Report on Carcinogens (RoC) Concept: Selected Viruses

Epstein-Barr virus, human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, Kaposi sarcoma-associated herpes virus, and Merkel cell polyoma virus

1 Background and rationale

Approximately 10% of cancers in the United States and 17.8% worldwide are linked to infectious disease, and 12% of cancers worldwide are caused by viruses (Carrillo-Infante, et al. 2007; Parkin 2006). Hepatitis B virus, hepatitis virus, and some human papilloma viruses of the genital-mucosal type are currently listed in the RoC as *known to be human carcinogens* The following five viruses be reviewed for possible listing in the RoC: Epstein-Barr virus (EBV, a herpes virus) and Kaposi sarcoma-associated herpes virus (KSHV), which are DNA viruses; Merkel cell virus (MCV), which is a recently discovered DNA virus (polyoma virus) associated with Merkel cell carcinoma; human immunodeficiency virus type 1 (HIV-1); and human T-cell lymphotropic virus type-1 (HTLV-1), which are RNA viruses (retroviruses). There is a large database of information o these agents and some authoritative reviews. significant number of people living in the United States are or have been infected with these viruses and they present an important public health concern for disease mortality and morbidity both in the United States and worldwide. The role of viruses and other infectious agents in the etiology of cancer is an important goal for public health – for vaccine development and for identifying populations at risk. Prevention of infection by these agents would prevent cancers as well as other non-malignant diseases they cause. Providing information in the RoC on these viruses would increase public awareness and improve the public's understanding of disease prevention.

These five viruses will be independently reviewed as candidate substances[a] but are presented in the same concept document, because a similar approach will be used for their evaluations.

2 Overview of data related to human exposure

Most of the information on exposure to each of these viruses in the United States is based on seroprevalence data among blood donors, which may underestimate exposure in the general population. For some viruses, information on incidence of infection or disease associated with infection is available. Exposure-related information, virus properties, and potential at-risk human populations are presented in Table 1. The seroprevalence of these viruses in the U.S. population varies from a high rate of infection with EBV (up to 89% seroprevalence) to an apparent low rate of infection with HTLV-1 (0.005% seroprevalence in U.S. blood donors). Viral transmission by sexual, parenteral, or perinatal routes is similar for two retroviruses, HIV-1 and HTLV-1, although the primary route of exposure differs — sexual transmission for HIV-1 and breastfeeding for HTLV-1. Transmission via saliva is the common route of exposure for two

[a] These five viruses have been selected as candidate substances and the scientific evaluation of these viruses will be captured in draft RoC monographs (for more details, see http://ntp.niehs.nih.gov/go/rocprocess). The approach, delineated in this concept document, for preparing the draft monographs, is tailored to the nature, extent, and complexity of the scientific information. This concept document also discusses information supporting the rationale and the approach for reviewing these viruses, including data on human exposure, an overview of the nature and extent of the scientific information for evaluating carcinogenicity in humans and/or animals, and scientific issues and questions relevant to the evaluation of carcinogenicity. I also includes the approach for conducting the scientific evaluation.

herpes viruses, EBV and KSHV; however, no mode of transmission has been established for MCV, a polyoma virus found in skin and saliva.

Table 1. Five selected viruses: Properties and exposure-related information

Virus Virus Class Properties	Infection Incidence or Prevalence/Associated Disease	Sources & Transmission	At Risk Populations
Epstein-Barr virus (EBV), also called human herpes virus 4 (HHV-4) Herpes virus Double-stranded DNA virus, enveloped	Subclinical infection in almost everyone before age 20 (95% of world wide population). U.S. seroprevalence 83% in 18-19 yr-olds[a] Infectious mononucleosis in 35-50% of EBV-infected individuals	Transmission through saliva is primary exposure route. Resting memory B cells are reservoir of latent virus in healthy carriers.	Immunocompromised individuals; individuals of low socioeconomic status
Human immunodeficiency virus, type 1 (HIV-1) Retrovirus Single-stranded RNA virus, enveloped	U.S. incidence ≈ 50,000 (0.012%) infections/yr; more than1.1 million infected (0.36%) in U.S. (2012) Causes acquired immunodeficiency syndrome (AIDS); 33,015 new AIDS cases and 476,732 people in U.S. living with AIDS in 2010.[b]	Sexual transmission is primary exposure route; transfer of infected body fluids such as semen, blood, breast milk; prenatal and perinatal infant exposure. Infects CD4+ T-cells, some macrophages and dendritic cells.	Populations engaging in unprotected sex; sharing contaminated needles
Human T-cell lymphotrophic virus type-1 (HTLV-1) Retrovirus Single-stranded RNA virus, enveloped	U.S. blood donors (2000—2009) seroprevalence 0.005% (HTLV-1) [c] Causes neuro-inflammatory disease: ~3.5% of infected develop HTLV-1-associated myelopathy and/or adult T-cell leukemia/ lymphoma; most patients have T-cell immunodeficiency.	Sexual/perinatal/ parenteral transmission similar to HIV; highest rates of transmission are due to breastfeeding. 20-40 yr latency; proposed reservoir in lymphoid organs and CD4+ T-cells.	Populations engaging in unprotected sex; sharing contaminated needles. In endemic areas, e.g., S.W. Japan, Caribbean basin, Melanesia, parts of Africa, prevalence can be 15%
Kaposi sarcoma herpes virus (KSHV), also called human herpes virus 8 (HHV-8) Herpes virus Double-stranded DNA virus,	U.S. blood donors (1994—1995) seroprevalence ~3.5%[d]; Distinctive skin lesions; incidence of viral-associated sarcoma in U.S. peaked in 1989 (~4.76%) and has	Transmission through saliva is primary route of exposure. CD19+ B cells are reservoir of latent virus.	Immunocompromised or HIV-positive individuals

Virus Virus Class Properties	Infection Incidence or Prevalence/Associated Disease	Sources & Transmission	At Risk Populations
enveloped	decreased to 0.63% (2010) with anti-retroviral therapies[e]		
Merkel cell[f] virus (MCV) Polyoma virus Double-stranded DNA virus, non-enveloped	U.S. healthy blood donors (2008) seroprevalence 25%- MCV 350, 42%- MCV 339[g,h] U.S. incidence of Merkel cell carcinoma (MCC): 1,500 cases/yr, ~ 80% of MCC are positive for MCV.	The mode of transmission, cellular tropism, and latency properties are not known. Commonly detected in the skin (& saliva) of adults (80%).	Risk factors for MCV infection and MCC: immunosuppression, e.g., age, disease status, HIV and UV exposure

Dowd JB, Palermo T, Brite J, McDade TW, Aiello A.2013 Seroprevalence of Epstein-Barr Virus Infection in U.S. Children Ages 6-19, 2003-2010. PLoS ONE 8(5): e64921.

[b] http://www.cdc.gov/hiv/basics/statistics.html.

[c] Chang YB, Kaidarova Z, Hindes D, Bravo M, Kiely N, Kamel H, Dubay D, Hoose B, Murphy EL. 2013 Seroprevalence and demographic determinants of human T-lymphotropic virus type 1 and 2 infections among first-time blood donors–United States, 2000–2009. J Inf Dis Advanced Access Oct 2013.

[d] Pellett PE et al. 2003 Multicenter comparison of serologic assays and estimation of human herpes virus 8 seroprevalence among US blood donors. Transfusion 43: 1260-1268.

[e] http://seer.cancer.gov/csr/1975_2010/ ; Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD.

[f] Mechanoreceptors in the skin sensitive to sustained pressure.

[g] Kean JM et al. 2009 Seroepidemiology of Human Polyoma viruses. PLoS Pathog 5(3): e1000363.

[h] MCV 350 and MCV 339 are different strains of MCV.

3 Overview of carcinogenicity data

An overview of cancer sites in humans, mechanisms of carcinogenesis, and large databases of human cancer studies highlighted in recent reviews are shown in Table 2. The World Health Organization's International Agency for Research on Cancer (IARC) has recently updated previous IARC reports on KSHV, EBV, HTLV-1, and HIV type-1 (IARC 2012; Bouvard et al. 2009) and, for the first time, has reviewed MCV (IARC 2013; Bouvard et al. 2012). These reviews were conducted by a panel of experts who applied specific criteria for cancer assessment to large databases of information related to exposures, human cancer studies of viral infections, and studies of potential mechanisms. KSHV, EBV, HTLV-1, and HIV type-1 were classified by IARC as Group 1 carcinogens (known human carcinogens) based on sufficient evidence in humans and established mechanistic events; MCV was classified as a Group 2A carcinogen (probably carcinogenic to humans) based on limited evidence in humans and strong mechanistic evidence.

Most oncogenic viruses are species specific and are trophic for specific tissues and cell types. The incidence of potentially viral-associated cancers is dependent upon whether there is an exposure, so the environment and geographic location are important for disease or cancer progression. Other factors are immune suppression and host genetic factors, which may increase susceptibility to viral infection or activate latent viral reservoirs. EBV life cycle is especially complex since the association with specific tumor types is dependent upon the stage

of the viral life cycle. For the viruses listed above, immunosuppression is a major risk factor for oncogenesis. Varying degrees of immunosuppression can occur with aging, stress, immunosuppressive medications, and disease status. The HIV virus itself causes immunosuppression and, although not present in cancer cells, increases cancer risk from acquired opportunistic infections and from increased expression of the effects from other oncogenic infections (e.g., KSHV or EBV). Although often associated with AIDs-related cancers, HIV infection also increases cancer risk independent of these cancers. Since most of the human viruses evaluated by the IARC working group are species specific, level of evidence conclusions were not made for experimental animals. However, the discussion of mechanisms did include information from genetically modified animal models of human cancer, such as transgenic animals.

Table 2. Five selected viruses: Overview of carcinogenicity information from IARC 2012, 2013

Virus IARC classification	Cancer sites linked to viral infection	Human cancer studies and cancer endpoints (studies reviewed in IARC 2012, 2013)
EBV IARC Group 1 (carcinogenic to humans)	**Sufficient evidence:** Nasopharyngeal carcinoma (NPC), Burkitt lymphoma (BL), immune suppression-related non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), extranodal NK/T-cell lymphoma (nasal type) **Limited evidence:** Gastric carcinoma, lymphoepithelioma-like carcinoma	Over 3 cohort, 35 case control, 10 case series B-cell, T-cell, NK lymphomas; cancers of nasopharynx, stomach, breast, testis, skin
HIV-1 IARC Group 1	**Sufficient evidence:** Kaposi sarcoma, NHL, HL, cancer of the cervix, anus, conjunctiva **Limited evidence:** Cancer of the vulva, vagina, penis, skin (non-melanoma), and liver (hepatocellular carcinoma)	Extensive database of HIV infection and cancers: Over 20 cohort and 30 new case-control studies of HIV-1 & Kaposi sarcoma, meta-analysis of risk of NHL or cervical cancer with HIV-1; studies of EBV in AIDS-related NHL and HL; studies of HIV-1 infection and cancer of the conjunctiva, lung and liver have also been reported.
HTLV-1 IARC Group 1	**Sufficient evidence:** Adult T-cell leukemia/lymphoma (ATLL)	Over 5 cohort studies in Japan, several nested case-control studies that also investigated if HTLV-1 is linked to solid tumors. Several case series studies on ATLL.
KSHV IARC Group 1	**Sufficient evidence:** Kaposi sarcoma, primary effusion lymphoma **Limited evidence:** Multicentric Castleman disease (a non-cancerous lymphoproliferative disorder)	Over 20 cohort studies (among cohorts of HIV-infected people or cohorts of transplant recipients) and over 80 case-control studies of HIV infected or transplant recipients and Kaposi sarcoma. 2 cohort, 19 case control, 17 case series, 95 case reports of association with other cancers, e.g., primary effusion lymphoma and multiple myeloma.
MCV IARC Group 2A (possibly carcinogenic to humans)	**Limited evidence:** Merkel cell carcinoma (MCC) – rare, highly malignant skin cancer	Association of MCV with MCC: No cohort studies; over 5 case-control studies; over 15 case-series studies in different populations.

4 Issues and key scientific questions relevant for cancer evaluation

For each virus, the cancer assessment will address the following questions.

- Is there significant U.S. exposure?
- How are people (sources, settings, and levels) exposed?
- Are the available studies in humans adequate for evaluating cancer hazard from exposure?
    - If so, what are the human cancer sites? Is the level of evidence limited or sufficient per RoC listing criteria?
    - What are other potential contributors (effect modifiers) to reported effects?
    - What are the major potential confounders for evaluating cancer hazard from exposure?
- What are the key mechanistic studies to determine viral oncogenesis in humans?
- What are potential mechanisms of carcinogenesis?
- What is the preliminary RoC listing recommendation?

5 Proposed approach for conducting the scientific evaluation

There is a very large scientific database on these viruses. Human cancer studies related to v infection and proposed mechanisms of site-specific viral oncogenesis have been published i authoritative reviews and IARC has recently conducted extensive evaluations on these virus IARC Monograph volume 100B (IARC 2012) updated information contained in volumes 67 a 70 o EBV, HIV, HTLV-1, KSHV, and monograph volume 10 (IARC 2013) reviewed MCV. Th proposed approach was developed to allow National Toxicology Program (NTP)/ORoC to efficiently use the information provided in these high quality assessments to conduct its ow assessment of the scientific review for potential listing in the RoC.

For each virus, the NTP plans to use the body of knowledge published in the IARC monograp on these viruses as a resource to develop its cancer assessment. The key human and mechanistic studies and the data discussed in the IARC monographs and any newer key stud will be considered and assessed this evaluation will use the RoC criteria to assess the scient evidence and be independent of IARC's conclusions.

protocol describing the proposed approach for development of the cancer assessments fro information in the IARC monographs and newer publications will be developed by monogr planning team (see section 5.1) and posted on the website for public and interagency input. cancer assessment will be developed by the planning team and released for interagency revi and public comment prior to evaluation by an external peer-review panel convened by NTP public forum.

The proposed approach should provide more efficient use of NTP resources, and optimizes t RoC process for non-controversial candidate substances with use of recent, authoritative re such as on these viruses, and does not reduce public or scientific input to the RoC process.

The following sections provide details on the proposed approach.

5.1 Establishment of a RoC monograph planning team

RoC monograph planning team (hereinafter called planning team) consisting of expert technical advisors and NTP and contractor staff will assist ORoC staff in protocol and cancer assessments, identifying key studies and providing input in the development of RoC monographs on these viruses. Since the extent of the databases for each of the five viruses vary, it is anticipated that some of the advisors will work on specific virus, whereas, others will serve in an overall advisory capacity. All advisors will be screened for conflict of interest. Experts from the government or private sectors will be identified from primary publications in fields such as mechanisms of viral oncogenesis, virology, oncology, and epidemiology.

5.2 Protocol development

For each virus, the NTP proposes to use the scientific information in the IARC monograph and key information in newer publications to conduct its assessment of the quality of the scientific evidence, apply the RoC criteria to the scientific information, and reach preliminary recommendation for listing in the RoC. For most of the viruses, the focus of the RoC evaluation will be specific human cancer endpoints; mechanistic information would be used to interpret the human cancer findings. protocol describing the proposed approach including the literature search strategy (see Attachment A) for the development of the cancer assessment will be posted on the ORoC website and announced through the NTP listserv with request for public comment and input, including request for any additional studies.

5.3 Development and peer review of the draft RoC monographs

The cancer assessment will include an evaluation of the quality of scientific evidence obtained from the IARC monographs and any new studies, and apply the RoC criteria to reach a preliminary listing recommendation for the RoC. The monograph planning team will assist with the cancer evaluation. The assessment will be captured in the draft RoC monograph. The profiles will contain the NTP's preliminary listing recommendation (*i.e.* not to list, list as *reasonably anticipated to be a human carcinogen* or list as *known to be a human carcinogen*) based on RoC listing criteria and the science considered to be key in reaching that recommendation for the agent, as well as information on sources of transmission, exposure, and any at-risk populations for each of the viral agents. U.S. exposure and U.S. guidelines to limit exposure will be included from other sources. The monographs will be reviewed by NIEHS/NTP and by NTP interagency partners, and released for public comment prior to NTP peer-review panel in a public forum[2]. The process for input, development, and review of the monographs and criteria for listing in the RoC will follow the RoC process. The NTP Office of Liaison, Policy and Review will manage the NTP expert panel peer review. Members of the peer-review panel may be identified from databases of the peer-reviewed literature, membership in relevant professional societies, and recommendations from other scientists or the public and will be screened for conflict of interest.

6 Public health significance

[2] NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166*.

The RoC is a congressionally mandated public health document listing substances that are known to be human carcinogens or reasonably anticipated to be human carcinogens. profile of the listed substance in the report contains information on production, use, exposure, human cancer studies, cancer studies in experimental animals, and other relevant cancer information. Federal guidelines and regulations that limit human exposure to the substance are also provided. For infective agents, information on physical characteristics, exposure, transmission, infection, replication, human cancer studies, mechanistic information and disease prevention will be addressed.

Recognition and review of these viral agents by NTP will provide an important benefit to public health by informing the public about disease transmission and prevention and increasing awareness of these agents as potential carcinogens.

References

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Carrillo-Infante C, *et al.* (2007). Viral infections as a cause of cancer (Review). *Int of Oncology* 30:1521-1528.s

Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int Cancer* 118: 3030–3044.

Attachment A: Preliminary Literature Search Strategies

This document summarizes the approach for identifying literature for the RoC reviews of Selected Viruses. If this topic is selected to move forward, a more detailed strategy for identifying and reviewing citations will be described in the protocol that will be posted on the RoC website. The goal of the literature search strategy is to identify information on U.S. exposure, new human cancer studies, and mechanistic information since the IARC reviews as well as incorporate key studies used in the IARC reviews on these viruses.

In general, literature will be identified from the following sources or methods:

1. **General and exposure-related data search:** This search covers a broad range of general data sources such as authoritative reviews (IARC monographs, U.S. federal, state, and international evaluations) and sources for general exposure information such as the Centers for Disease Control and Prevention.

2. **Database searches in PubMed, Scopus, and Web of Science:** The majority of the primary literature will be identified from these three databases using search strategies that combine terms for exposure (virus name) with terms for the monograph subject (i.e., human cancer). Additional biomedical literature database (such as Embase) may also be searched. Technical advisors will be consulted regarding details on exposure and identification of human cancer studies. Search terms for each virus will be developed in consultation with an information specialist.

3. **QUOSA library:** number of QUOSA libraries will be created. Full-text searches of the libraries will be conducted using search terms related to the viruses.

4. **Special topic-focused searches:** Searches may be conducted on special topics or specific issues identified in the monograph development.

5. **Secondary sources:** Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science "Cited Reference Search", will be added.

Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level review of the literature are conducted, with initial screening based on titles and abstracts only, followed by full-text screening. Searches will be updated by creating monthly search alerts in the relevant databases (such as PubMed, Scopus, and Web of Science).