

**Review Summary of the National Institute of Environmental Health Sciences (NIEHS/NTP) RoC
Review Committee (RG1)**

Nomination: Human Papilloma Viruses (HPV)

Review Committee: RG1

Date: 2002 December 17

Major issues discussed

Application of criteria

Exposure: HPV clearly meets the criteria for listing in the RoC. In the United States, over two million people per year are infected.

Human studies: Multiple cohort and case-control studies in various populations worldwide and in the United States have clearly shown that infection with HPV-16 or -18 is causally associated with cervical cancer. Less overwhelming but still compelling evidence indicates that other HPVs, including 31, 33, 35, 39, 45, 51, 52, 58, and 59 are also associated with increased risk of cervical cancer, as are so-called high-risk HPVs as a class (which usually includes 56, 66, and 68 in addition to the viruses listed above). HPV-16 and possibly -18 are also associated with increased risk of vulvar, vaginal, penile, and anal cancers.

Experimental animal studies: HPV is specific to humans. Studies in monkeys, cattle, rabbits, and sheep have shown that animal papilloma viruses cause cancer in their natural hosts. Studies of transgenic mice have demonstrated that HPV proteins play a role in the development of dysplasia and progression to tumors. Female mice containing HPV-18 LCR and part of E1, E6 and E7 genes developed cervical neoplasms at one to two years.

Genotoxicity and mechanistic concerns: High risk HPV infection is associated with chromosome aberrations in human cervical cancer cells. HPV (high-risk) can integrate into host DNA and immortalize and transform cells. Viral proteins E6 and E7 alter transcriptional control and cell cycle progression and affect growth regulation. The E6 protein degrades p53 and the E7 protein disrupts transcription complexes with pRb and related cell control proteins. Most mechanistic studies have been conducted using HPV-16 and -18.

Other concerns: Most discussion focused on the title of the listing. The committee was concerned that listing all HPVs was inappropriate since some are not associated with cancer. Most available evidence concerns a group of viruses identified as "high risk," but the specific members of this group vary from study to study and may change in the future. Because of this, and to avoid any confusion with risk assessment, the committee decided against use of the term "high risk" in the nomination title. The committee further noted that all the viruses associated with cervical cancer are of the genital mucosa type. Ultimately, the committee voted 4 to 1 to identify the listing as "Some HPVs, genital mucosa type." The dissenting vote reflected dissatisfaction with the word "some."

Recommendation: The committee voted unanimously (7 yes / 0 no) to list *some HPVs, genital mucosa type as known to be human carcinogens* based on significant exposure in the US population and overwhelming positive cancer epidemiology data in humans.