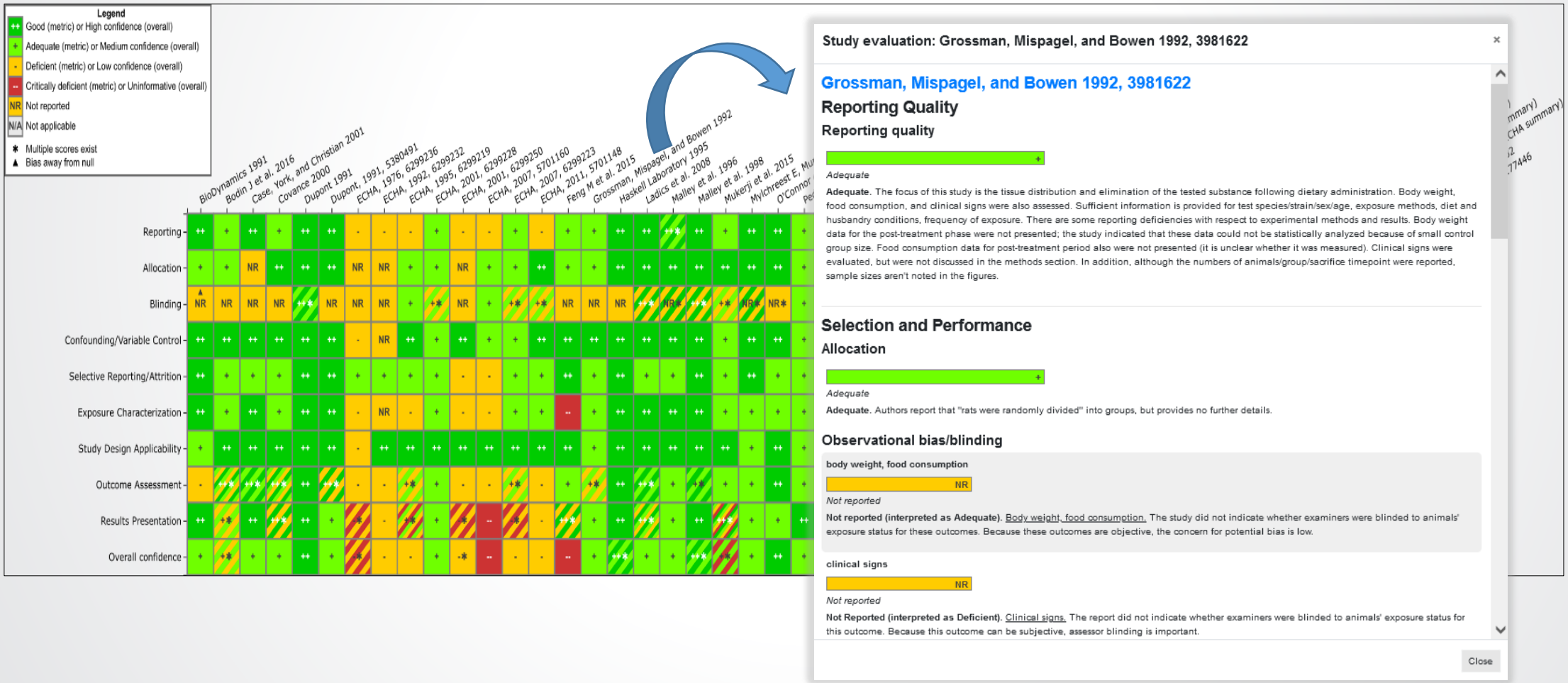


Dataset

Dose (mg/kg-day)	Number of Animals	Response (g)	Standard Deviation
0	10	15.94	1.9
5	10	16.09	1.9
25[a]	10	16.62	2.02
125[b,c]	10	19.09	1.89
250[b]	8	22.84	2.39

[a] NEL (No effect level)
[b] Significantly different from control ($p < 0.01$)
[c] LEL (Lowest effect level)

Interactive Displays: Study Evaluation



Findings to Date

- Many PFAS are data poor
  - PFAS 150: 136 animal studies for 35 PFAS, 166 human studies for 11 PFAS
  - PFAS 430: 341 unique chemicals searched that were not included in prior search; 142 had data
  - PFAS 9000: 9,266 PFAS chemicals were searched; 416 have records
- Data extraction has been extended to shorter-term studies (<1 month)
- When a specific PFAS is identified as of interest, additional higher level of effort steps are taken to identify evidence (i.e., availability of CBI studies)
- Very few inhalation toxicity studies available
  - ORD exploring approaches for extrapolating from oral administration studies

Status

- PFAS 150: Manuscript submitted September 2021
- PFAS 430: Manuscript planned for FY22
  - 119 animal bioassay studies undergoing extraction and study evaluation; 48 human studies identified
- PFAS 9000: Screening underway
  - 26,000 records being screened at title and abstract level
- Overall goal is to create a single repository that can be readily updated

Contributors

- Laura M. Carlson, CPHEA/HEEAD
- Michelle Angrish, CPHEA/CPAD
- Elizabeth G. Radke, CPHEA/CPAD
- Brittany Schultz, CPHEA/HEEAD
- Andrew Kraft, CPHEA/CPAD
- Avanti Shirke, CPHEA/CPAD
- Richard Judson, CCTE/BCTD
- Grace Patlewicz, CCTE/CCED
- Robyn Blain, ICF International Inc.
- Cynthia Lin, ICF International Inc.
- Nicole Vetter, ICF International Inc.
- Courtney Lemeris, ICF International Inc.
- Pamela Hartman, ICF International Inc.
- Heidi Hubbard, ICF International Inc.
- Xabier Arzuaga, CPHEA/CPAD
- Allen Davis, CPHEA/CPAD
- Laura V. Dishaw, CPHEA/CPAD
- Ingrid Druwe, CPHEA/CPAD
- Hillary Hollinger, CPHEA/HEEAD
- Ryan Jones, CPHEA/HEEAD
- J. Phillip Kaiser, CPHEA/CPAD
- Lucina Lizarraga, CPHEA/CPAD
- Pamela Noyes, CPHEA/CPAD
- Michele Taylor, CPHEA/CPAD
- Andrew J. Shapiro, CPHEA/HEEAD
- Antony J. Williams, CCTE/CCED
- Kristina A. Thayer, CPHEA/CPAD

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