Draft Report on Carcinogens Concept: Shift Work at Night, Light at Night, and Circadian Disruption

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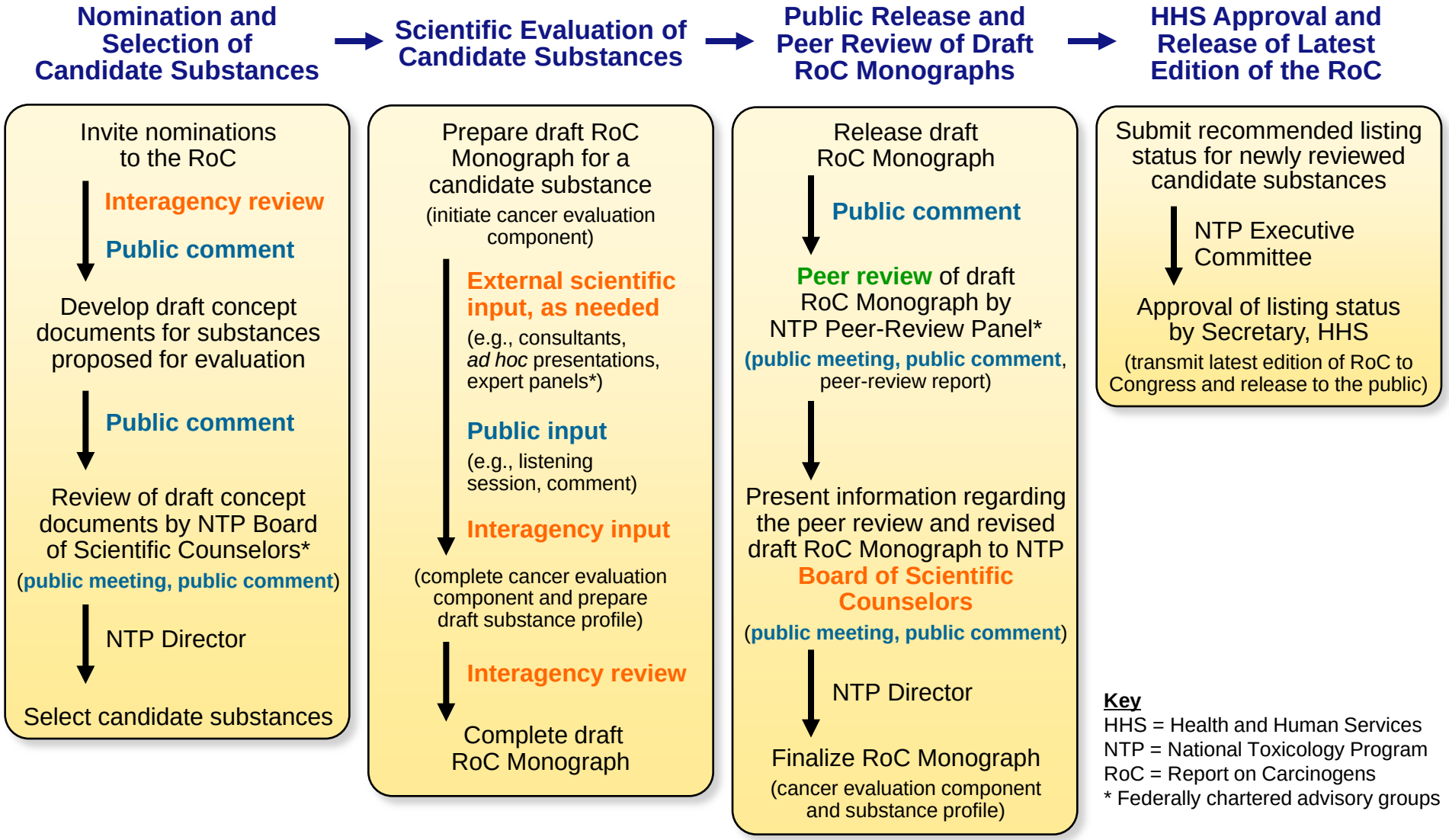
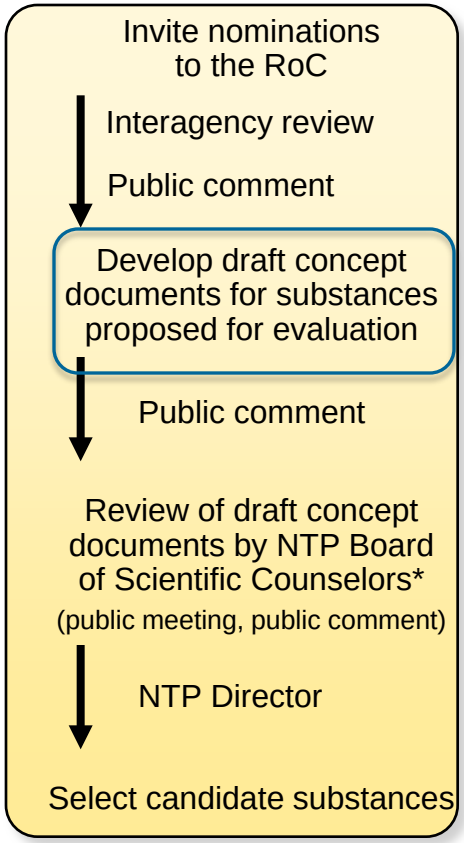
Process for Preparation of the Report on Carcinogens



Key

HHS = Health and Human Services
NTP = National Toxicology Program
RoC = Report on Carcinogens
* Federally chartered advisory groups

Draft Concept Document Outlines:



- Rationale for reviewing the proposed candidate substance
- Overview of human exposure data
- Overview of the extent and nature of the carcinogenicity information
  - Not an assessment of the data
- Key scientific questions and issues based on preliminary knowledge
- Proposed approach for conducting the cancer evaluation
  - Preliminary literature search strategy
  - Scope and focus of the draft monograph
  - Proposed approach for obtaining external scientific and public inputs

Nomination History

- Light at night (LAN) was nominated by several individuals
- IARC concluded that “shiftwork that involves circadian disruption” is probably carcinogenic to humans (Group 2A)
  - Limited evidence of increased breast cancer among women working a night shift
  - Sufficient evidence in experimental animals of carcinogenicity of light during daily periods of dark (biological night)
- Office of the RoC (ORoC) solicited public comment on “shiftwork involving light at night”
  - Three public comments were received
    - Supported the review of light at night
    - Concerned about environmental exposure to light at night (light pollution)

LAN Hypothesis (Stevens et al. 1992)

- Artificial LAN may be a cause of high rates of breast cancer among women in industrial nations
  - Electrical light (depending on the intensity and wavelength) can suppress nighttime melatonin production by the pineal gland
  - Decreased melatonin levels may play a role in breast cancer development
- Epidemiologic studies of shift work were initiated in the mid-1990s to test LAN hypothesis
  - Shift work is considered to be an exposure surrogate for LAN
- Increased interest of cancer research (experimental and epidemiologic studies) on light exposure, melatonin and circadian disruption

Circadian Disruption

- Circadian rhythms are daily and predictable variations in biological, physiological, and behavioral processes that are regulated by endogenous clocks
  - Entrained to the external environment by repetitive signals, of which the light/dark cycle is the most important.
  - Light exposure transmits time information from the retinal cells in the eye to the central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus
  - SCN regulates the numerous peripheral clocks (oscillators) via humoral, endocrine or neural signals
  - Melatonin transmits time information (day, year) to body tissues
- Circadian disruption occurs when the endogenous circadian rhythms are out of phase with the external environment or with each other

Circadian Disruption: Shift Work and Time Zone Travel

- Circadian rhythms of individuals who are synchronized to daytime activity and nighttime sleep undergo phase-adjustment after a change in work schedule or travel across multiple time zones.
- Phase shifts in circadian rhythms
  - Advances: exposure to light in latter part of biological evening; eastward travel, backward rotating shift.
  - Delays: exposure to light in early part of biological evening, traveling westward, forward rotating shift.
- Extent of disruption depends on work schedule, direction of phase shift, individual susceptibility.
- Changes in work schedule can affect quality and quantity of sleep and lead to fatigue.

Human Studies		Related Animal Studies
Population Exposure surrogates and metrics	Exposure associated with circadian disruption	Exposure: Type of study
Shift workers Shift work at night: Ever, frequency duration of exposure, type and direction of shift schedule, effect modifiers	LAN Phase shift (rotating schedule) Sleep deprivation	Stimulated jet lag/shift work: Tumor growth SCN lesions: Tumor growth Clock gene mutations: Incidence, initiation/promotion
Airline personnel Most studies: job title; few studies: duration, international, time zone, sleep disruption	Phase shift (time zone changes/jet lag) LAN Sleep deprivation	Simulated jet lag: Tumor growth Circadian studies (above)
Non-Occupational Environmental exposure to LAN: Self reported; satellite measures (ecological)	LAN (evening and ambient)	Constant LAN: Incidence studies Circadian studies (above)
Population based and shift workers Nocturnal urinary melatonin levels	LAN or phase shift	Removal of pineal gland: Tumor growth/initiation/promotion studies Physiological melatonin levels: Tumor growth

Significant Number of People Potentially Exposed to Conditions Leading Circadian Disruption

- Shift workers: U.S. data (2004)
  - An estimated 17 million people work non-daytime shifts
  - Occupations with highest number of night shift work include protective services, leisure and hospitality, healthcare practitioners and healthcare support, transportation and warehousing, manufacturing, and mining
- Airline personnel: U.S. data (2010)
  - 100,000 airline and commercial pilots and over 90,000 flight attendants
- Environmental exposure to LAN
  - 30% of the population exposed to light pollution exceeding threshold of 10% above natural sky brightness

Rationale: Exposures Associated with Circadian Disruption

- Adequate database of studies
  - Numerous studies have evaluated cancer risk among people, who by virtue of the nature of their work, lifestyle choices or residence, are subjected to interruptions in the natural light dark and sleep-wake cycles, and have the potential for circadian disruption
    - Shift work, airplane personnel, environmental exposure to LAN, nocturnal melatonin levels
  - Experimental studies of carcinogenicity related to exposure to LAN, melatonin production and the circadian system
- Widespread U.S. exposure
- Challenges with defining the nomination

Issues and Questions: Defining the Candidate Substance and Identifying Studies for Inclusion

- How should the candidate substance be defined so that it accurately reflects the underlying exposure? Is “light at night,” “circadian disruption,” “environmental exposures that induce circadian disruption” best or is something else more appropriate?
  - Light at night has been indirectly assessed in the human cancer studies using exposure surrogates such as shift work.
  - Shift work is also associated with other factors, of which changes in sleeping patterns leading to sleep deprivation is a particular concern.
    - “Exposure to light that induces circadian disruption and sleep deprivation”
  - Defining common exposures or exposure surrogates (such as shift work at night) that is partly defined by an effect (circadian disruption) provides a challenge for communicating useful information to the public.
- Are there other study populations or exposure scenarios that are surrogates for light at night or circadian disruption that should be included in the monograph?

Issues and Questions: Developing Protocols to Assess the Human Cancer Studies

- What are the exposure metrics of shift work that are the best surrogates for circadian disruption or light at night?
  - Epidemiologic studies do not have clear and uniform definitions of shift work
- What are the important effect modifiers (e.g., chronotype, genetic susceptibility)?
  - Individuals vary considerably in sensitivity to light at night and their ability to adapt to changes in time zones or work schedules
- How should mechanistic data be used to inform interpretation of the epidemiologic studies?
  - Depending on the proposed causal pathways, other characteristics (such as sleep duration) of the study populations (shift-workers, airline personnel) could be considered as potential confounders or intermediate variables

Issues and Questions: Evaluation of Cancer Studies in Humans and Animals, and Mechanistic Data

- Human cancer studies
  - What is the level of evidence (sufficient, limited) for the carcinogenicity of the candidate substance(s) from studies in humans? Can chance, confounding, and bias be ruled out with reasonable confidence?
  - What are the cancer sites?
  - Does the level of evidence vary for the different exposure surrogates?
- Cancer studies in experimental animals and mechanistic data
  - What is the level of evidence (sufficient, limited) for the carcinogenicity of the candidate substances from studies in experimental animals?
  - Does the level of evidence vary for the different types of exposures?
  - Many of the studies evaluate tumor promotion or growth rather than tumor incidence. How should that data be considered in the evaluation?
  - What are the potential mechanisms of carcinogenicity?
  - Are the findings from the studies in humans consistent with the toxicological data?

Approaches to Receive Scientific Input: Technical Advisors

- Expertise in light at night, circadian disruption, breast cancer and occupational epidemiologic studies
- Sources for identifying advisors: Literature database, recommendations from the scientific community, and public.
  - Scientists at NIOSH, OSHA and other agencies have expertise on this topic and may serve as advisors.
- Advisors may meet as a group to share information across disciplines
- Technical advisors will provide input on the following:
  - Define the candidate substance more clearly, and identify the types of studies to be included in the monograph
  - Protocols to evaluate cancer studies in humans and experimental animals
  - ORoC assessment of the studies

Approaches to Receive Scientific and Public Input: Website and Webinars

- Establish a website to share information with the public and receive input from the public
  - Documents related to the development of the draft monograph
    - Concept
    - Literature search strategies and preliminary list of references
    - Protocols for evaluating cancer studies in humans and experimental animals
  - Public comments, meeting information and other RoC products
- Webinar(s): Potential topics
  - Define the underlying exposure(s)
  - Evaluate the studies, focusing on the most informative exposure metrics
  - Discuss causal models including how mechanistic data can help inform the interpretations of the human cancer studies

Charge: To review and comment on the draft concept document and advise whether the proposed evaluation is an appropriate use of NTP resources

1. Comment on whether, based upon the information provided in the draft concept, it is reasonable that a significant number of people living in the United States are exposed to light at night or other exposures that may cause circadian disruption.
2. Please comment on the potential contribution/importance to public health of ORoC undertaking this evaluation. The NTP will use these comments in assessing the relative priority of evaluations of RoC candidate substances
3. Comment on whether the extent and nature of the scientific information on carcinogenicity is clearly described and adequate (studies in humans, animals, and/or mechanistic information) to support a RoC evaluation.
4. Advise as to whether the scientific issues identified as relevant are reasonable. Are you aware of any other scientific issues that should be considered?
5. Comment on whether the proposed strategy for obtaining scientific and public inputs in identifying the candidate substance and developing the cancer evaluation component of the draft RoC monograph is reasonable.
6. Provide any other comments you feel staff should consider in developing this evaluation.