NTP
National Toxicology Program

Report on the Peer Review of the RoC Draft Monographs on Selected Viruses

Gloria D. Jahnke, DVM, DABT
Office of the Report on Carcinogens, DNTP
National Institute of Environmental Health Sciences

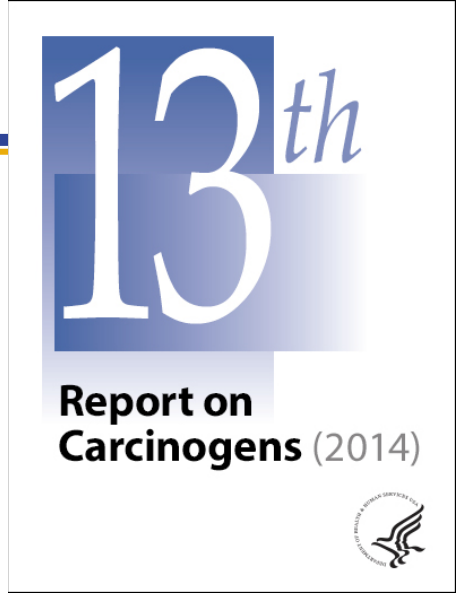
NTP Board of Scientific Counselors Meeting
June 15 – 16, 2016

Selected Viruses Peer-Review Meeting

Outline

- Report on Carcinogens (RoC) process
- Development of five viruses monographs
- Peer-review meeting and reports
- Panel recommendations and comments
- Next steps and 14th RoC status

The Report on Carcinogens (RoC) is congressionally mandated

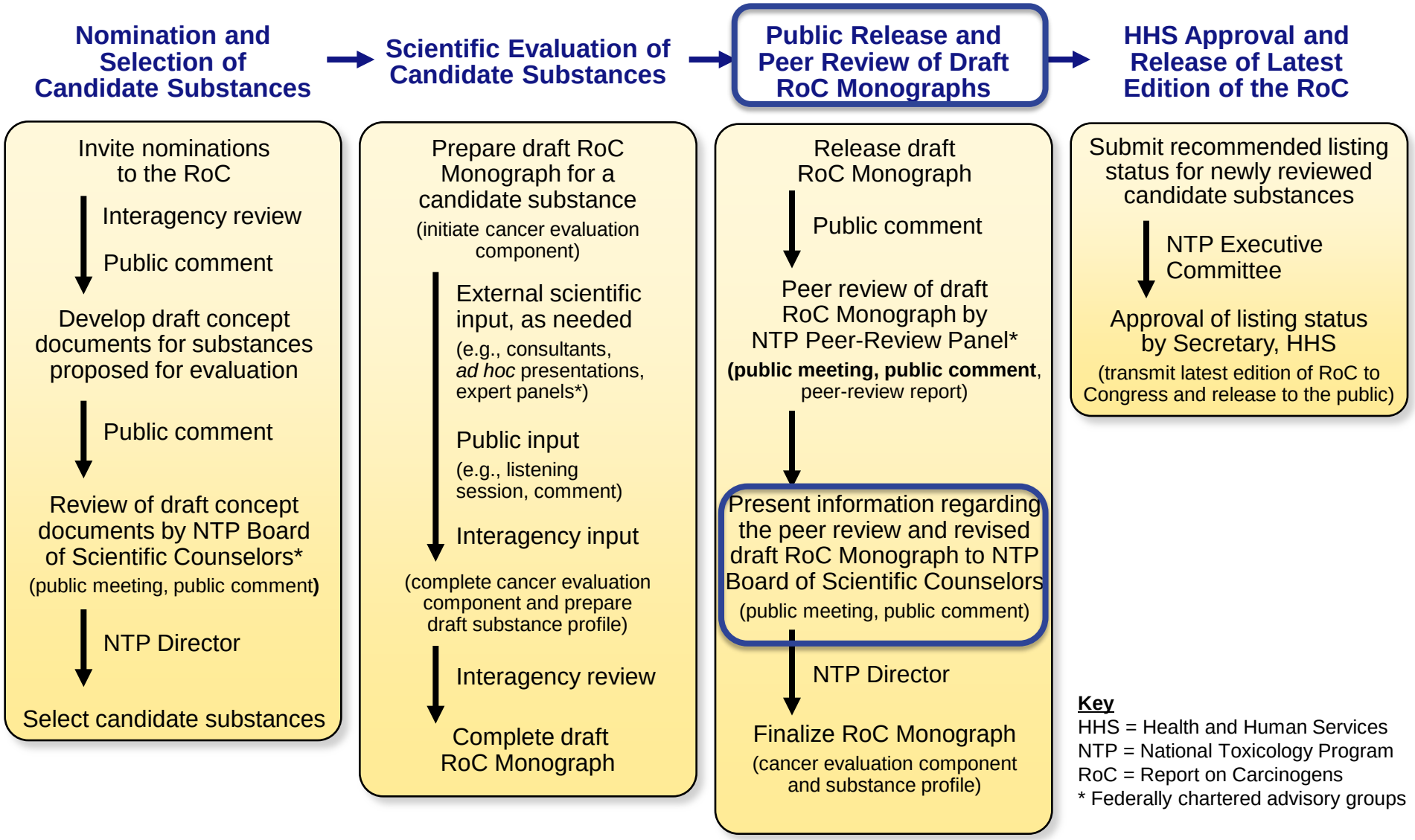


- Public Health Service Act, Section 301(b)(4) (1978, amended 1993)
  - Directs Secretary, Health and Human Services (HHS) to publish a list of carcinogens
  - Lists substances as "*known*" or *"reasonably anticipated human carcinogens"*
- Identifies substances that pose a cancer hazard for people in the United States
- Each edition of the report is cumulative
- NTP prepares the RoC for the Secretary, HHS

http://ntp.niehs.nih.gov/go/roc

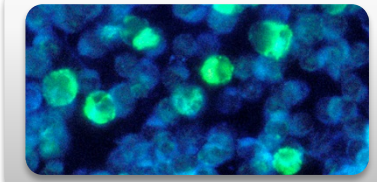
NTP process for preparing the RoC

Current status in selected viruses review



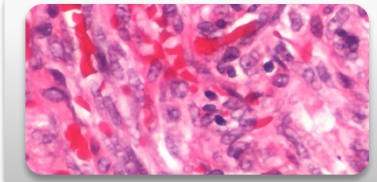
Key
HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

Selected viruses



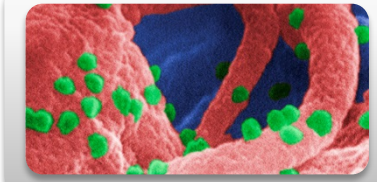
Epstein-Barr Virus (EBV)

- Herpesvirus
- Double stranded DNA virus enveloped



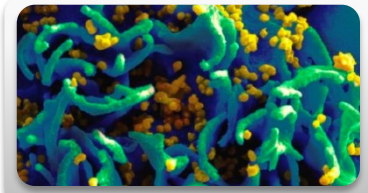
Kaposi sarcoma-associated herpesvirus (KSHV)

- Herpesvirus
- Double stranded DNA virus enveloped



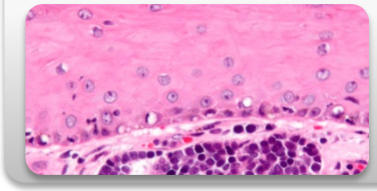
Human immunodeficiency virus type 1 (HIV-1)

- Retrovirus
- Single stranded RNA virus enveloped



Human T-cell lymphotropic virus type 1 (HTLV-1)

- Retrovirus
- Single stranded RNA virus enveloped

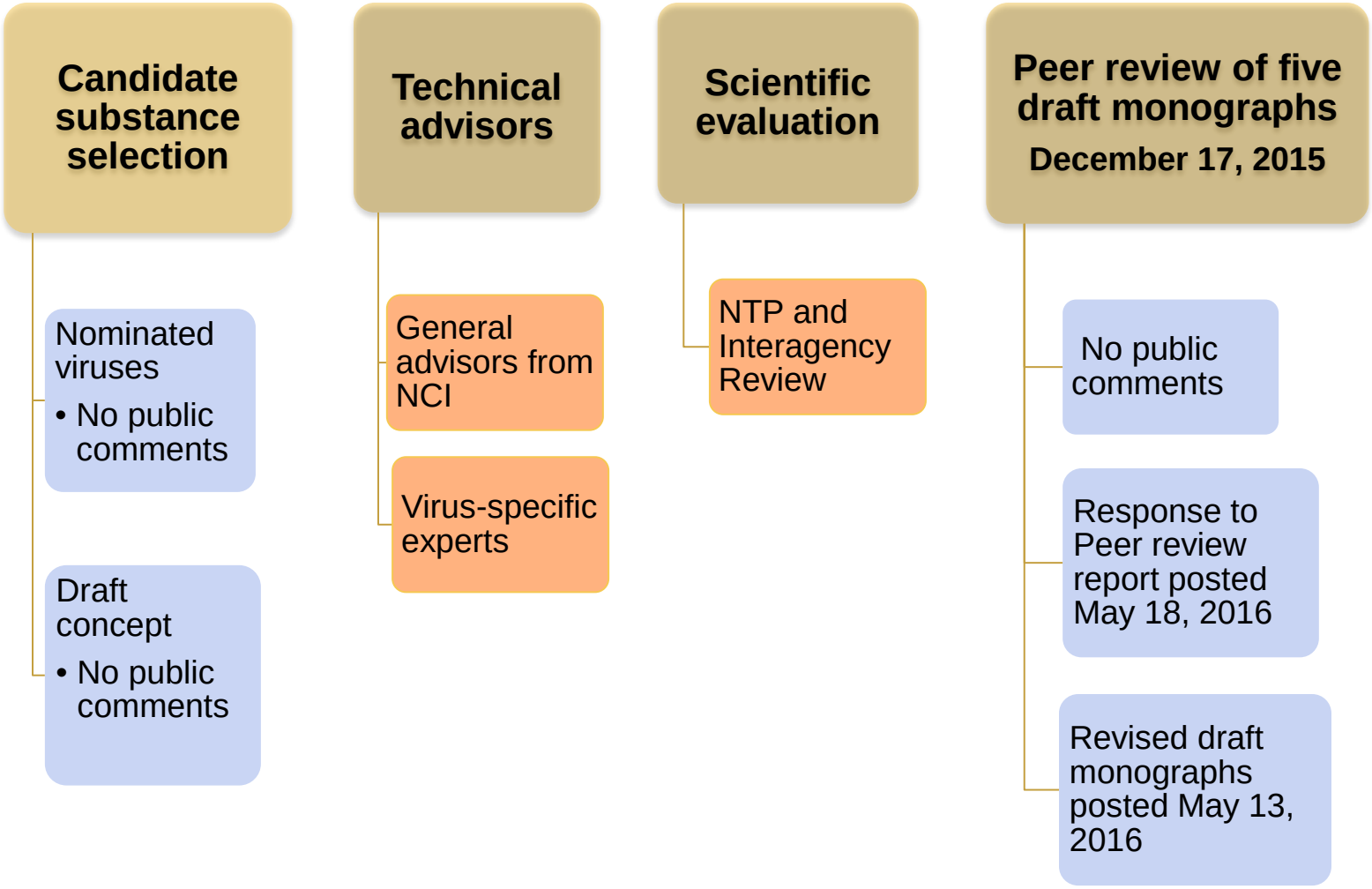


Merkel cell polyomavirus (MCV)

- Polyoma virus
- Double stranded DNA virus non-enveloped

Development and review of the draft monograph

Scientific input and public comments



.

Development of draft monographs

Technical advisors

- Overall technical advisors:
  - Elizabeth Read-Connole, PhD and Jim Goedert, MD, National Cancer Institute (NCI)
- Expert reviewers of draft monographs (all from NCI)
  - EBV: Sam M. Mbulaiteye, MD
  - KSHV: Denise Whitby, PhD
  - HIV-1: Robert Yarchoan, MD
  - HTLV-1: Genoveffa Franchini, MD
  - MCV: Christopher B. Buck, PhD

Selected viruses peer-review panel

Member	Affiliation
Andrew F. Olshan, PhD (Chair)	School of Public Health University of North Carolina
Blossom Damania, PhD	School of Medicine University of North Carolina
Paul F. Lambert, PhD	University of Wisconsin School of Medicine and Public Health
Margaret M. Madeleine, PhD, MPH	Program in Epidemiology Fred Hutchinson Cancer Research Center
Edward L. Murphy, Jr., MD, MPH	Departments of Laboratory Medicine and Epidemiology/Biostatistics University of California
Charles S. Rabkin, MD, MSc	Infections and Immunoepidemiology Branch National Cancer Institute
Rosemary Rochford, PhD	Immunology and Microbiology Environmental and Occupational Health University of Colorado
BSC Liaison: Steven Markowitz, MD, DrPH	

RoC listing criteria

- *Known to be a human carcinogen*
  - Sufficient evidence of carcinogenicity from studies in humans.
    - Evidence can include traditional cancer epidemiology studies, data from clinical or molecular studies derived from tissues or cells from humans exposed to the substance in question.
- *Reasonably anticipated to be a human carcinogen*
  - Limited evidence of carcinogenicity from studies in humans.
  - Sufficient evidence of carcinogenicity from studies in experimental animals.
  - Convincing mechanistic data.

RoC Listing criteria available at http://ntp.niehs.nih.gov/go/15209

Peer-review meeting

Charge	To comment on each draft cancer evaluation component, specifically, whether it is technically correct and clearly stated, whether the NTP has objectively presented and assessed the scientific evidence, and whether the scientific evidence is adequate for applying the listing criteria.
	To comment on each draft substance profile, specifically, whether the scientific evidence supports the NTP's preliminary RoC listing status of each virus.
Actions (votes)	Whether the scientific evidence supports the NTP's conclusion on the level of evidence for carcinogenicity from cancer studies in humans of the five viruses.
	Whether the scientific evidence supports the NTP's preliminary listing decision of viruses in the RoC.

Steps after the peer review meeting

Peer-review report, NTP response, revised monograph

Peer-review report

- Recommendations on NTP draft conclusions.
- Scientific and technical peer-review comments.

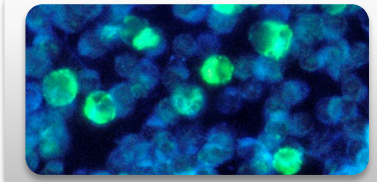
NTP response to the peer-review report

- Responses to Panel comments.
- Rationale for accepting/not accepting peer review recommendations.

Revised draft monograph

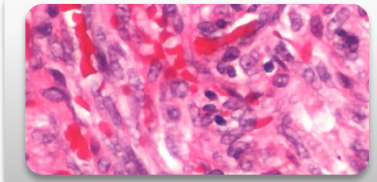
- Revised based on NTP review of peer-review comments.

Significant U.S. Exposure



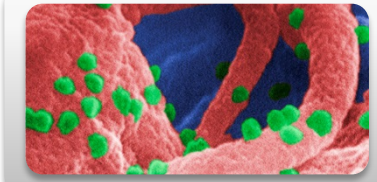
Epstein-Barr Virus (EBV)

U.S. seroprevalence (2009–2010) 50% in 6–8 year olds and 89% in 18–19 year-olds.



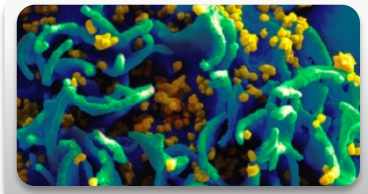
Kaposi sarcoma-associated herpes virus (KSHV)

U.S. seroprevalence approximately 7% for both sexes.



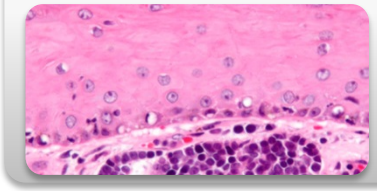
Human immunodeficiency virus type 1 (HIV-1)

U.S. incidence ≈ 50,000 new infections per year; 1.2 million infected (2015).



Human T-cell lymphotropic virus type 1 (HTLV-1)

The number of HTLV-1-infected persons in the United States estimated to range from 90,000 to 100,000 persons.



Merkel cell polyomavirus (MCV)

U.S. MCV seroprevalence rates have been reported to range from 23% to 88% in adults.

ACTION: Preliminary listing decision

Peer-review panel agreed with the preliminary listing recommendation of *known to be a human carcinogen* for all five viruses reviewed.

(Unanimous vote)

- Epstein-Barr Virus
- Kaposi Sarcoma-Associated Herpesvirus
- Human Immunodeficiency Virus Type 1
- Human T-Cell Lymphotrophic Virus Type 1

(5 agree, 1 disagrees)

- Merkel Cell Polyomavirus

Panel Recommendations: EBV

Actions: Level of evidence conclusions

Cancer endpoint	Draft RoC monograph	Peer-Review Panel	Revised RoC monograph
• Burkitt lymphoma (endemic) • Hodgkin lymphoma • Nasopharyngeal cancer • Immunosuppression-related non-Hodgkin lymphoma • Extranodal NK/T-cell lymphoma (nasal type) • Gastric cancer	*Sufficient*	Agreed	*Sufficient* evidence of carcinogenicity
• Burkitt lymphoma (sporadic)	*Limited*	Agreed	*Limited* evidence of carcinogenicity
• Lymphoepithelial cancer of the salivary gland	*Limited*	Inadequate • Case reports • Molecular evidence (few samples) • No mechanistic evidence	*Inadequate* evidence of carcinogenicity

Panel Recommendations: KSHV

Actions: Level of evidence conclusions

Cancer endpoint	Draft RoC monograph	Peer-Review Panel	Revised RoC monograph
• Kaposi sarcoma • Primary effusion lymphoma	*Sufficient*	Agreed	*Sufficient* evidence of carcinogenicity
• Multicentric Castleman disease	*Limited*	Sufficient for plasmablastic variant of multicentric Castleman disease	*Sufficient* evidence of carcinogenicity for multicentric Castleman disease (plasmablastic variant)

Panel Recommendations: HTLV-1

Actions: Level of evidence conclusions

Cancer endpoint	Draft RoC monograph	Peer-Review Panel	Revised RoC monograph
Adult T-cell leukemia/lymphoma	*Sufficient*	Agreed	*Sufficient* evidence of carcinogenicity
Liver cancer	*Limited*	Inadequate • Small number of studies or exposed subjects • Potential confounding from hepatitis C or B virus	*Inadequate* evidence of carcinogenicity

Panel Recommendations: MCV

Actions: Level of evidence conclusions

Cancer endpoint	Draft RoC monograph	Peer-Review Panel	Revised RoC monograph
Merkel cell carcinoma	*Sufficient*	Agreed	*Sufficient* evidence of carcinogenicity

Panel Recommendations: HIV-1

Actions: Level of evidence conclusions

Cancer endpoint	Draft RoC monograph	Peer-Review Panel	Revised RoC monograph
• Kaposi sarcoma • Non-Hodgkin lymphoma • Hodgkin lymphoma • Invasive anal cancer • Genital cancer • Conjunctival cancer • Non-melanoma skin cancer	*Sufficient*	Agreed	*Sufficient* evidence of carcinogenicity
• Liver cancer • Oral cancer	*Limited*	Agreed	*Limited* evidence of carcinogenicity

Cervical cancer: HIV-1

Panel recommendations and rationale

- 5 limited and 1 sufficient evidence
- Modest association with HIV-1; possibly related to higher prevalence of HPV*; unrelated to CD4 (T-cell) count or HAART*.

NTP's rationale for sufficient evidence

- Consistent evidence of statistically significant increased risk (2 to 25-fold) in over 17 cohort studies.
- Clear association with CD4 (T-cell) counts or HAART not observed but also true of some other cancers linked to HIV-1.
- Cervical cancer is an AIDS-defining malignancy.

* HPV = Human papilloma virus; HAART = highly active anti-retroviral therapy

Lung cancer: HIV-1

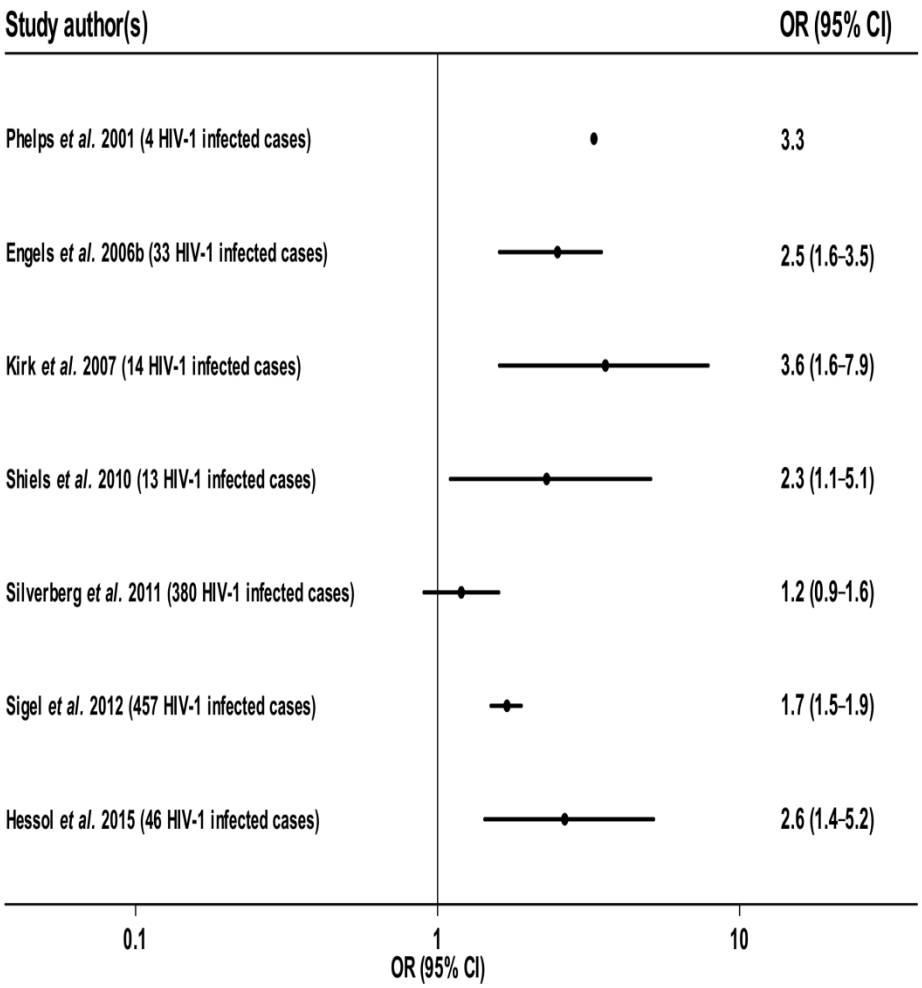
Panel recommendations and rationale

- 5 inadequate; 1 limited evidence
- Modest, heterogeneous associations, confounded by smoking; no clear mechanism.

NTP's rationale for limited evidence

- At least 2-fold statistically significant increase in most cohort studies that controlled or modeled for smoking.
- Possible residual confounding.
- Mechanism not required by RoC listing criteria.

Relative risk of lung cancer in studies that controlled for smoking



Panel's comments on the draft monograph

Overarching scientific issues

- The Panel noted that cancer causation by oncogenic viruses is not unusual; cancer does not need to occur in all exposed individuals for an agent to be carcinogenic.
  - Example: Smoking can cause lung cancer but not all smokers get lung cancer.
- The presence of an oncogenic virus alone can be sufficient for oncogenesis.
  - Example: KSHV alone is sufficient to cause Kaposi sarcoma, in that classic, pediatric, and iatrogenic Kaposi sarcoma occur in the absence of HIV co-infection, and over 95% of tumors contain KSHV.

Next Steps

Process for preparation of the RoC

Nomination and Selection of Candidate Substances

Invite nominations to the RoC

↓ Interagency review

↓ Public comment

Develop draft concept documents for substances proposed for evaluation

↓ Public comment

Review of draft concept documents by NTP Board of Scientific Counselors*

(public meeting, public comment)

↓ NTP Director

Select candidate substances

Scientific Evaluation of Candidate Substances

Prepare draft RoC Monograph for a candidate substance

(initiate cancer evaluation component)

↓ External scientific input, as needed

(e.g., consultants, *ad hoc* presentations, expert panels*)

↓ Public input

(e.g., listening session, comment)

↓ Interagency input

(complete cancer evaluation component and prepare draft substance profile)

↓ Interagency review

Complete draft RoC Monograph

Public Release and Peer Review of Draft RoC Monographs

Release draft RoC Monograph

↓ Public comment

Peer review of draft RoC Monograph by NTP Peer-Review Panel*

(public meeting, public comment, peer-review report)

Present information regarding the peer review and revised draft RoC Monograph to NTP Board of Scientific Counselors

(public meeting, public comment)

↓ NTP Director

Finalize RoC Monograph

(cancer evaluation component and substance profile)

HHS Approval and Release of Latest Edition of the RoC

Submit recommended listing status for newly reviewed candidate substances

↓ NTP Executive Committee

Approval of listing status by Secretary, HHS

(transmit latest edition of RoC to Congress and release to the public)

Key

HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

Preparation of the 14th Report on Carcinogens

- Status
  - Anticipated submission to the Secretary HHS late summer/early fall 2016.
- Newly reviewed substances and recommendation

Candidate Substance	NTP Recommendation
Trichloroethylene	Known human carcinogen
Cobalt and cobalt compounds that release cobalt ions *in vivo*	Reasonably anticipated to be a human carcinogen
Viruses (selected) EBV, KSHV, HIV-1, HTLV-1, MCV	Known human carcinogen

Acknowledgments

- **NTP/ORoC**
  - Ruth Lunn, Director
  - Gloria Jahnke
  - Diane Spencer
- **Office of Liaison, Policy and Review**
  - Mary Wolfe, Director
  - Lori White, Federal Officer
- **ILS, Inc.**
  - Sandy Garner, Principal Investigator
  - Stan Atwood
  - Ella Darden
  - Andy Ewens
  - Jessica Geter
  - Alton Peters
  - Jennifer Ratcliffe
  - Tracy Saunders
  - Pam Schwingl
- **SSS, Inc.**
  - Whitney Arroyave

Questions