Process for Preparing Five Draft Monographs on Viruses

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Office of the Report on Carcinogens
National Institute of Environmental Health Sciences
December 17, 2015
Viruses Peer-Review Meeting

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*
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- 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

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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
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 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

- 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

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

<table>
<thead>
<tr>
<th>Congressional mandate</th>
</tr>
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<tbody>
<tr>
<td>Publish a report that lists substances which are <em>known</em> or <em>reasonably anticipated to be human carcinogens</em> and to which a significant number of persons residing in the United States are exposed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluate data</th>
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<tbody>
<tr>
<td>Exposure primarily inferred by seroprevalence data (such as NHANES and blood bank)</td>
</tr>
<tr>
<td>Blood bank data may underestimate exposure</td>
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<th>Reviewer instructions</th>
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<tr>
<td>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.</td>
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</table>
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.
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.
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.*
RoC Listing Criteria

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
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<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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<td>NTP has objectively presented and assessed the scientific evidence,</td>
<td>Whether the scientific evidence supports the NTP’s preliminary listing decision</td>
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<td>and whether the scientific evidence is adequate for applying the</td>
<td>of viruses in the RoC</td>
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<td>listing criteria</td>
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Acknowledgements

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