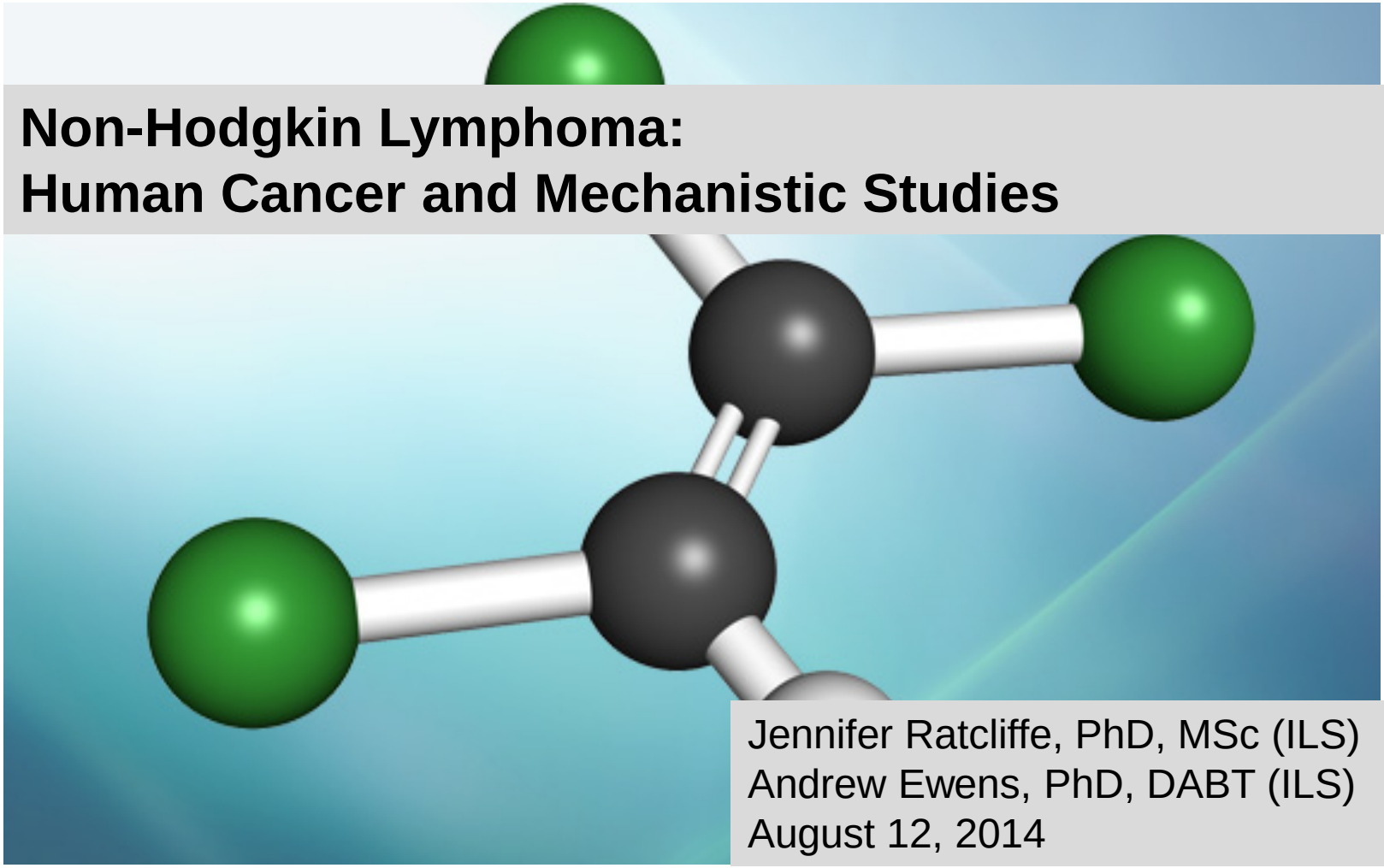
Non-Hodgkin Lymphoma: Human Cancer and Mechanistic Studies



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Outline

- Evidence from cancer epidemiologic studies on non-Hodgkin lymphoma (NHL) and exposure to trichloroethylene
  - Peer review comments and panel discussion
- Evidence from mechanistic studies
  - Peer review comments and panel discussion
- Integration of human and mechanistic data
- Panel discussion and vote on the NTP preliminary level of evidence conclusion for NHL

NHL: Background information

- Relatively uncommon with high survival:

US rates (per 100,000)*	Men	Women
Incidence	23.9	16.3
Mortality	8.2	5.1

  - 5-year survival rate: approx. 70%

- Risk factors:
  - Occupational (limited evidence): **benzene**, ethylene oxide, 2,3,7,8-TCDD, polychlorinated biphenyls, **phenoxy herbicides**, styrene, **ionizing radiation,** possibly **chlorinated solvents or other organic solvents**
  - Non-occupational: smoking (follicular lymphoma only), viral infections, immunosuppressive disorders and drugs, certain autoimmune diseases, chemotherapy drugs

*Data: NCI SEER 2006-10

Agents in **bold reported in one or more studies included in evaluation

Studies of NHL and TCE: Cohort and nested case-control studies (10)

Population	Studies	Exposure assessment
Nordic (occupational populations) (3)	Hansen 2013	Urine TCA and job
	Vlaanderen 2013	JEM and census linkage
	Raaschou-Nielsen 2003	Blue collar workers in TCE companies
	Lipworth 2011	
US aircraft/aerospace (degreasing) (4)	Radican 2008	Qualitative or semi-quantitative JEM based on work histories
	Boice 2006	
	Morgan 1998	
	Bahr 2011	Qualitative JEM
Other US (electronics mfg, uranium workers, environmental) (3)	Silver 2014	Work history link to dept.-year exposure matrix
	Bove 2014	Estimated cumulative TCE in water by residence

JEM = job-exposure matrix

Studies of NHL and related subtypes: Case-control studies (7)

Population	Studies	Exposure assessment
Europe and US populations	Cocco 2013 (pooled)	Detailed semi-quantitative JEM, multiple metrics
US population (women)	Deng 2013/Wang 2009	Generic JEM
Montreal population	Christensen 2013	Semi-quantitative JEM
Nordic populations	Persson-Fredriksson 1999	Self-reported ranked exposure
	Hardell 1994	Self-reported exposure; work histories

JEM = job-exposure matrix

- 2 meta-analyses (Scott-Jinot 2011, Karami 2013)

Study quality: NHL

Study Quality	Studies
High	Cocco 2013
Moderate	Hansen 2013
	Radican 2008
Low/moderate	Christensen 2013
	Lipworth 2011
	Wang 2009
	Costantini 2008
	Raaschou-Nielsen 2003
	Morgan 1998
Low	Silver 2014
	Bove 2014
	Vlaanderen 2013
	Bahr 2011
	Boice 2006
	Persson-Fredrikson 1999
	Hardell 1994

Grey = quality; Blue = study sensitivity (light = high); Peach = positive bias; Tan = multiple types of bias or other limitations

- Most studies of low or low to moderate quality and with limited sensitivity to detect associations
- One study had potential bias that would likely overestimate risk
- Two studies had other methodological concerns

NHL: Most informative studies

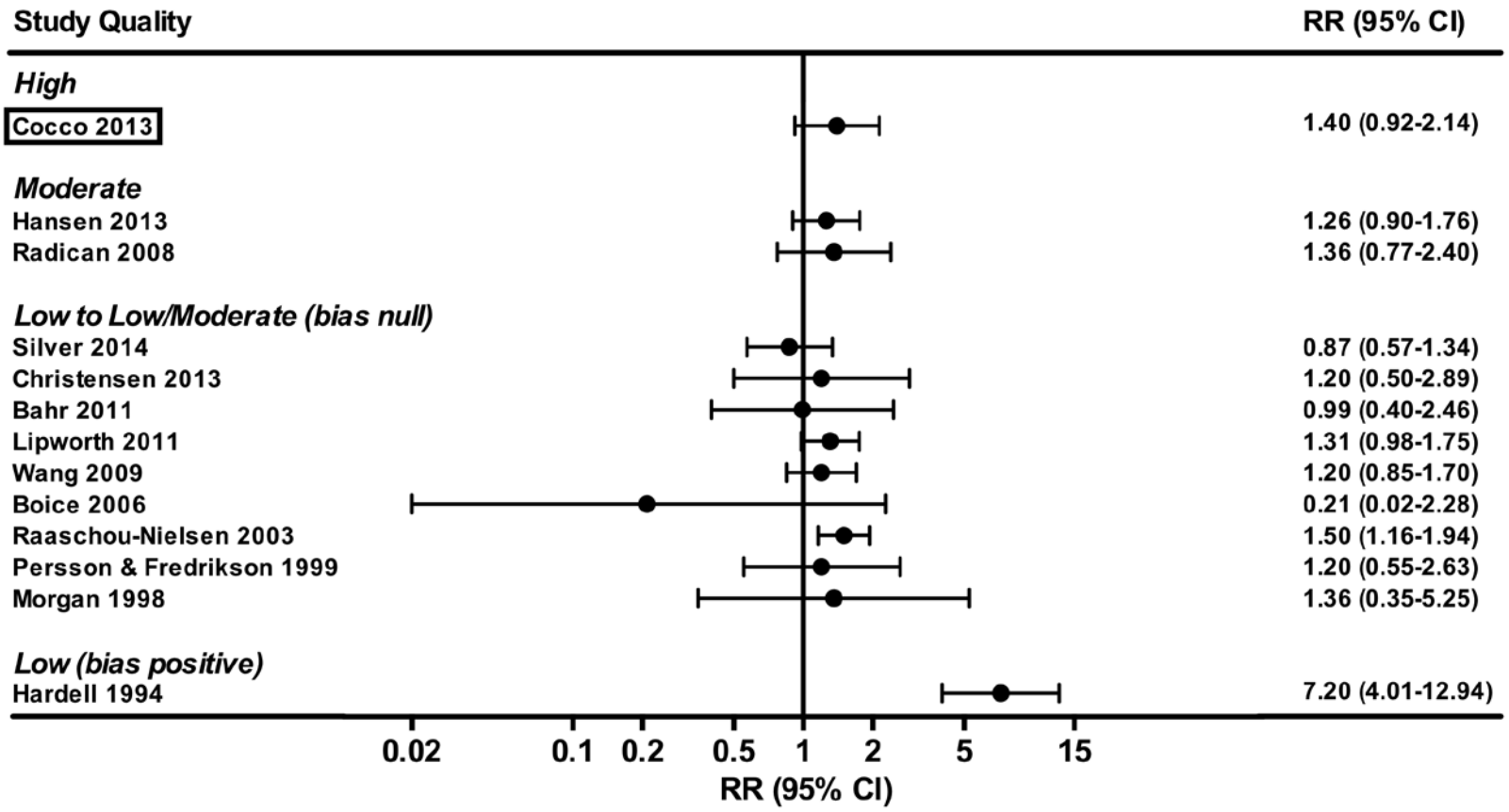
Study	Study design/population	Strengths/limitations
Cocco *et al.* 2013	Pooled case-control study Europe; 4 constituent studies	Large study Semi-quantitative exposure assessment Exposure-response relationships Detailed assessment NHL and subtypes
Hansen *et al.* 2013	Pooled and updated cohort incidence Nordic pop.; various occupations	Moderately large study Biomonitoring Misclassification of exposure a concern for levels of exposure
Radican *et al.* 2008	Cohort mortality US aircraft workers	Moderately large study Semi-quantitative exposure assessment Confounding by co-exposures cannot be ruled out

Light grey = high quality; mid-grey = moderate quality

Limited evidence of an association between NHL or related subtypes and exposure to TCE

- Moderately elevated risks observed in several studies with different study designs and in different populations, but the strength of the evidence varies across studies
- Relatively strong association and positive exposure-response trends in the most informative (InterLymph) study (Cocco *et al.* 2013) and its component study (Purdue *et al.* 2011)
- Meta-analyses suggest statistically significant increased risk for NHL across studies
- Limitations
  - Lack of strong association and exposure-response relationships in cohort studies
  - Some case-control studies had methodological limitations
  - Confounding by co-exposure to chlorinated or organic solvents cannot be ruled out in some (e.g., aircraft workers) studies

NHL ever-exposed to TCE by study quality: Consistent findings of modest increase in several studies



Positive exposure-response for multiple exposure metrics in the most informative study

Exposure metric	NHL (all types)	Follicular cell	CLL
InterLymph (Cocco et al. 2003): High probability of exposure			
High intensity > 75 ppm	2.2 (0.7–6.7)*	1.5 (0.2–13)*	3.2 (0.6–18)*
Duration (years)	P_{trend} = 0.009	P_{trend} = 0.028	P_{trend} = 0.010
NCI- SEER (Purdue et al. 2011) (Component study)			
Average weekly exposure Per 99 ppm-hr/wk	*P_{trend} = 0.02* 1.11 (1.02–1.21)*	*P_{trend} = 0.005* 1.15 (1.04–1.28)*	*P_{trend} = 0.16* 1.09 (0.96–1.24)*
Cumulative Per 65,520 ppm-hr	*P_{trend} = 0.08* 1.10 (0.99–1.22)*	*P_{trend} = 0.01* 1.17 (1.04–1.32)*	*P_{trend} = 0.16* 1.11 (0.96–1.27)*

Fisher test for combined probability (probability, duration, frequency, and intensity)
P = 0.004 NHL, 0.015 follicular cell, and 0.005 CLL (Cocco *et al.* 2013)

* Adjusted OR (95% CI)

Increased risk of NHL across studies in meta-analyses

Exposure category	Scott & Jinot 2011 mRR (95% CI) # studies	Karami *et al.* 2013 mRR (95% CI) # studies
Ever exposure	1.23 (1.07-1.42) 17	1.32 (1.14-1.54) 19
Highest exposure	1.43 (1.13-1.82) 13	NR

Low sensitivity to removal of individual studies or selection of alternative RRs (Scott & Jinot 2011)

Low to moderate heterogeneity

Some evidence of publication bias

NHL human cancer 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 NHL 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.

Mechanistic data for NHL

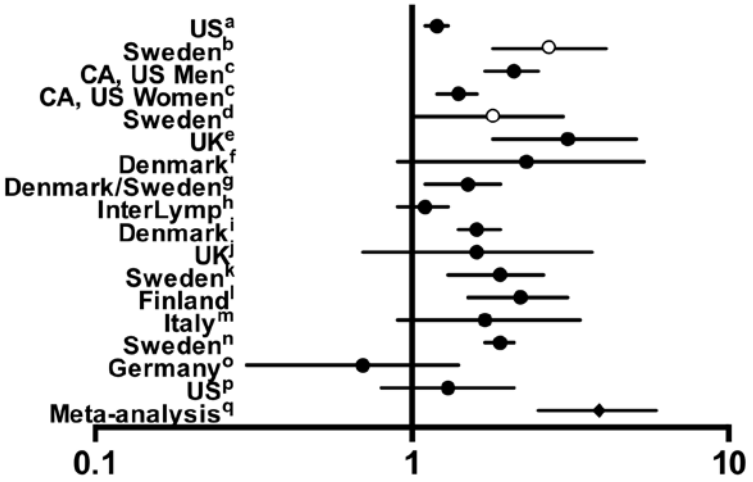
- TCE is associated with lymphomas in both humans and experimental animals
  - Seen in female mice from TCE inhalation
- Little is known about the mechanisms of NHL: Most are B cells
- Immunomodulation is a strong risk factor for B cell NHL
  - Antigenic stimulation is proposed as a potential mode of action (MOA) for immunomodulation-induced NHL, but other MOAs may be possible
- TCE immune effects have been evaluated in both humans and animals
  - Measured immune biomarkers
  - No studies directly evaluated immunomodulation as a MOA for TCE-associated NHL
- Informational group focused on whether TCE-induced immune effects were consistent with the proposed MOA for cancer

Immunomodulation is linked to cancer including NHL

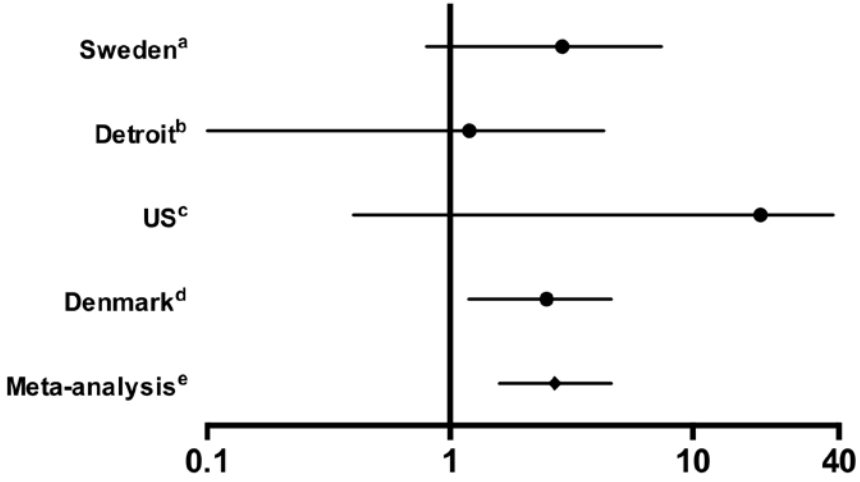
- Evidence comes from studies of patients with immunosuppression associated diseases or autoimmune diseases
- Immunosuppression-associated diseases or conditions
  - Organ transplant patients
    - Stopping immunosuppressant therapy causes partial to complete regression
  - HIV patients
  - Genetically immunodeficient patients

Autoimmune diseases and NHL risk

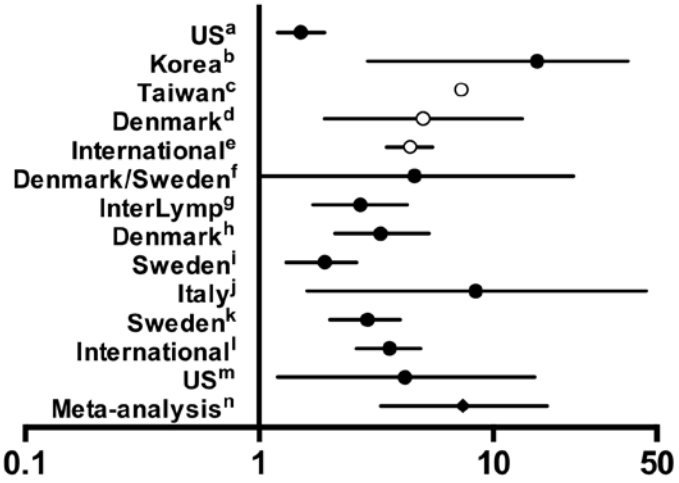
Rheumatoid arthritis



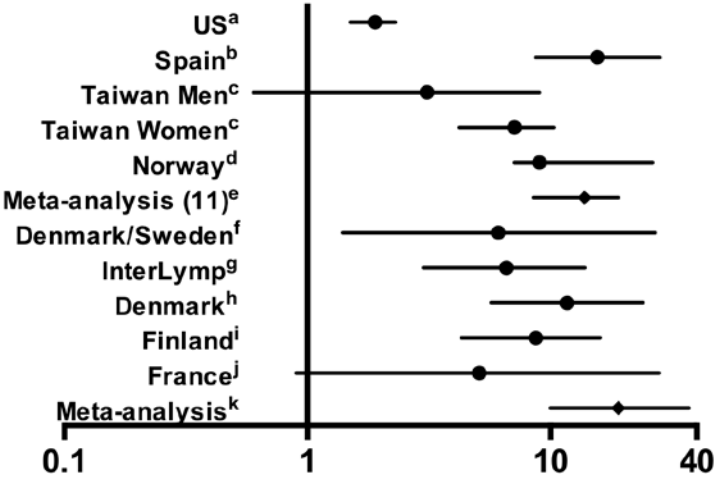
Scleroderma



Systemic lupus erythematosus

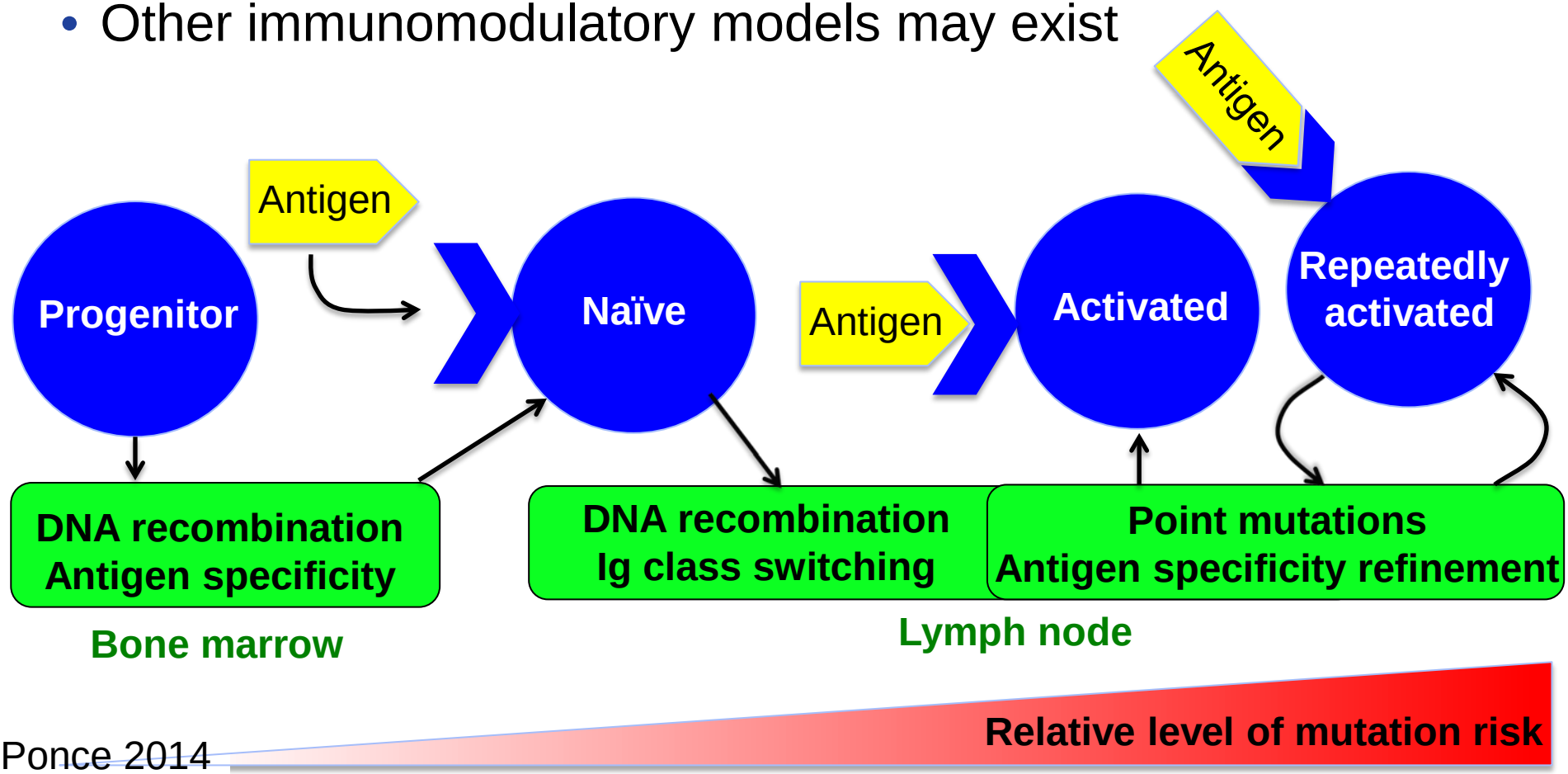


Sjogren's Syndrome



Proposed MOA for NHL induction: Antigen-induced B cell activation

- Only B cells undergo somatic mutation after they mature
- Antigen stimulation increases the risk of mutation
- Other immunomodulatory models may exist



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Human immunomodulation studies

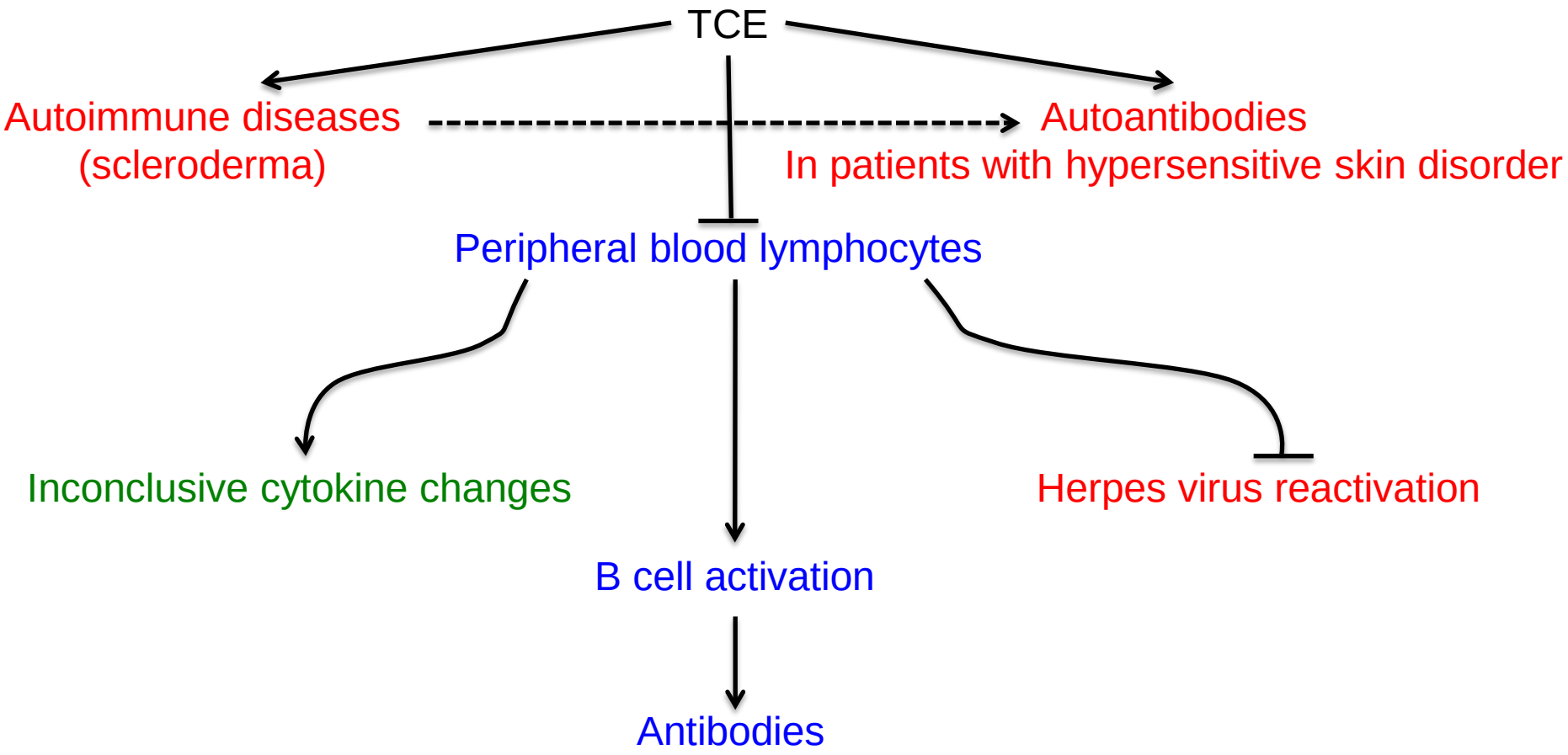
Types of studies

- Prospective cohort study
- Case-control studies
  - Individual
  - Pooled
- Cross-sectional studies
  - Occupational
  - Population

Endpoints measured

- Scleroderma
- B cell numbers
- B cell activity
- Antibody isotypes
- Autoantibodies
- Cytokines
- Viral reactivation

Evidence of TCE-induced immunomodulation in human studies



Red = Detected increase
Blue = Detected decrease
Green = Detected increase and decrease

Experimental animal immunomodulation studies

Chemical

- Trichloroethylene
- Metabolites

Species

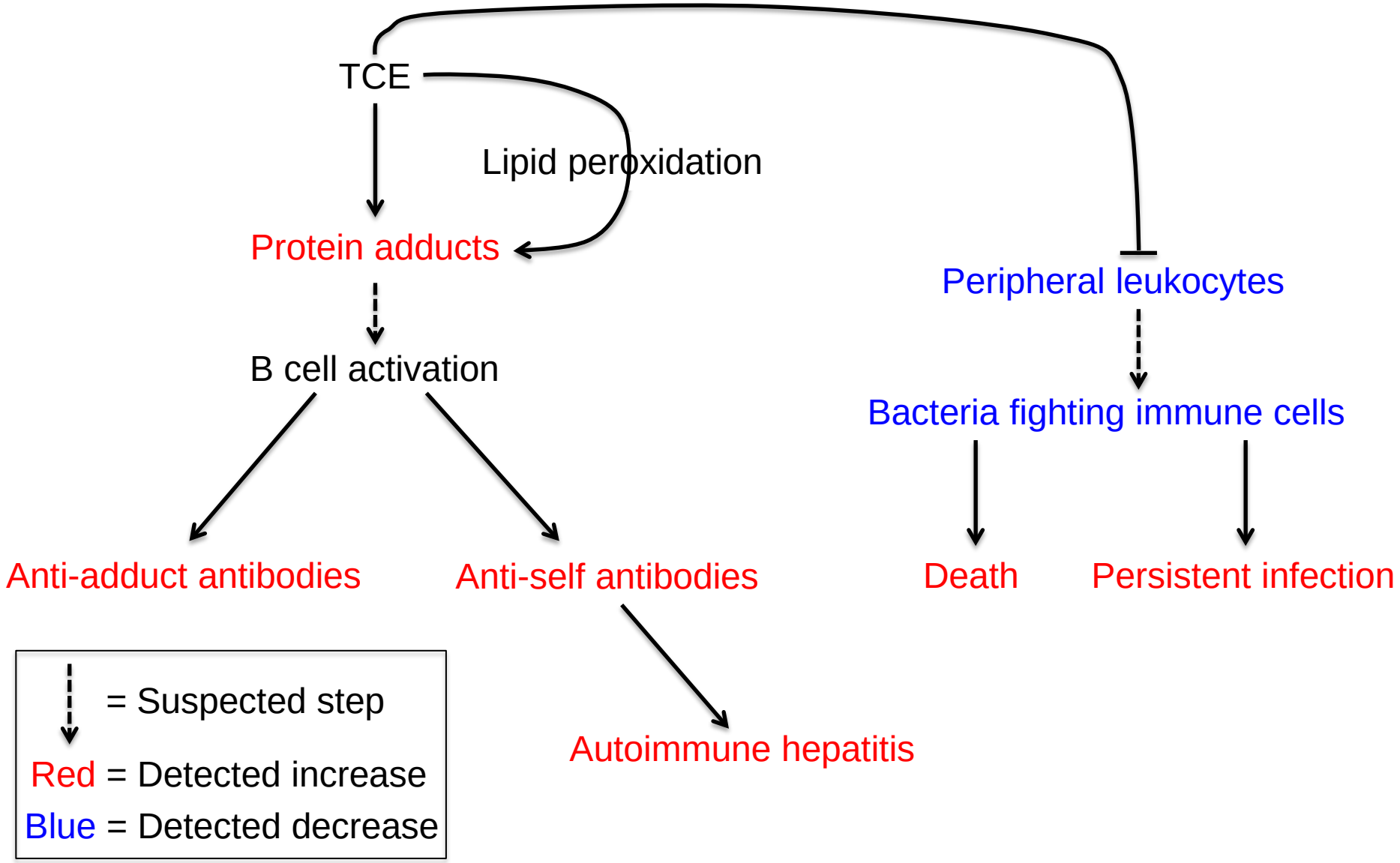
- Mouse*
- Rat
- Guinea pig
- Dog

Endpoints

- Protein adducts
- Anti-adduct antibodies
- Autoantibodies
- Cytokines
- Leukocyte number
- Leukocyte activity
- Bacterial infection

*Mostly $MRL^{+/+}$ mice which spontaneously develop a lupus-like autoimmunity

TCE-induced immunomodulation in experimental animal studies



TCE-induced B cell-activity and proposed MOA

Consistent

- Increased autoimmune disease
- Increased autoantibodies
- Increased anti-adduct antibodies
- Increased IgG
  - Experimental animals
- Increased microbial infection/reactivation

Inconsistent

- Decrease in B cell numbers
- Decrease/no effect in B cell activation
- Decreased IgG, IgM
  - Human

Limitation of mechanistic data

- Few human studies looked at TCE-induced immunomodulation
- Most experimental animal studies used a transgenic mouse model ($MRL^{+/+}$)
- Endpoints in experimental animals don't match those in humans
- No studies looked at immunomodulation and cancer
- B cell activity endpoints are inconsistent

Mechanistic data: Summary

- Immunomodulation is strongly linked to NHL
- TCE cause immunomodulation in humans and experimental animals
  - Evidence for autoimmunity
  - Some evidence for immunosuppression
- The available studies were not able to provide convincing evidence that TCE causes NHL via the proposed immunomodulatory MOA
  - No studies were designed to test hypothesis
  - Might be other MOAs
- Overall, TCE-induced immunomodulation resulting in NHL is biologically plausible

NHL mechanistic studies: Reviewer questions

- Comment on whether the mechanistic data for NHL 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.

NHL: Integration of evidence

- Epidemiology studies provide limited evidence of an association between exposure to TCE and NHL in humans
- TCE causes lymphoma in experimental animals
- Toxicological/mechanistic evidence for TCE-induced immunomodulation leading to NHL is biologically plausible, but not conclusive

Preliminary level of evidence: NHL (Vote)

Preliminary level of evidence conclusion

- Limited evidence of a causal association between exposure to trichloroethylene and NHL from studies in humans

Reviewer questions

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