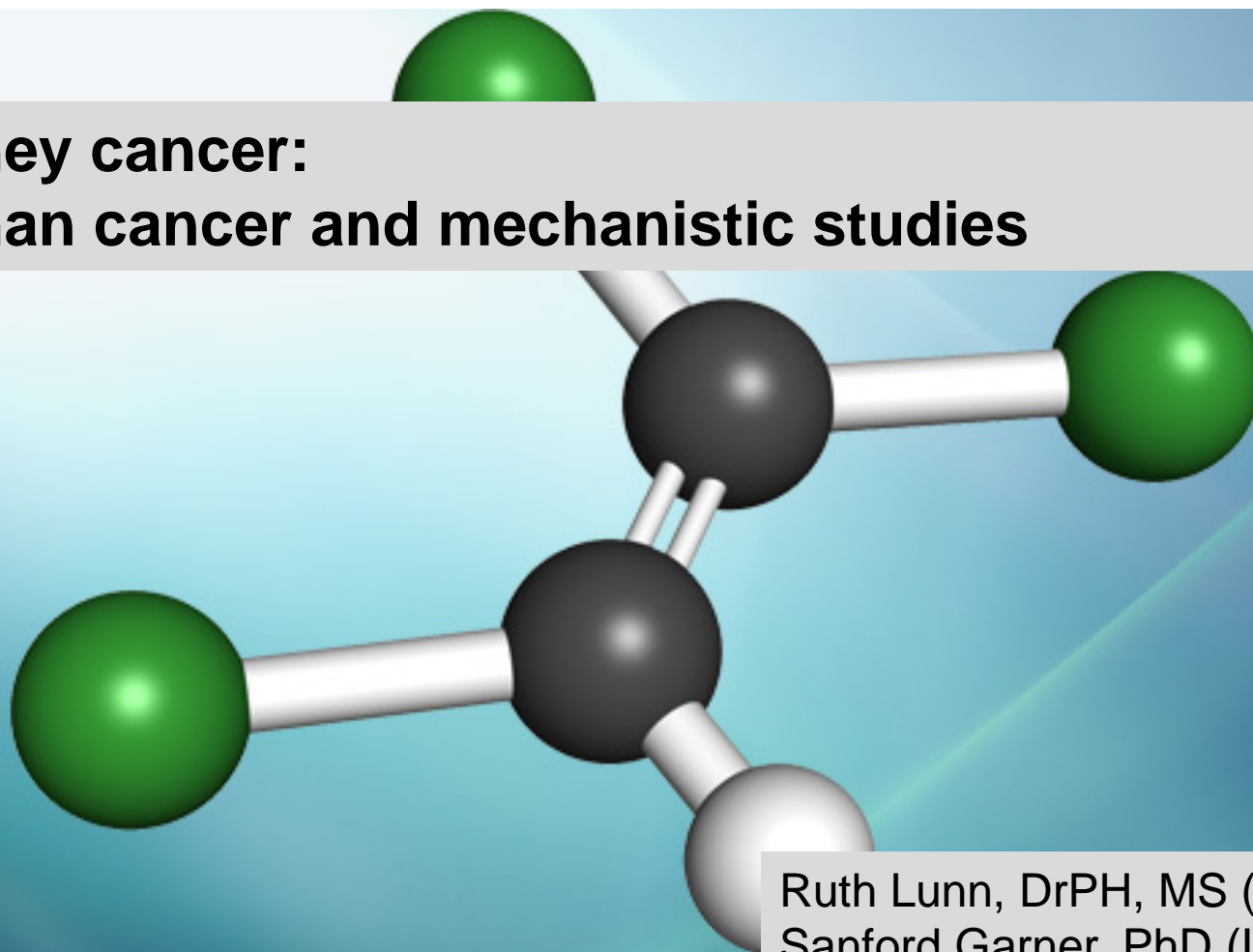




NTP

National Toxicology Program

Kidney cancer: Human cancer and mechanistic studies



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Outline

- Evidence from cancer epidemiologic studies on kidney cancer and exposure to trichloroethylene
 - Peer reviewer comments and panel discussion
- 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 kidney cancer

Kidney cancer: Background information

- Relatively rare with high survival

SEER Rate (100,000)	Men	Women
Incidence	21	10.6
Mortality	5.8	2.6

- 5 year survival 70%
- Risk factors
 - Occupational: IARC classifications
 - Sufficient evidence: X-radiation
 - Limited evidence: Arsenic, cadmium and printing processes
 - Non-occupational: tobacco smoking, obesity, diabetes, hypertension, X-radiation

Kidney cancer: 12 Cohort or nested case-control studies

Study	Exposure Assessment
<i>Nordic studies: TCE-exposed workers identified from broad occupation or population databases</i>	
Hansen <i>et al.</i> 2013	Urine TCA
Raaschou-Nielsen <i>et al.</i> 2003	Blue-collar workers in companies
Vlaanderen <i>et al.</i> 2013	Linkage of census data with JEM
<i>USA Aerospace and aircraft manufacturing workers</i>	
Boice <i>et al.</i> 2006	Qualitative JEM
Zhao <i>et al.</i> 2005	Semi-qualitative JEM
Lipworth <i>et al.</i> 2011	Qualitative JEM
Radican <i>et al.</i> 2008/Blair <i>et al.</i> 1998	Semi-qualitative JEM
Morgan <i>et al.</i> 2013	Semi-qualitative JEM
<i>Other studies</i>	
Silver <i>et al.</i> 2014	US Microelectronic workers Individual work history linked to dept.-year exposure matrix
Henschler <i>et al.</i> 1996	German cardboard mfg. workers Job location/knowledge of exposure setting
Greenland <i>et al.</i> 1994	US Electrical workers Qualitative JEM
Bove <i>et al.</i> 2014	Camp Lejeune Duration of residence and modeled TCA concentration

Kidney cancer: Case-control studies & meta-analyses

Case-control study	Location/Industry	Exposure Assessment
<i>Specific areas or focus on TCE</i>		
Moore <i>et al.</i> 2010	Central & Eastern Europe Higher intensity	Expert assessment (knowledge of local industries)
Charbotel <i>et al.</i> 2006, 2009	Arve Valley, France Screw-cutting industry	Semi-quantitative JEM
Brüning <i>et al.</i> 2003	Arnsberg Germany Metal and electronic work	Self-exposure, symptoms, JEM
Vamvakas <i>et al.</i> 1998		Expert assessment - symptoms, and other information
<i>Other case-control studies</i>		
Christensen <i>et al.</i> 2013	Montreal, Quebec Canada Diverse	Expert assessment
Pesch <i>et al.</i> 2000a	Germany	JEM/JTEM
Dosemeci <i>et al.</i> 1999	Connecticut (women), USA Diverse	Generic JEM

2 Meta-analyses: Scott & Jinot 2011, Karami *et al.* 2012

Kidney cancer studies: Study quality evaluation

High	Moore 2010
	Charbotel 2006
	Zhao 2005
Moderate	Hansen 2013
	Radican 2008
	Bruning 2003
	Morgan 1998
Low/moderate	Raaschou-Nielsen 2003
	Lipworth 2011
	Pesch 2000
	Christensen 2013
	Dosemec 1999
Low	Silver 2014
	Bove 2014
	Vlaanderen 2013
	Greenland 1984
	Vamvakas 1998
	Henschler 1995

- Most studies of low to moderate quality had limited sensitivity to detect an association
- Two studies had potential biases that would likely lead to overestimate of the risk estimate

Grey: Studies ranked into 4 categories Most informative (lightest) to the least informative studies (darkest).

Blue: Study sensitivity: darkest shade least sensitive; Peach: Overall bias away from the null; Tan: Other concerns

Kidney cancer: Most informative studies

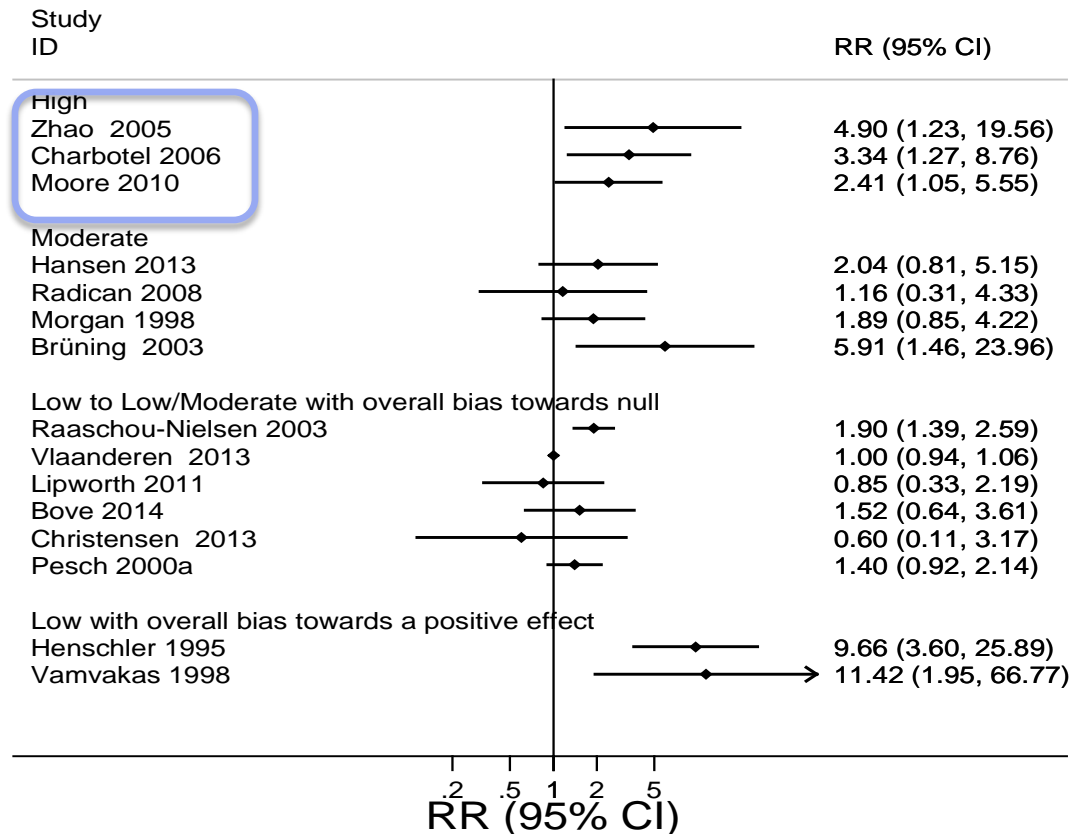
Study	Study design/population	Strengths
Zhao <i>et al.</i> 2005 USA	Cohort study Aerospace workers	Semi quantitative exposure assessment High exposure Control for co-exposures Exposure response relationships
Charbotel <i>et al.</i> 2006, 2009 France	Case-control study Screw-cutting workers	Semi quantitative exposure assessment High exposure Control for co-exposures Exposure response relationships
Moore <i>et al.</i> 2010 Central and Eastern Europe	Case-control study Eastern and central Europe	Large size Semi quantitative exposure assessment Exposure response relationships

Credible evidence of a causal association between increased kidney cancer risk and exposure to TCE

- Consistent evidence of increased risk across studies of different study designs, in different geographical locations and in different occupational settings
- Evidence of increasing risk with increasing level or duration of exposure
- Meta-analyses showing statistically significant increased risk across studies
- Findings unlikely to be explained by chance, bias or confounding

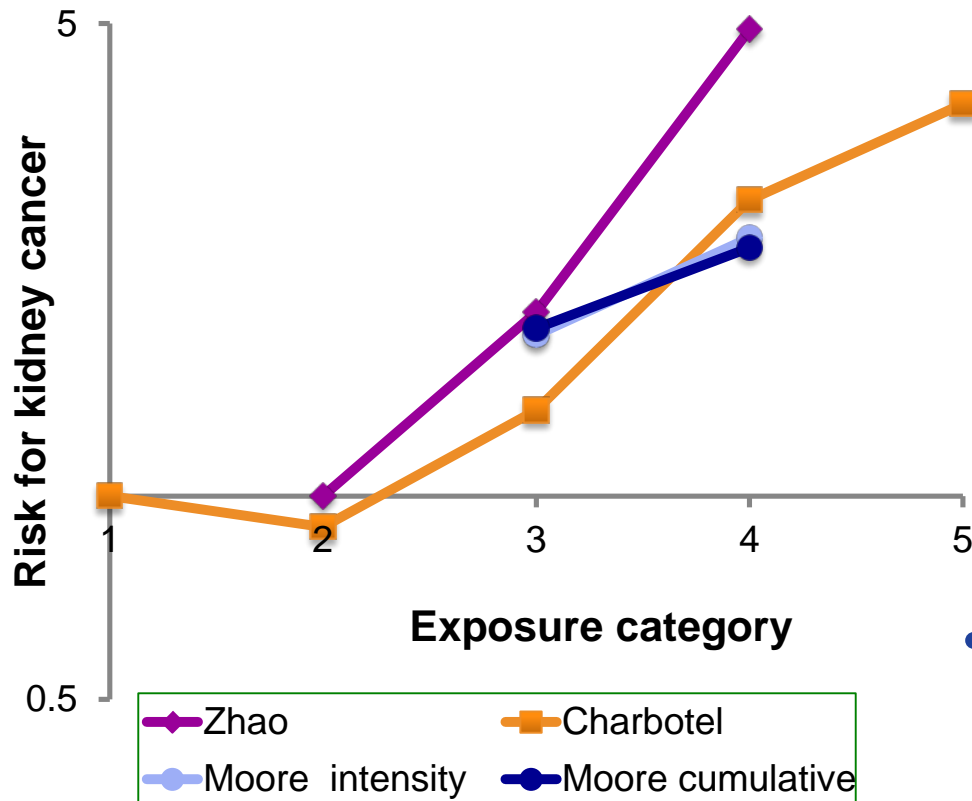
Consistent findings across studies

TCE & Kidney Cancer High Exposure By Study Quality



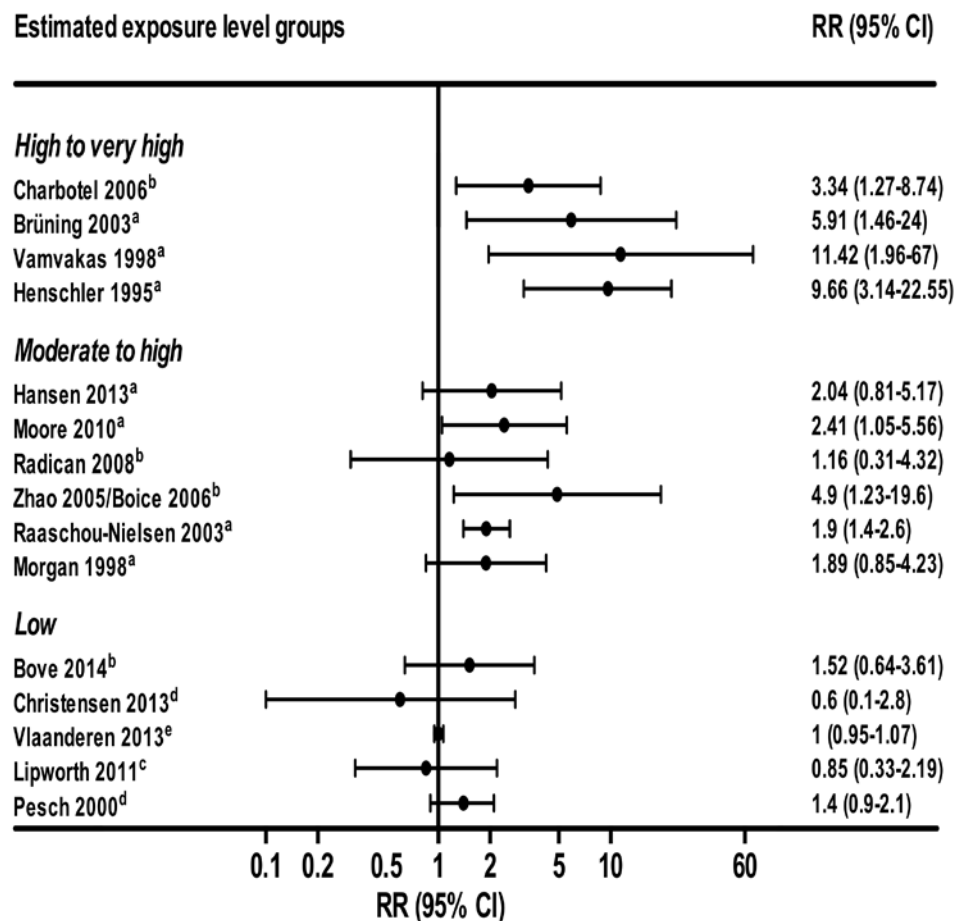
For each study, risk estimates (SMR, SIR, RR, HR, or OR) were extracted for the highest estimated exposure group (intensity or cumulative exposure), if reported. Studies findings are grouped by broad categories of study quality. Studies only reporting ever exposure (except Henschler 1995) are not graphed).

Risks of kidney cancer increased with increasing TCE exposure in several well-conducted studies



- Cumulative Exposure Category (Zhao and Charbotel)
 - 1 no exposure
 - 2 low exposure
 - 3 medium exposure
 - 4 high
 - 5 high + peaks (Charbotel)
- Moore only evaluated two different exposure categories for each metric

Highest risk found in studies with estimated higher exposure



- Studies were grouped by broad categories of estimated exposure for the highest exposure category for that study
- Estimated exposure levels values were reported in several reviews or by study authors.
- Limitation: Studies reported different metrics of exposure

Different metrics of exposure were graphed. a = exposure intensity, b = cumulative exposure, c = exposure duration, d = categories including confidence of probability of exposure with level and/or duration, and e = cumulative exposure measures that included exposure prevalence.

Robust findings from two meta-analyses

	Scott & Jinot 2011	Karami <i>et al.</i> 2012
Ever exposed	1.27 (1.13–1.43); 15*	1.32 (1.17–1.50); 18*
Highest exposure	1.58 (1.28–1.96); 13*	NR

- mRR for case-control studies higher, but not significantly so, than cohort studies
- No evidence of publication bias or heterogeneity
 - Did not include Vamvakas *et al.* and Henschler *et al.*
- Robust and not sensitive to removal of individual studies or selection of alternative RRs (Scott & Jinot 2011)

*mRR (95% CI); # of studies

Findings unlikely to be explained by confounding or biases

- Studies of specific industries found positive associations after consideration of known co-exposures in their analyses (Zhao *et al.* 2005, Charbotel *et al.* 2006, 2009)
- Other studies included workers of diverse occupations with varying types and patterns of co-exposures, and the prevalence of exposure to any specific co-exposure was likely low
- Smoking not likely to explain association
 - No excess risk of lung cancer across cohort studies (meta-analysis)
 - Most case-control studies controlled for smoking
- Potential biases (such as selection) unlikely to explain all of the excess risk of kidney cancer associated with trichloroethylene exposure

Kidney 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 kidney 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.

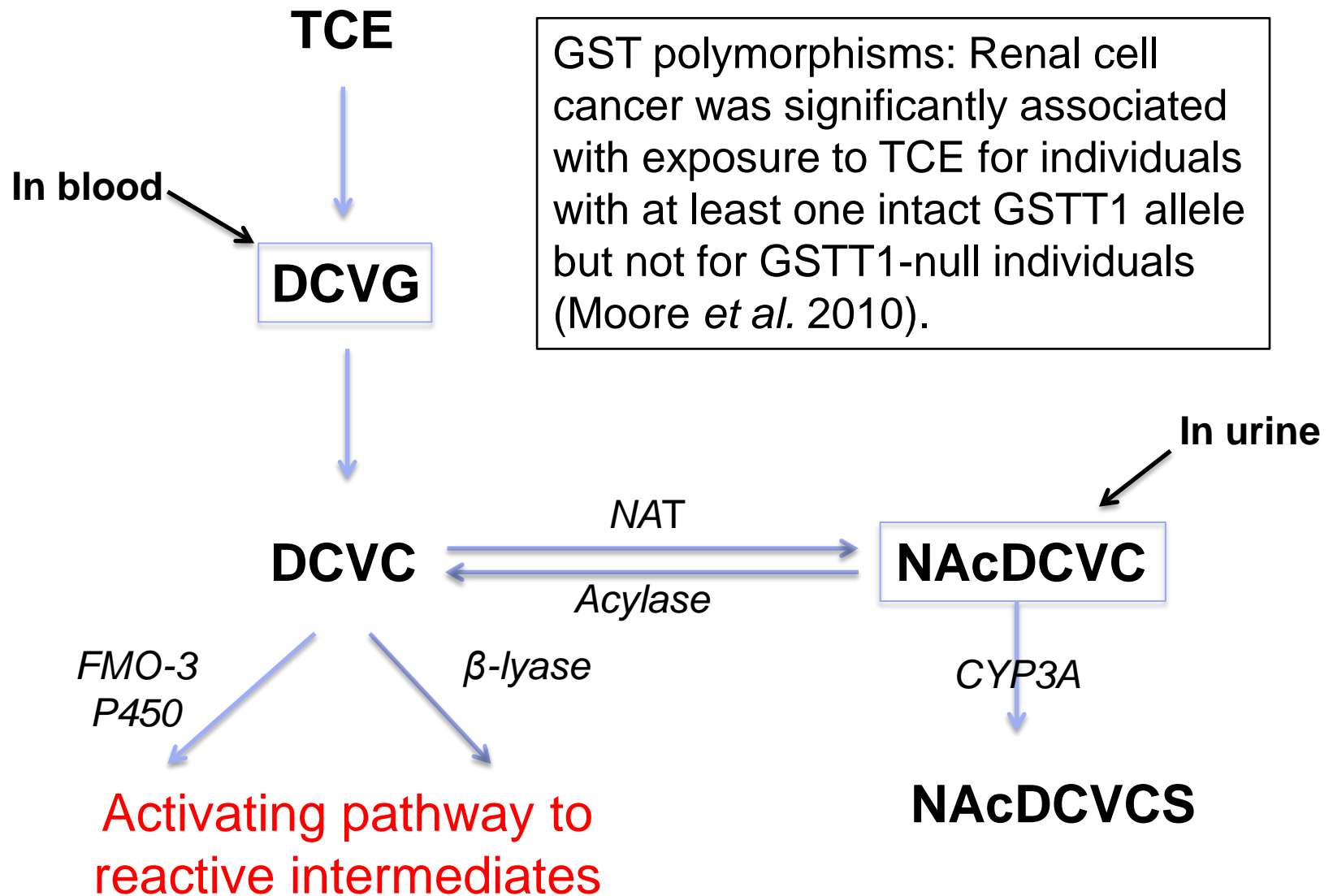
Credible mechanistic evidence exists for renal carcinogenicity of TCE

- Tissue site concordance for kidney in humans and rats
- Toxicokinetic and mechanistic data in both humans and animals provide evidence for biologically plausible modes of action for TCE's carcinogenicity in humans.
 - GSH-conjugation-derived metabolites produced *in situ* or delivered systemically to the kidneys
 - Mutagenic and genotoxic effects induced by GST-mediated metabolites
 - Cytotoxicity (nephrotoxicity) and regenerative cellular proliferation

Cancer studies in experimental animals

- TCE caused tumors in both mice and rats and by different routes of exposure.
- Rats
 - Kidney tumors in males exposed to TCE by inhalation or stomach tube

GSH-conjugation-derived metabolites



Genotoxicity of TCE and its metabolites

- **Genotoxicity in kidney**

- TCE (oral exposure) increased numbers of micronucleated cells in rat kidney
- The GSH-conjugation-derived TCE metabolite DCVC (oral exposure) increased DNA strand breaks in kidney of rats and mice

- **Genotoxicity in other tissues-** DCVC induced gene mutation and UDS, and increased cell transformation in a variety of other cell types

- **VHL mutations-** Inactivation of the VHL tumor suppressor gene is thought to be an early and causative event in human renal clear-cell carcinoma; however, epidemiological studies of VHL mutations and exposure to TCE have been inconclusive

Nephrotoxicity of TCE and its metabolites

- DCVC causes necrosis in human proximal tubule cells *in vitro* at high concentration and increased cell proliferation and apoptosis at lower concentrations
- DCVC also is nephrotoxic in rats, mice, guinea pigs, rabbits, cats, and dogs
- Rats and mice exposed to DCVC in drinking water showed nephrotoxicity progressing from tubular necrosis to increased karyomegaly and cytomegaly that were similar to chronic effects of TCE
- Although cytotoxicity alone is insufficient for tumor formation, chronic tubular damage has been proposed as a precondition for nephrocarcinogenic effects of TCE in humans

Hypothesized Modes of Action of Oxidative Metabolites: TCA, DCA, TCOH

Mechanism	Evidence
PPAR α activation	Peroxisome proliferation observed only in male mouse liver
Alpha _{2u} -globulin-related nephropathy	No renal alpha _{2u} detected Kidney toxicity in both male and female rats
Formic acid-related nephropathy (indirect effect of TCE metabolites)	Dissimilarities in nephrotoxicity from formic acid compared with TCE or DCVC

Summary of evidence for mechanisms of TCE-induced kidney cancer in humans and animals

- Humans (and experimental animals) metabolize TCE by both oxidative (CYP450 mediated) pathways and GSH conjugation resulting in similar mixtures of TCE and metabolites in their tissues
- NAcDCVC has been detected in urine and DCVG in blood in humans (and experimental animals)
- Elevated risk of kidney cancer only among humans with active GST genotypes (Moore *et al.* 2010)
- Exposure to TCE is associated with nephrotoxicity in humans

Kidney cancer mechanistic studies: Reviewer questions

- Comment on whether the mechanistic data for kidney 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.

Kidney cancer: Integration

- Epidemiological studies demonstrate a causal association between exposure to TCE and kidney cancer that cannot be explained by chance, bias or confounding
 - Consistent evidence across studies and evidence of an exposure response relationship in studies with high quality
- Exposure to TCE causes kidney cancer in male rats
- Toxicological and mechanistic data provide credible evidence for the biological plausibility of the proposed mechanisms of TCE's carcinogenicity in humans
 - Mutagenic and cytogenetic mode of action mediated by GSH-conjugated metabolites
 - Key events likely occurs in humans

Preliminary level of evidence: Kidney cancer

Preliminary level of evidence conclusion

- Human epidemiologic studies, together with toxicokinetic, toxicological, and mechanistic studies in humans, provide sufficient evidence of a causal relationship between exposure to TCE and kidney cancer

Reviewer questions

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