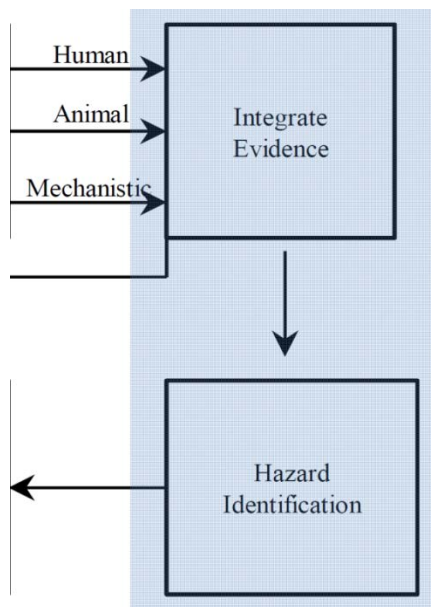


Integrating Evidence... It is not a novel challenge

NRC, 2014



International Agency for Research on Cancer

		EVIDENCE IN EXPERIMENTAL ANIMALS			
		Sufficient	Limited	Inadequate	ESLC
EVIDENCE IN HUMANS	Sufficient	Group 1			
	Limited	↑1 <u>strong evidence in exposed humans</u> Group 2A	↑2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
	Inadequate	↑1 <u>strong evidence in exposed humans</u> ↑2A <u>strong evidence ... mechanism also operates in humans</u> Group 2B ↓3 <u>strong evidence ... mechanism does not operate in humans</u>	↑2A belongs to a mechanistic class ↑2B with supporting evidence from mechanistic and other relevant data Group 3	↑2A belongs to a mechanistic class ↑2B with strong evidence from mechanistic and other relevant data Group 3	Group 3 ↓4 <u>consistently and strongly supported by a broad range of mechanistic and other relevant data</u>
	ESLC	Group 3			Group 4

Globally Harmonized System of Classification and Labelling of Chemicals

		EVIDENCE IN EXPERIMENTAL ANIMALS		
		Sufficient	Limited	Inadequate
EVIDENCE IN HUMANS	Sufficient	Category 1A (known human carcinogen)		
	Limited	Category 1B (presumed human carcinogen)	Category 2 (suspected carcinogen)	
	Inadequate			

National Toxicology Program Report on Carcinogens

		EVIDENCE IN EXPERIMENTAL ANIMALS		
		Sufficient	Limited	Inadequate/ESLC
EVIDENCE IN HUMANS	Sufficient	Known to be a human carcinogen		
	Limited	Reasonably anticipated to be a human carcinogen		
	Inadequate/ESLC	Not listed (unless the agent belongs to a well-defined class of carcinogens)		

Integrating Evidence... What IS “evidence”?

NRC 2014 (Review of the Formaldehyde Assessment in the NTP 12th RoC):

“The statement of task specifically asked the committee to “integrate the level-of-evidence conclusions, and considering all relevant information in accordance with the RoC listing criteria, make an independent listing recommendation for formaldehyde and provide scientific justification for its recommendation” (Appendix B). **The committee notes that the term *integrate* does not have a standard definition in the context of hazard assessment. The committee understood the term in its conventional sense of bringing together parts into a whole.**”

Point #1: “Not all evidence was created equal...”

NRC 2014 (Review of the Formaldehyde Assessment in the NTP 12th RoC):

“To be listed as “*reasonably anticipated as a human carcinogen*” or “*known to be a human carcinogen*”, the RoC listing criteria only requires **information to be integrated across human studies or across animal studies**, and supporting information [...] from mechanistic studies.”

NRC 2014 (Review of the EPA IRIS process):

“...the EPA guidelines for cancer risk assessment state that classification of a chemical as a human carcinogen is reached when there is “convincing epidemiologic evidence of a *causal* association between human exposure and cancer” (EPA 2005). According to the guidelines, the **determination can be made irrespective of the strength of the animal data.**”

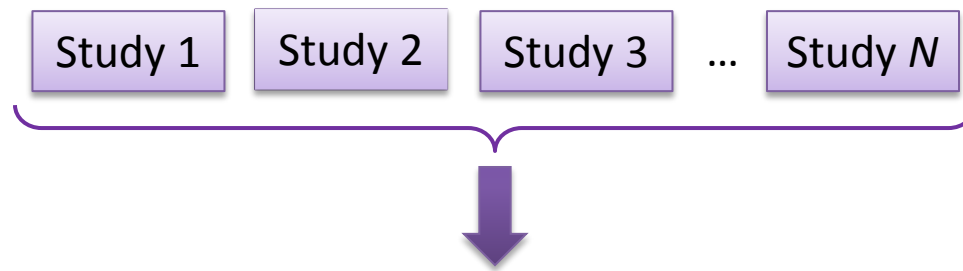
NRC 2014 (Review of the Formaldehyde Assessment in the NTP 12th RoC):

“The committee notes that *evidence in experimental animals* and a *known mechanism of action* **is not required** by the RoC listing criteria in making a listing recommendation that a substance is known to be a human carcinogen if the evidence from studies in humans is sufficient and indicates an association between exposure and human cancer.”

Integrating Evidence for Hazard Identification ...within each “data domain”

Point #2: *We should not attempt to integrate ALL evidence*

Human or Animal
Evidence



- **Sufficient** epidemiologic evidence of an association consistent with causation
- **Suggestive** epidemiologic evidence of an association consistent with causation
- **Inadequate** epidemiologic evidence to infer a causal association
- Epidemiologic evidence consistent with **no causal association**

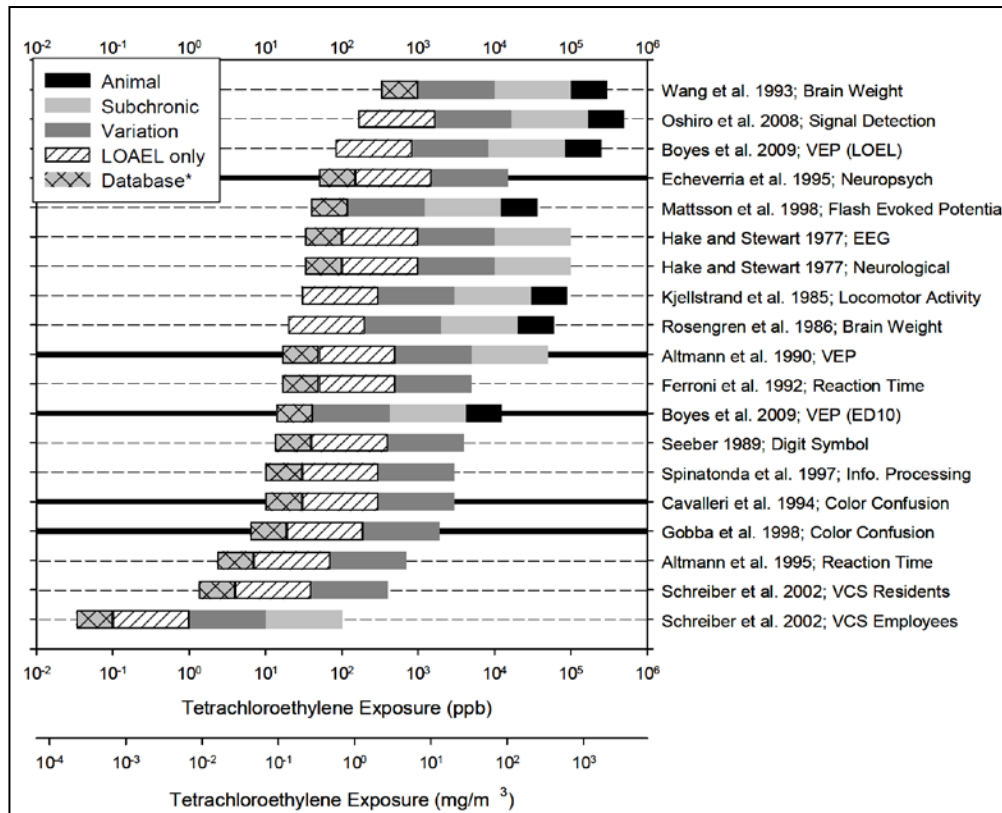
NRC 2014 (Review of the EPA IRIS process)

Point #3: *It is more important to define how “sufficient,” “suggestive,” and “inadequate” terms are ascribed to the body of evidence within each “data domain”*

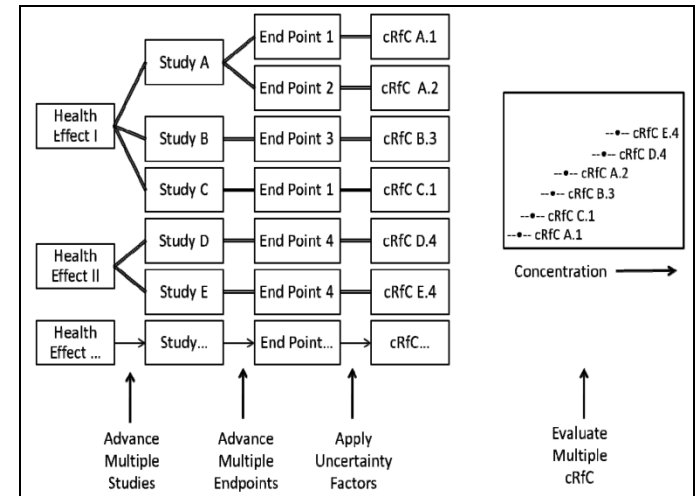
Integrating Evidence for Dose Response Assessment

Point #4: Evidence integration does not stop at “hazard identification”

NRC, 2010 and NRC, 2014



NRC, 2011



NRC, 2014

