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

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National Institute of Environmental Health Sciences

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

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, \textit{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
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 lymphotrophic virus type 1 (HTLV-1)**
  - Retrovirus
  - Single stranded RNA virus enveloped

- **Merkel cell polyomavirus (MCV)**
  - Polyoma virus
  - Double stranded DNA virus non-enveloped
Scientific input and public comments

**Candidate substance selection**
- Nominated viruses
  - No public comments
- Draft concept
  - No public comments

**Technical advisors**
- General advisors from NCI
- Virus-specific experts

**Scientific evaluation**
- NTP and Interagency Review

**Peer review of five draft monographs**
- December 17, 2015
  - No public comments
  - Response to Peer review report posted May 18, 2016
  - Revised draft monographs posted May 13, 2016
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
<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
</tr>
</thead>
</table>
| 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
<table>
<thead>
<tr>
<th>Charge</th>
<th>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.</th>
</tr>
</thead>
</table>

To comment on each draft substance profile, specifically, whether the scientific evidence supports the NTP’s preliminary RoC listing status of each virus.

<table>
<thead>
<tr>
<th>Actions (votes)</th>
<th>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.</th>
</tr>
</thead>
</table>

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
- 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.
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

<table>
<thead>
<tr>
<th>Cancer endpoint</th>
<th>Draft RoC monograph</th>
<th>Peer-Review Panel</th>
<th>Revised RoC monograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma (endemic)</td>
<td>Sufficient</td>
<td>Agreed</td>
<td>Sufficient evidence of carcinogenicity</td>
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<tr>
<td>Hodgkin lymphoma</td>
<td></td>
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<tr>
<td>Nasopharyngeal cancer</td>
<td></td>
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<tr>
<td>Immunosuppression-related non-Hodgkin lymphoma</td>
<td></td>
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<tr>
<td>Extranodal NK/T-cell lymphoma (nasal type)</td>
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<tr>
<td>Gastric cancer</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Burkitt lymphoma (sporadic)</td>
<td>Limited</td>
<td>Agreed</td>
<td>Limited evidence of carcinogenicity</td>
</tr>
<tr>
<td>Lymphoepithelial cancer of the salivary gland</td>
<td>Limited</td>
<td>Inadequate</td>
<td>Inadequate evidence of carcinogenicity</td>
</tr>
<tr>
<td>Case reports</td>
<td>Molecular evidence (few samples)</td>
<td>No mechanistic evidence</td>
<td></td>
</tr>
</tbody>
</table>
## Actions: Level of evidence conclusions

<table>
<thead>
<tr>
<th>Cancer endpoint</th>
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<tbody>
<tr>
<td>• Kaposi sarcoma</td>
<td><em>Sufficient</em></td>
<td>Agreed</td>
<td><em>Sufficient</em> evidence of carcinogenicity</td>
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<tr>
<td>• Primary effusion lymphoma</td>
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<tr>
<td>• Multicentric Castleman disease</td>
<td><em>Limited</em></td>
<td>Sufficient for plasmablastic variant of multicentric Castleman disease</td>
<td><em>Sufficient</em> evidence of carcinogenicity for multicentric Castleman disease (plasmablastic variant)</td>
</tr>
</tbody>
</table>
## Panel Recommendations: HTLV-1

### Actions: Level of evidence conclusions

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<tbody>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
<td><em>Sufficient</em></td>
<td><em>Agreed</em></td>
<td><em>Sufficient</em> evidence of carcinogenicity</td>
</tr>
<tr>
<td>Liver cancer</td>
<td><em>Limited</em></td>
<td><em>Inadequate</em></td>
<td><em>Inadequate</em> evidence of carcinogenicity</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Inadequate</strong> evidence of carcinogenicity</td>
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<td></td>
<td>- Small number of studies or exposed subjects</td>
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<td>- Potential confounding from hepatitis C or B virus</td>
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<tr>
<td>Cancer endpoint</td>
<td>Draft RoC monograph</td>
<td>Peer-Review Panel</td>
<td>Revised RoC monograph</td>
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<tr>
<td>Merkel cell carcinoma</td>
<td><em>Sufficient</em></td>
<td>Agreed</td>
<td><em>Sufficient</em> evidence of carcinogenicity</td>
</tr>
</tbody>
</table>
### Panel Recommendations: HIV-1

**Actions: Level of evidence conclusions**

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<th>Cancer endpoint</th>
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<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td><em>Sufficient</em></td>
<td><em>Agreed</em></td>
<td><em>Sufficient</em> evidence of carcinogenicity</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Hodgkin lymphoma</td>
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<td></td>
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<tr>
<td>Invasive anal cancer</td>
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<tr>
<td>Genital cancer</td>
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<tr>
<td>Conjunctival cancer</td>
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<tr>
<td>Non-melanoma skin cancer</td>
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<td></td>
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</tr>
<tr>
<td>Liver cancer</td>
<td><em>Limited</em></td>
<td><em>Agreed</em></td>
<td><em>Limited</em> evidence of carcinogenicity</td>
</tr>
<tr>
<td>Oral cancer</td>
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</tbody>
</table>
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
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

<table>
<thead>
<tr>
<th>Study author(s)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phelps et al. 2001 (4 HIV-1 infected cases)</td>
<td>3.3</td>
</tr>
<tr>
<td>Engels et al. 2006b (33 HIV-1 infected cases)</td>
<td>2.5 (1.6-3.5)</td>
</tr>
<tr>
<td>Kirk et al. 2007 (14 HIV-1 infected cases)</td>
<td>3.6 (1.6-7.9)</td>
</tr>
<tr>
<td>Shiels et al. 2010 (13 HIV-1 infected cases)</td>
<td>2.3 (1.1-5.1)</td>
</tr>
<tr>
<td>Silverberg et al. 2011 (380 HIV-1 infected cases)</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>Sigel et al. 2012 (457 HIV-1 infected cases)</td>
<td>1.7 (1.5-1.9)</td>
</tr>
<tr>
<td>Hessol et al. 2015 (46 HIV-1 infected cases)</td>
<td>2.6 (1.4-5.2)</td>
</tr>
</tbody>
</table>
• 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.
Process for preparation of the RoC

Next Steps

Nomination and Selection of Candidate Substances

- Invite nominations to the RoC
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Preparation of the 14th Report on Carcinogens

• Status
  – Anticipated submission to the Secretary HHS late summer/early fall 2016.

• Newly reviewed substances and recommendation

<table>
<thead>
<tr>
<th>Candidate Substance</th>
<th>NTP Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichloroethylene</td>
<td>Known human carcinogen</td>
</tr>
<tr>
<td>Cobalt and cobalt compounds that release cobalt ions in vivo</td>
<td>Reasonably anticipated to be a human carcinogen</td>
</tr>
<tr>
<td>Viruses (selected) EBV, KSHV, HIV-1, HTLV-1, MCV</td>
<td>Known human carcinogen</td>
</tr>
</tbody>
</table>
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