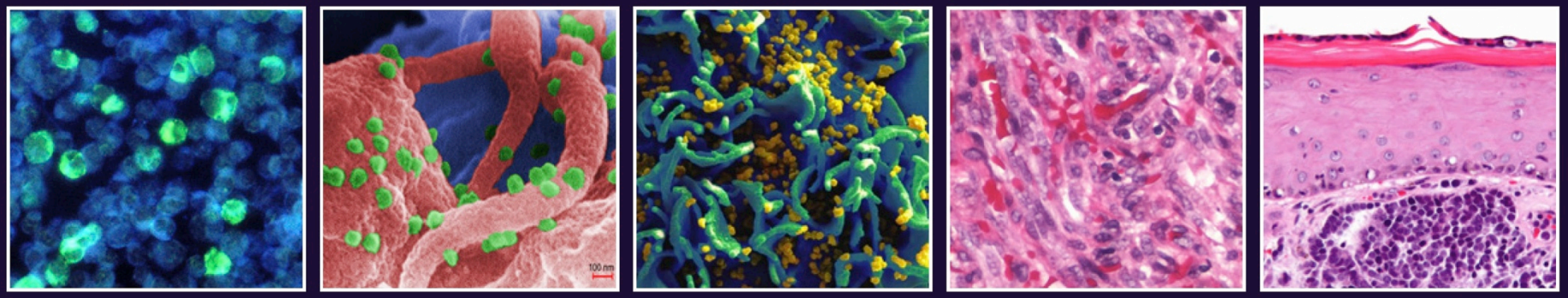
NTP
National Toxicology Program



Process for Preparing Five Draft Monographs on Viruses

Ruth M. Lunn, DrPH

Office of the Report on Carcinogens

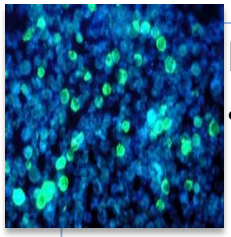
National Institute of Environmental Health Sciences

December 17, 2015

Outline

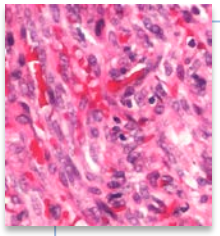
- Background on Report on Carcinogens (RoC)
- Selection of viruses for review for the RoC
- Preparation of the draft RoC monographs
- Evaluation of cancer hazards and RoC listing criteria
- Peer-review charge
- Next steps

Five selected viruses



Epstein Bar Virus (EBV)

- Herpes virus

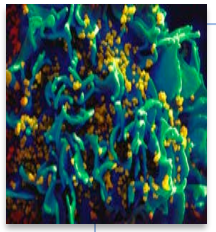


Kaposi sarcoma herpesvirus (KSHV)

- Herpes virus

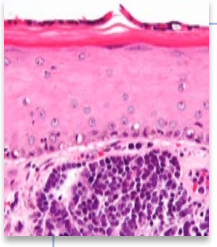
Human immunodeficiency virus, type 1 (HIV-1)

- Retrovirus



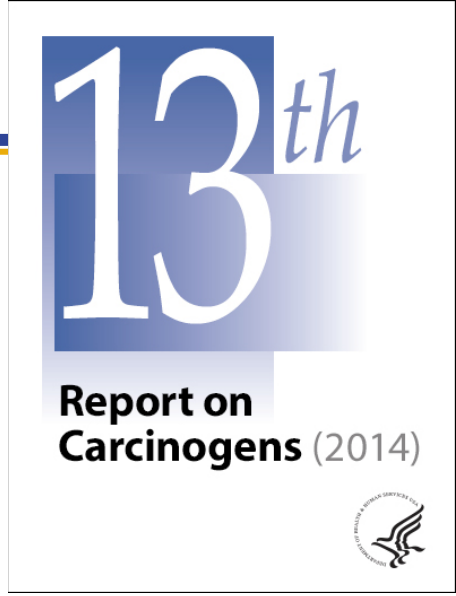
Human T-cell lymphotropic virus, type 1 (HTLV-1)

- Retrovirus



Merkel cell polyomavirus

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

Process for the 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

RoC related products

- Concept document
  - Contains rationale and proposed approach for the substance review
- Draft RoC monograph consists of two parts
  - Cancer hazard evaluation component
  - Substance profile
- Report on Carcinogens
  - Compilation of substance profiles for each listed substance

Selection of 5 Viruses as Candidate Substances

Important public health concern

Nominated by private individual

Interagency review

Public comment (N = 0)

January 19, 2012: FR

Developed draft concept

Public comment (N = 0)

March 7, 2014: FR

Draft concept reviewed by BSC

April 16-18, 2014 public mtg

NTP Director

Selected as candidate substance

- Many individuals living in the United States are infected with the 5 viruses
- ~12% of cancers worldwide are linked to viruses*
  - Hepatitis C virus, hepatitis B virus, and and selected human papillomaviruses are listed in the 13th RoC
- Currently, no vaccines are available for any of these five viruses
- Large database of cancer studies
- Evaluated over 24 specific types of cancers

*Parkin, 2006

Preparation of the RoC monographs

Prepared draft RoC monograph

- Established website
- Selected monograph team and technical advisors
- Draft monograph
- Technical advisor review
- Internal review

Prepared substance profile

- Interagency review

Completed draft RoC monograph
November 5, 2015

- Drs. Goedert and Read-Connole, NCI
- Additional experts for specific viruses

- Monographs relied on information and data presented in IARC monographs (*100B* 2012, *104*, 2013)
- Literature searches for key or new information published since the monograph

Monograph Preparation: Contents

Cancer hazard evaluation component

- Overview and introduction
- Properties and detection
- Human exposure
  - Prevalence and transmission
  - Diseases, prevention, treatment
- Cancer studies in humans
- Other relevant data
- Overall cancer evaluation
- Literature search strategy

Substance profile

- Listing recommendation
- Carcinogenicity
- Biological properties
- Detection
- Exposure
- Regulations

Reach RoC Conclusions

Evaluate whether a significant number of U.S. residents are exposed to viruses

Congressional mandate	• Publish a report that lists substances which are *known* or *reasonably anticipated to be human carcinogens* **and to which a significant number of persons residing in the United States are exposed.**
Evaluate data	• Exposure primarily inferred by seroprevelance data (such as NHANES and blood bank) • Blood bank data may underestimate exposure
Reviewer instructions	• Use their judgment as to whether the exposure information in the draft monograph supports the NTP conclusion that a significant number of U.S. residents are exposed to each virus.

Reach preliminary listing recommendation

Known to be a human carcinogen

- Sufficient evidence of carcinogenicity from studies in humans

Reasonably anticipated to be a human carcinogen

- Limited evidence from studies in humans
  OR
- Sufficient evidence from studies in experimental animals
  OR
- Less than sufficient evidence in humans or experimental animals
  - Agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous RoC as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen.
    OR
  - Convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Guidance (final paragraph of criteria)

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information.

Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance.

For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

RoC Listing Criteria

Reach level of evidence conclusion for carcinogenicity from studies in humans*

Sufficient evidence

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

Limited evidence

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or **data derived from the study of tissues or cells from humans exposed to the substance** in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Evaluate mechanistic and other relevant data

- Provides context for biological plausibility of findings reported in human and experimental animal cancer studies
- Mechanistic data are often sparse and for most listed substances, mechanisms are not completely understood
  - Mechanistic data are not a requirement for listing a substance in the RoC
- Can be used to list/not list a substance or support findings in humans and experimental animals
  - Agent belongs to a well-defined, structurally related class of substances whose members are listed in the RoC
  - Convincing data that a substance operates by a mechanism that would cause cancer in humans
  - Compelling data that a substance causes cancer by a mechanism that would not occur in humans

Human evidence comes from epidemiology and/or molecular studies

- Epidemiological issues some of which are unique to viruses
- NTP approach for applying the RoC criteria
  - Hill considerations for human epidemiological studies
  - Review of mechanistic evidence in humans and considerations developed by others
    - IARC (EBV) to address whether the presence of virus in a tumor is the cause of the cancer or effect of the tumor
    - Zur Hausen consideration of molecular and epidemiological evidence
    - Multi-causality issues
      - Cause is not a single component but a set of minimal set of conditions that produces outcome
      - Not necessary to identify all components to prevent the disease outcome
      - Each disease may have more than one sufficient cause

Process for the 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

Peer-Review Meeting

Charge	To comment on the 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 justification presented in the substance profile supports the NTP's preliminary policy decision on the RoC listing status of each virus
Actions (votes)	Whether the scientific evidence supports the NTP's conclusions 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

Next Steps

Process for the 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

Acknowledgements

Office of the RoC (ORoC), NTP

Ruth Lunn (Director ORoC)
Gloria Jahnke (Project Leader)
Diane Spencer

ILS Contractor Staff

Sanford Garner (PI)
Stanley Atwood
Ella Darden
Andrew Ewens
Jessica Geter
Alton Peters
Jennie Ratcliffe
Tracy Saunders
Pam Schwingl

Social and Social and Scientific Systems Contractor Staff

Whitney Arroyave

Office of Liaison, Policy and Review

Mary Wolfe, Director
Lori White (Designated Federal Official)
Robbin Guy