



NTP

National Toxicology Program

Report on Carcinogens Selected Viruses Concept Review

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Background

12% of cancers worldwide are caused by viruses;
10% of cancers in U.S. are linked to infectious agents.

Oncogenic viruses listed in the *12th Report on Carcinogens (2011)* as *known human carcinogens*.

- Hepatitis B virus
- Hepatitis C virus
- Human papilloma viruses: some genital mucosal types

Selected Viruses for Review

- Epstein-Barr virus (EBV)
- Kaposi sarcoma-associated herpes virus (KSHV)
- Human immunodeficiency virus type 1 (HIV-1)
- Human T-cell lymphotropic virus type 1 (HTLV-1)
- Merkel cell polyoma virus (MCV)
- Evaluation of viruses
 - Similar approach to evaluate all five – one concept.
 - Each virus will be reviewed independently.
 - All listed viruses will be in one section of the RoC.

Rationale

- A significant number of people living in the United States are infected; these 5 viruses represent a public health concern.
- Large cancer database on these viruses and recent authoritative reviews by International Agency for Research on Cancer (IARC 2012, 2013).

Viral Types, Transmission and Populations at Risk

Virus	Type	Transmission	Populations at Risk for cancer
EBV	Herpes virus	Saliva	Immunocompromised individuals.
KSHV	Herpes virus	Saliva	Immunocompromised or HIV positive individuals.
HIV-1	Retrovirus	<p>Transfer of infected body fluids such as semen, blood, breast milk; prenatal and perinatal infant exposure.</p> <p>HIV-1 – highest rates of transmission: populations using unprotected sex and sharing contaminated needles.</p>	HIV-1 causes immunosuppression.
HTLV-1	Retrovirus	HTLV-1–highest rates of transmission: breastfeeding.	Immunocompromised individuals.
MCV	Polyoma virus	Unknown mode of transmission, identified in skin and saliva.	Immunocompromised individuals.

U.S. Exposure-Related Information

- **EBV** – U.S. seroprevalence (2003–2010) 83% in 18 –19 yr-olds.
- **KSHV** – U.S. blood donors (1994–1995) seroprevalence ~3.5%.
- **HIV-1** – U.S. incidence \approx 50,000 infections per year; 1.1 million infected (2009).
- **HTLV-1** – U.S. blood donors (2000–2009) seroprevalence 0.02%.
 - In endemic areas – S.W. Japan, Caribbean Basin, Melanesia, parts of Africa – prevalence can be 15%.
 - Immigration can raise numbers in local populations in U.S.
- **MCV** – U.S. blood donors (2008) seroprevalence up to 42%.

Scope and Extent of Human Cancer Database

Virus	Cancer Endpoints	Cancer Studies (IARC)
EBV	<ul style="list-style-type: none"> • B-cell, T-cell, NK lymphomas • Cancers of nasopharynx, stomach, breast, testis, skin 	3 cohort, 35 case control, 10 case series
HIV-1	<ul style="list-style-type: none"> • Kaposi sarcoma • Hodgkin and non-Hodgkin lymphoma • Cancers of cervix, anus, and conjunctiva • Cancers of lung, liver, other sites 	Over 20 cohort, 30 case control studies; meta analysis of risk of non-Hodgkin lymphoma or cervical cancer
HTLV-1	<ul style="list-style-type: none"> • Adult T-cell leukemia/lymphoma 	5 cohort, several nested case control, several case series
KSHV	<ul style="list-style-type: none"> • Kaposi sarcoma • Primary effusion lymphoma • Multiple myeloma • Multicentric Castleman disease 	<p>For HIV infected or transplant recipients, over 20 cohort, 80 case control studies of Kaposi sarcoma</p> <p>For other cancers, 2 cohort, 19 case control, 17 case series, 95 case reports</p>
MCV	<ul style="list-style-type: none"> • Merkel cell carcinoma 	5 case control and 15 case series

Key Considerations for Conducting Scientific Review

- IARC has conducted authoritative evaluations.
 - Large cancer database.
 - IARC monograph volume 100B (2012) updated information from previous reviews of EBV, HIV, HTLV-1, KSHV.
 - IARC monograph volume 104 (2013) reviewed MCV.
- The Office of the Report on Carcinogens (ORoC) plans to use the information provided in these IARC monographs to conduct its own cancer assessment.

Proposed Approach for Scientific Input

- ORoC monograph planning team – external expert technical advisors, NTP, ORoC, and Contractor staff.
 - Assist in protocol development, identification of key studies (from IARC reports and new publications), and cancer assessments.
- Protocol development.
 - Focus on human cancer studies and supporting mechanistic studies.
 - Literature search strategy and approach for evaluating the quality of studies published since the IARC review.
 - Approach for using IARC monograph review and assessment of individual cancer studies.

Proposed Approach for Public Input

- Public comments requested throughout the review process.
 - Nomination, draft concept, and draft monograph.
 - Public comments and documents posted on RoC webpage.
- RoC webpage for candidate substances under review.
 - Protocol posted on RoC webpage.
 - Provide information on public meetings.
 - Mechanism to receive public input.

Public Health Significance

- Provide information on physical characteristics, exposure, transmission, human cancer studies, and potential cancer mechanisms of these viruses.
- Inform the public about transmission and increase awareness of these agents as potential carcinogens.

BSC Review Questions

1. Comment on whether there appears to be evidence of past and/or current exposure to people living in the U.S.
2. Comment on whether the extent and nature of the scientific database appears to be adequate to support a RoC evaluation.
3. Advise as to whether the relevant scientific issues are identified. Are you aware of any other scientific issues that need to be considered during the evaluation?
4. Comment on the proposed approach for obtaining scientific and public input in development of the evaluation.
5. Rate the overall significance and public health impact of this evaluation as low, moderate, or high. NTP will use this rating in assessing the relative priority of evaluations of RoC candidate substances.
6. Provide any other comments you feel staff should consider in developing this evaluation.