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, 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
<table>
<thead>
<tr>
<th>Virus</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 lymphototropic virus type 1 (HTLV-1)| - Retrovirus  
|                                            | - Single stranded RNA virus enveloped            |
| Merkel cell polyomaviruses (MCV)           | - Polyoma virus  
|                                            | - Double stranded DNA virus non-enveloped        |
Scientific input and public comments

Development and review of the draft monograph

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
- No public comments

Peer review of five draft monographs
- December 17, 2015
- 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
## Selected viruses peer-review panel

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrew F. Olshan, PhD (Chair)</td>
<td>School of Public Health&lt;br&gt;University of North Carolina</td>
</tr>
<tr>
<td>Blossom Damania, PhD</td>
<td>School of Medicine&lt;br&gt;University of North Carolina</td>
</tr>
<tr>
<td>Paul F. Lambert, PhD</td>
<td>University of Wisconsin School of Medicine and Public Health</td>
</tr>
<tr>
<td>Margaret M. Madeleine, PhD, MPH</td>
<td>Program in Epidemiology&lt;br&gt;Fred Hutchinson Cancer Research Center</td>
</tr>
<tr>
<td>Edward L. Murphy, Jr., MD, MPH</td>
<td>Departments of Laboratory Medicine and Epidemiology/Biostatistics&lt;br&gt;University of California</td>
</tr>
<tr>
<td>Charles S. Rabkin, MD, MSc</td>
<td>Infections and Immunoepidemiology Branch National Cancer Institute</td>
</tr>
<tr>
<td>Rosemary Rochford, PhD</td>
<td>Immunology and Microbiology Environmental and Occupational Health&lt;br&gt;University of Colorado</td>
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<tr>
<td>BSC Liaison: Steven Markowitz, MD, DrPH</td>
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</table>
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>Actions (votes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To comment on each draft cancer evaluation component, specifically,</td>
<td>Whether the scientific evidence supports the NTP’s conclusion on the level of</td>
</tr>
<tr>
<td>whether it is technically correct and clearly stated, whether the</td>
<td>evidence for carcinogenicity from cancer studies in humans of the five viruses.</td>
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<tr>
<td>NTP has objectively presented and assessed the scientific evidence,</td>
<td></td>
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<tr>
<td>and whether the scientific evidence is adequate for applying the</td>
<td>Whether the scientific evidence supports the NTP’s preliminary listing decision</td>
</tr>
<tr>
<td>listing criteria.</td>
<td>of viruses in the RoC.</td>
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<tr>
<td></td>
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<tr>
<td>To comment on each draft substance profile, specifically, whether</td>
<td></td>
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<tr>
<td>the scientific evidence supports the NTP’s preliminary RoC listing</td>
<td></td>
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<tr>
<td>status of each virus.</td>
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</tbody>
</table>
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.

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

NTP response to the peer-review report
- Responses to Panel comments.
- Rationale for accepting/not accepting peer review recommendations.
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 lymphotrophic 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></td>
</tr>
<tr>
<td>• Hodgkin lymphoma</td>
<td></td>
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<tr>
<td>• Nasopharyngeal cancer</td>
<td></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>
<td></td>
</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>
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<tr>
<td></td>
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</tbody>
</table>

- *Sufficient* evidence of carcinogenicity
- *Limited* evidence of carcinogenicity
- *Inadequate* evidence of carcinogenicity
- *Case reports*
- *Molecular evidence (few samples)*
- *No mechanistic evidence*
## Panel Recommendations: KSHV

### Actions: Level of evidence conclusions

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

### 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>Adult T-cell leukemia/lymphoma</td>
<td>Sufficient</td>
<td>Agreed</td>
<td>Sufficient evidence of carcinogenicity</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Limited</td>
<td>Inadequate</td>
<td>Inadequate evidence of carcinogenicity</td>
</tr>
</tbody>
</table>
|                                  |                     |                   | - Small number of studies or exposed subjects
|                                  |                     |                   | - Potential confounding from hepatitis C or B virus |
## Panel Recommendations: MCV

### 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>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

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

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 <em>in vivo</em></td>
<td>Reasonably anticipated to be a human carcinogen</td>
</tr>
<tr>
<td>Viruses (selected)</td>
<td></td>
</tr>
<tr>
<td>EBV, KSHV, HIV-1, HTLV-1, MCV</td>
<td>Known human carcinogen</td>
</tr>
</tbody>
</table>
### Acknowledgments

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