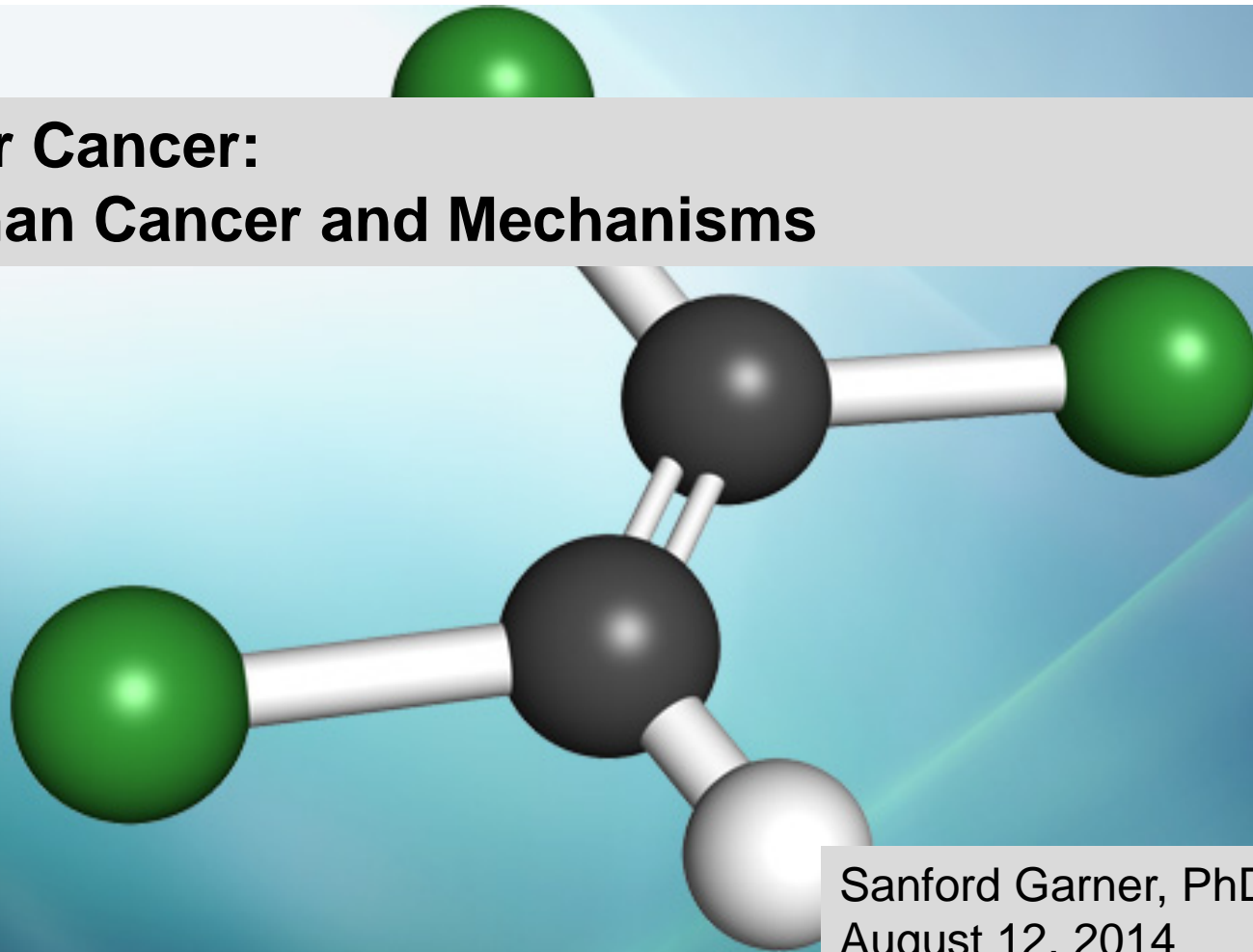




NTP

National Toxicology Program

Liver Cancer: Human Cancer and Mechanisms



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Outline

- Evidence from cancer epidemiologic studies on liver cancer and exposure to trichloroethylene
 - Peer reviewer comments and panel discussion
- Evidence from experimental animal studies
- Evidence from mechanistic studies
 - Peer reviewer comments and panel discussion
- Integration of human and mechanistic data
 - Panel discussion and vote on the NTP preliminary level of evidence conclusion for liver cancer

Liver cancer: Background information

- Relatively rare with low survival

US Rate (100,000)	Men	Women
Incidence	11.9	4.0
Mortality	8.3	3.4

- 5 yr. survival ~17%

- Risk factors

- Occupational/environmental: known – some types of radiation (plutonium, thorium and its decay products), vinyl chloride, polychlorinated biphenyls limited evidence – arsenic and X- and gamma radiation
- Non-occupational: alcohol consumption, aflatoxins, estrogen-progestogen contraceptives, tobacco smoking, betel quid use without tobacco, viral infections and parasites, long-term use of anabolic steroids, and ionizing radiation

Liver cancer studies

Moderate	Hansen 2013
	Radican 2008
	Morgan 1998
Low/moderate	Lipworth 2011
	Boice 2006
	Raaschou-Nielsen 2003
Low	Bove 2014
	Silver 2014
	Vlaanderen 2013
	Christensen 2013
	Bahr 2011
	Ritz 1999
	Greenland 1994

- 12 cohort or nested case-control studies and 1 case-control study (1 exposed case)
- Some studies reported on primary liver cancer, others combined liver and intrahepatic bile ducts and a few combined liver and intrahepatic and extrahepatic bile ducts and gallbladder
- Major limitation: Limited sensitivity to evaluate risks or exposure-response relationships
- Potential confounding from exposure to radiation – Ritz *et al.* 1999.

Grey = study quality: darkest = lowest study quality;

Blue = overall direction of bias towards null based on study sensitivity: darkest shade = least sensitive;

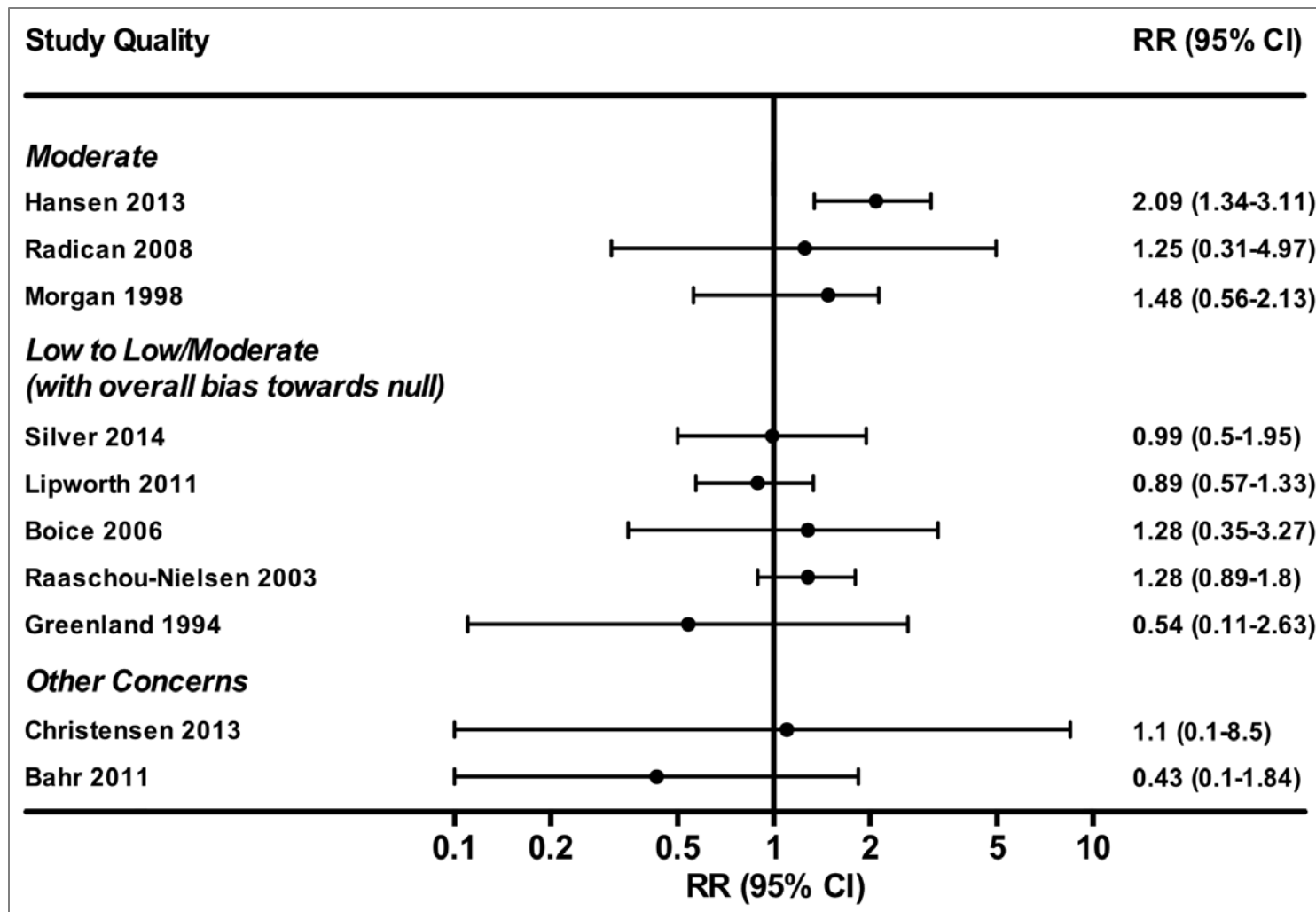
Peach = overall direction of bias towards a positive effect; Tan = multiple methodological concerns OR 1 exposed case (for Christensen *et al.* 2013).

Data are inadequate to evaluate the relationship between liver cancer and exposure to TCE

- Evidence for an association primarily comes from a few cohort studies and statistically significant increased risks in 2011 and 2007 meta-analyses
 - Evidence from recent studies, published since the most recent meta-analysis (EPA 2011), appears to be weaker
- Little evidence for an exposure-response relationship
- Confounding cannot be ruled out especially in the aircraft manufacturing studies
 - Some co-exposures cause liver cancer in experimental animals
- Findings inconsistent across studies

Inconsistent findings across studies

RR for liver cancer and ever exposed to TCE stratified by study quality



Liver cancer human studies: Reviewer questions

- Comment on whether the scientific information from the cancer studies in humans for TCE is clear, technically correct, and objectively presented.
- Provide any scientific criticisms of NTP's liver cancer assessment of the epidemiologic studies of exposure to TCE, including how the findings from the individual studies were interpreted and the evidence across studies was synthesized.
- Identify any information that should be added or deleted.

Cancer studies in experimental animals

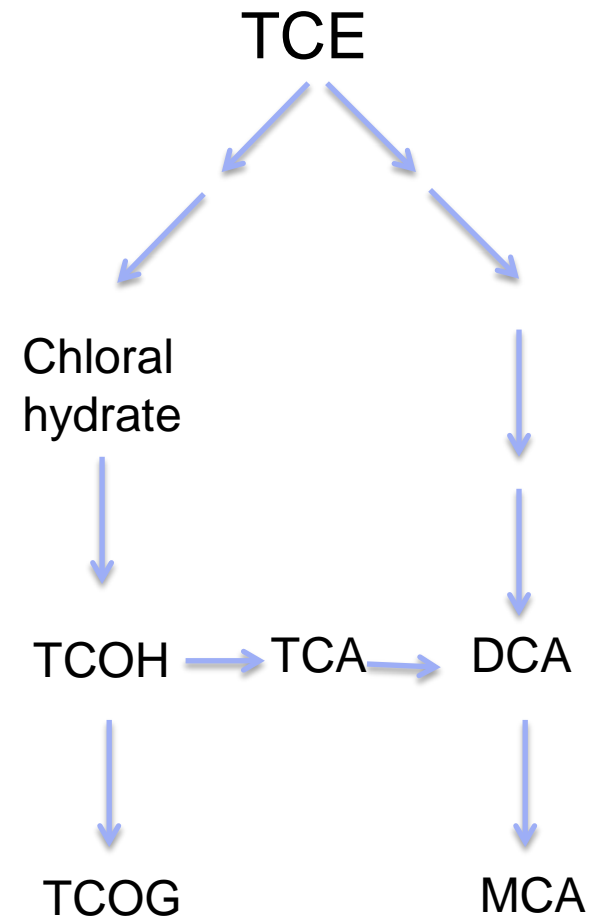
- TCE caused tumors in both mice and rats and by different routes of exposure
- Mice
 - Liver tumors in both sexes exposed to TCE by inhalation or stomach tube

Available data support a role for oxidative metabolites of TCE in liver carcinogenicity

- Oxidative metabolites of TCE include chloral hydrate, TCA, and DCA
- Several biologically plausible modes of action, including mechanisms that are potentially relevant to humans, have some supporting evidence, but overall no definite conclusion can be reached
- The available data suggest that the mode of action is complex and likely involves key events from several pathways

Oxidative metabolites of TCE are involved in liver carcinogenesis

- The liver in both humans and animals is exposed to oxidative metabolites of TCE
 - Chloral hydrate concentrations *in vivo* may be less than those that cause genotoxicity
 - Neither TCA nor DCA alone causes the full characteristics of TCE-induced liver tumors (e.g., immunostaining for c-Jun and H-*ras* mutation frequency)



TCE-induced liver cancer is likely caused by complex mechanisms involving multiple pathways

Mode of action	Supporting evidence
Genotoxicity	Some oxidative metabolites are genotoxic and are produced in or reach the liver
PPAR α activation	Oxidative metabolites activate PPAR α and PPAR α activation affects cell proliferation
Oxidative stress	TCE and its oxidative metabolites induce oxidative stress, which can lead to chronic inflammation, mutations, and other damage
Epigenetic changes	TCE, TCA, and DCA induce hypomethylation and increase cell proliferation
Autoimmune hepatitis	Oxidative metabolites can form protein adducts and induce immunomodulation in MRL ^{+/+} mice

Biologically plausible modes of action for TCE-induced liver cancer lack data to draw definite conclusions

- Although several mechanisms are biologically plausible, no one mode of action has adequate supporting data to identify a single mechanism for liver carcinogenicity of TCE
- Interactions between several modes of action are possible and key events from several pathways may be involved

Liver cancer mechanistic studies: Reviewer questions

- Comment on whether the mechanistic data for liver cancer are clear, technically correct, and objectively presented.
- Provide any scientific criticisms of the NTP's interpretation and application of the mechanistic data for assessing effects of TCE.
- Identify any information that should be added or deleted.

Liver cancer: Summary of preliminary level of evidence

- The data available from studies in humans are inadequate to evaluate the relationship between liver cancer and exposure to trichloroethylene
 - Inconsistent findings from studies in humans with little evidence for exposure-response relationships
 - Human studies had limited ability to evaluate rare cancer such as liver cancer
- Mechanism(s) of liver carcinogenicity have not been established but are likely complex involving key events from multiple modes of action
 - No data suggest that trichloroethylene causes liver tumors in mice by mechanisms that are not relevant to humans

Preliminary level of evidence: Liver cancer

Preliminary level of evidence conclusion

- The data available from studies in humans are inadequate to evaluate the relationship between liver cancer and exposure to trichloroethylene.

Reviewer questions

- Comment on the overall cancer evaluation for liver cancer and whether the available data support NTP's preliminary level of evidence conclusion.
- Provide any scientific criticism of the liver overall assessment and integration of the human cancer and mechanistic data.
- Vote on whether the science information supports NTP preliminary level of evidence for liver cancer.