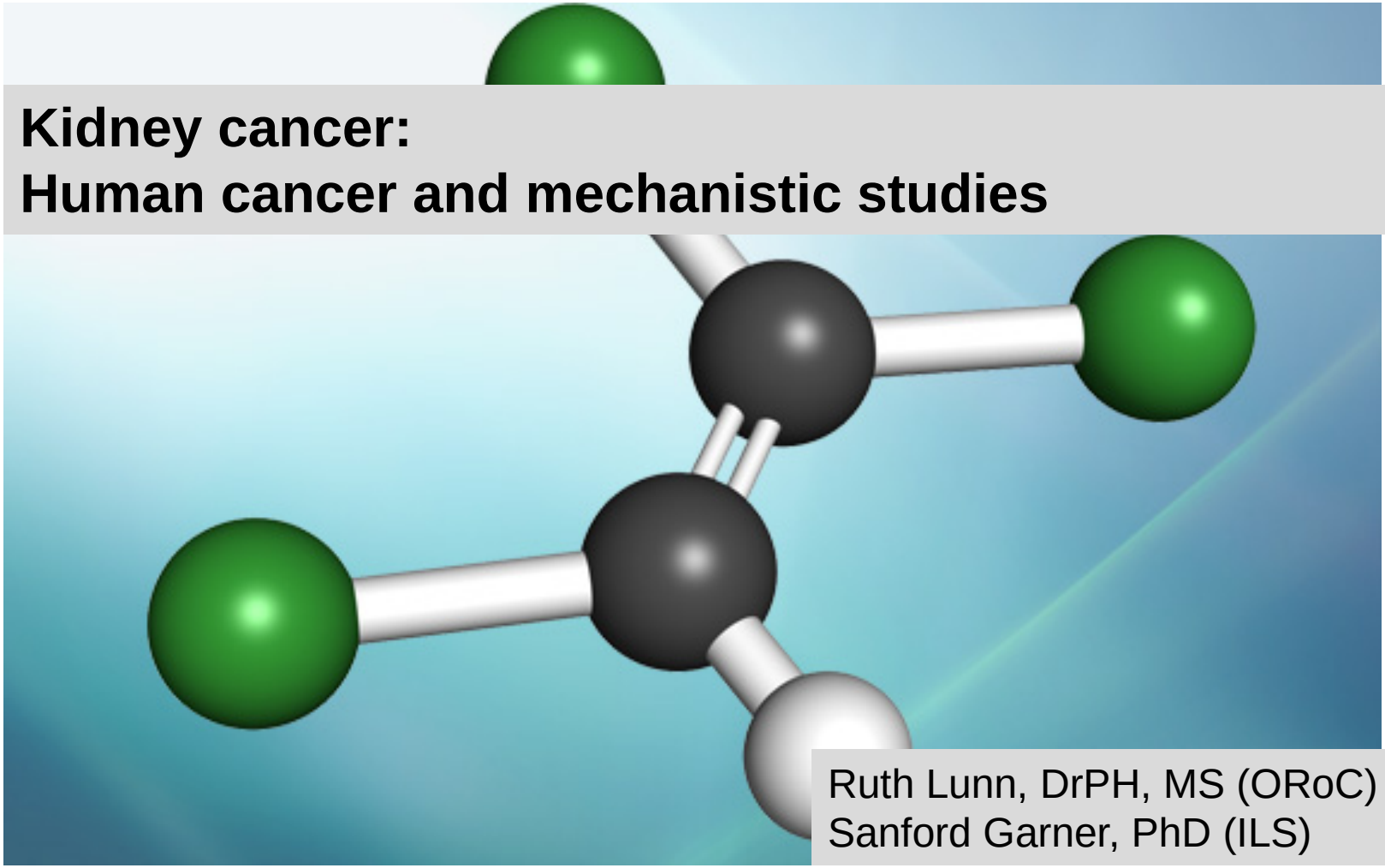
# Kidney cancer:
# Human cancer and mechanistic studies



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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

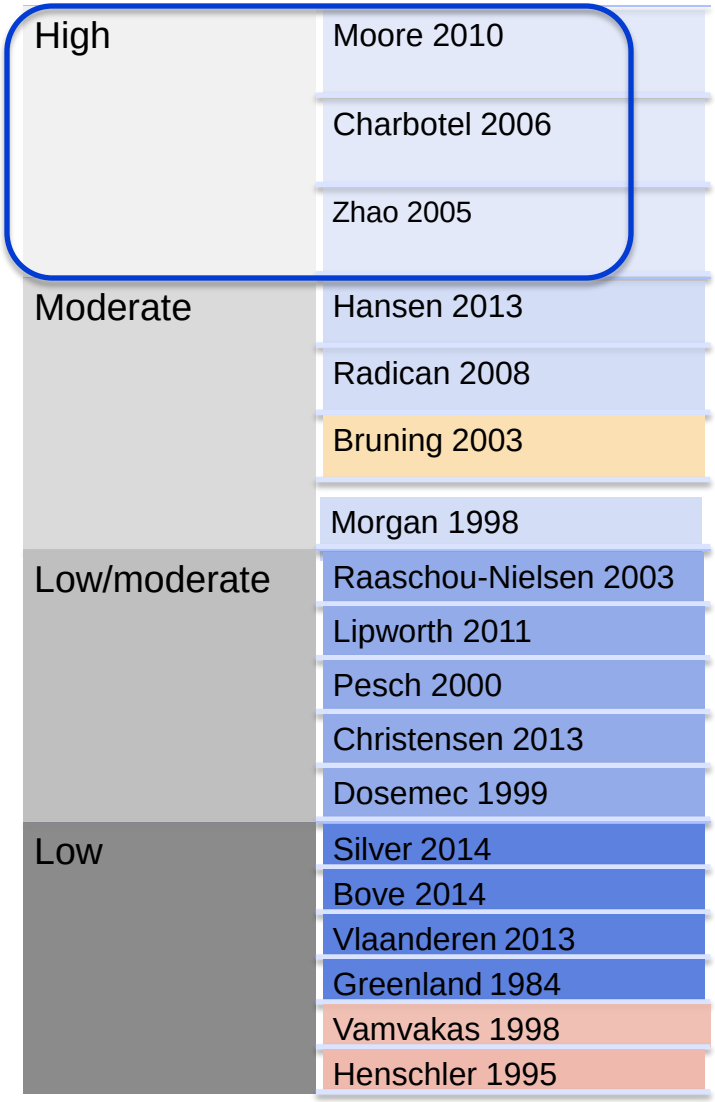
| Study | Exposure Assessment |
|---|---|
| ***Nordic studies: TCE-exposed workers identified from broad occupation or population databases*** | |
| Hansen *et al.* 2013 | Urine TCA |
| Raaschou-Nielsen *et al.* 2003 | Blue-collar workers in companies |
| Vlaanderen *et al.* 2013 | Linkage of census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

# Kidney cancer: Case-control studies & meta-analyses

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

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

# Kidney cancer studies: Study quality evaluation




- 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

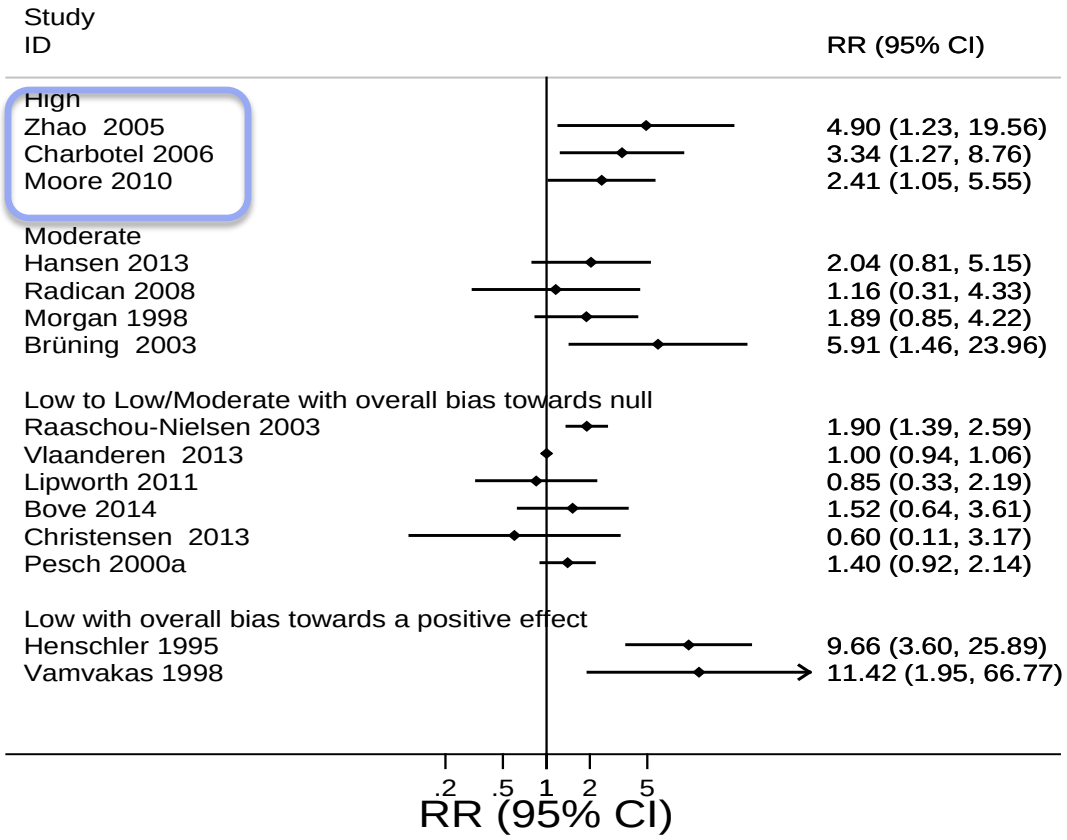
| Study | Study design/population | Strengths |
|---|---|---|
| Zhao *et al.* 2005<br>USA | Cohort study<br>Aerospace workers | Semi quantitative exposure assessment<br>High exposure<br>Control for co-exposures<br>Exposure response relationships |
| Charbotel *et al.* 2006, 2009<br>France | Case-control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

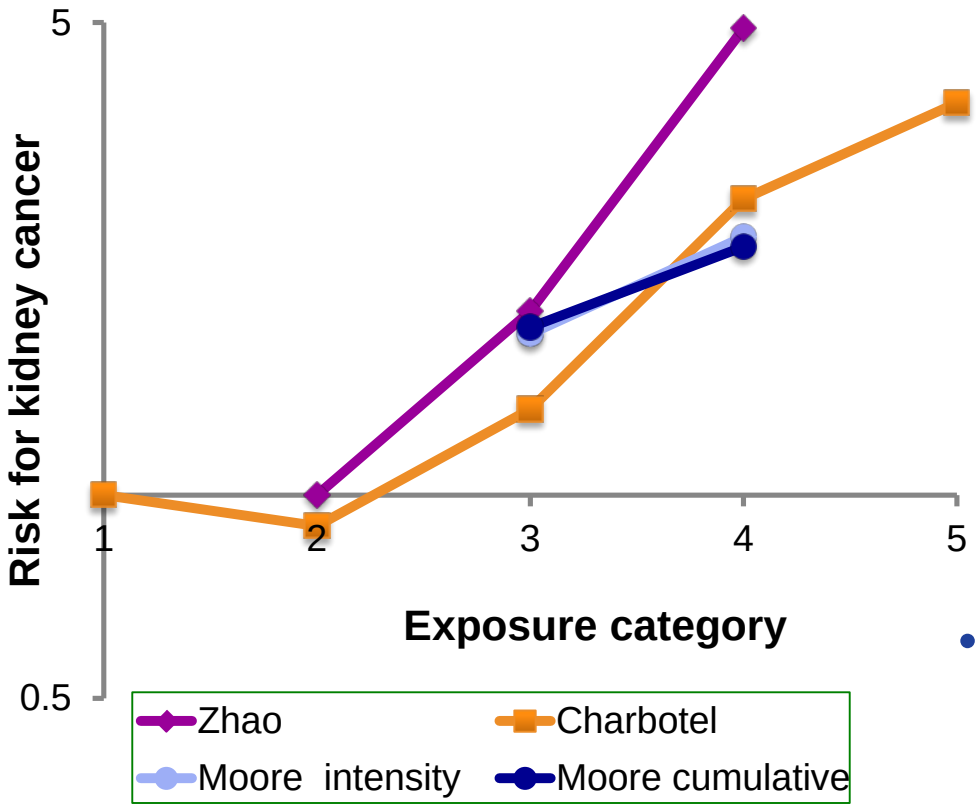
# Consistent findings across studies

TCE & Kidney Cancer High Exposure By Study Quality



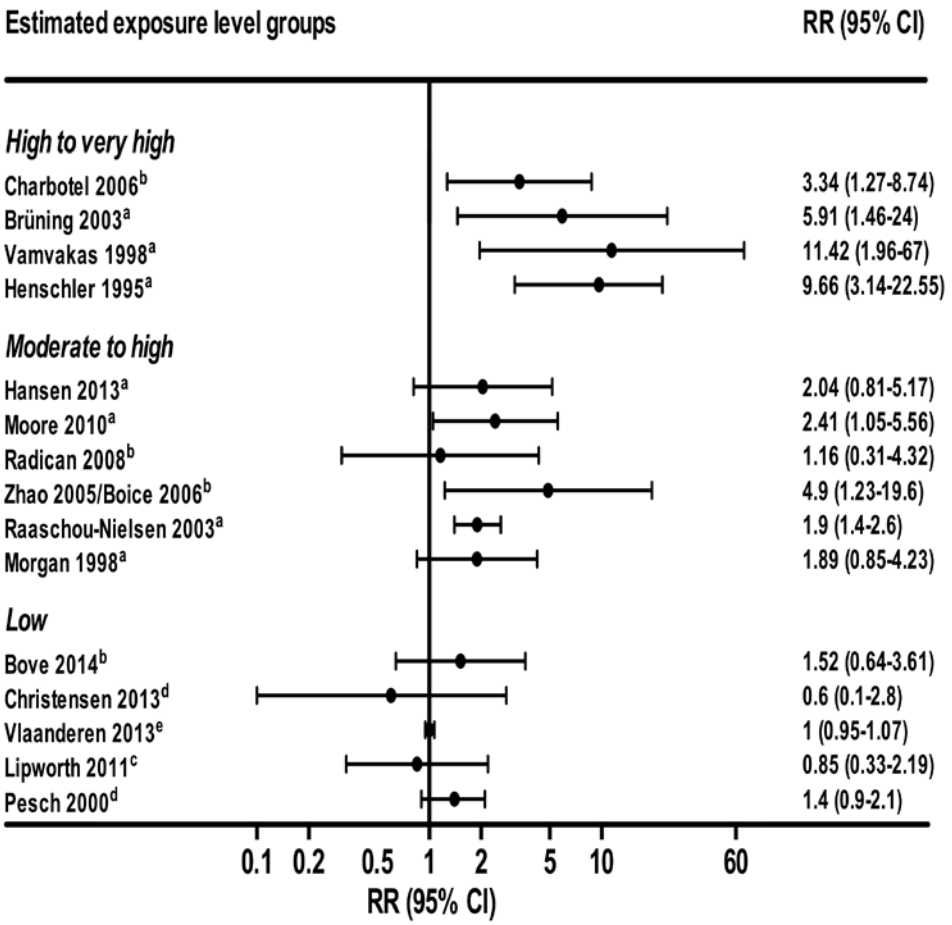

For each study, risk estimates (SMR, SIR, RR, HR, or OR) were extracted for the highest estimated exposure group (intensity or cumulative exposure), if reported. Studies findings are grouped by broad categories of study quality. Studies only reporting ever exposure (except Henschler 1995) are not graphed).

# 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 *et al.* 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.

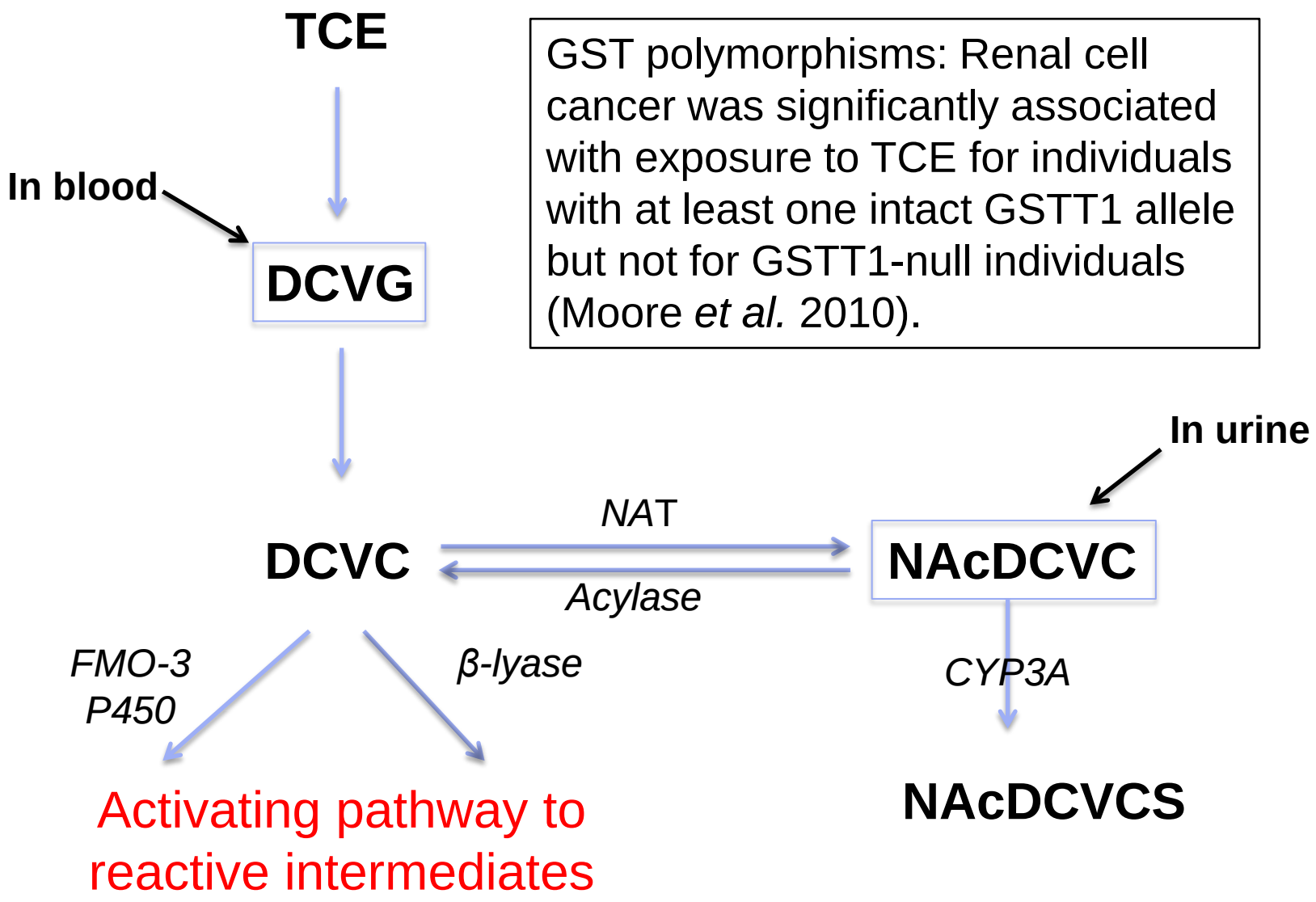
# Credible mechanistic evidence exists for renal carcinogenicity of TCE

- 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 |
|---|---|
| PPARα 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