International Agency for Research on Cancer

World Health Organization

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IARC Monographs evaluate the carcinogenicity of hepatitis D virus, human cytomegalovirus, and Merkel cell polyomavirus

Questions and Answers (Q&A)

IARC Monographs Volume 139

The meeting for *IARC Monographs* Volume 139: Hepatitis D Virus, Human Cytomegalovirus, and Merkel Cell Polyomavirus, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, took place on 3–10 June 2025.

The Working Group of 17 international experts from 10 countries evaluated the carcinogenicity of hepatitis D virus, human cytomegalovirus, and Merkel cell polyomavirus.

More information about the meeting is available on the *IARC Monographs* website: https://monographs.iarc.who.int/iarc-monographs-volume-139/.

The outcome of the assessment has been published in a summary article in *The Lancet Oncology*[1] and will be described in detail in Volume 139 of the *IARC Monographs*, to be published in 2026.

1. Why did IARC decide to evaluate these three viruses, and have they been evaluated previously?

Hepatitis D virus (HDV) was previously evaluated by the *IARC Monographs* programme in 1993 (Volume 59)[2] and was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3). The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029[3] recommended that HDV should be re-evaluated with high priority, based on new evidence for cancer in humans.

Merkel cell polyomavirus (MCPyV) was previously evaluated by the *IARC Monographs* programme in 2012 (Volume 104)[4] and was classified as *probably carcinogenic to humans* (Group 2A). The Advisory Group to

[1] Karagas MR, Kaldor J, Michaelis M, Muchengeti MM, Alfaiate D, Argirion I, et al. (2025). Carcinogenicity of hepatitis D virus, human cytomegalovirus, and Merkel cell polyomavirus. *Lancet Oncol*. Published online 27 June 2025; https://doi.org/10.1016/S1470-2045(25)00403-6

[2] IARC (1994). Hepatitis viruses. *IARC Monogr Eval Carcinog Risks Hum*. 59:1–286. Available from: https://publications.iarc.who.int/77 PMID:7933461

[3] IARC (2024). Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2024/11/AGP_Report_2025-2029.pdf.

[4] IARC (2013). Malaria and some polyomaviruses (SV40, BK, JC, and Merkel cell viruses). *IARC Monogr Eval Carcinog Risks Hum*. 104:1–353. Available from: https://publications.iarc.who.int/128 PMID:26173303

Recommend Priorities for the *IARC Monographs* during 2025–2029 also recommended that MCPyV should be re-evaluated with high priority, based on new human cancer and mechanistic evidence to warrant re-evaluation of the classification.

Human cytomegalovirus (HCMV) has not been previously evaluated by the *IARC Monographs* programme. The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029 recommended that HCMV should be evaluated with high priority, based on relevant human cancer and mechanistic evidence.

2. How are these viruses transmitted?

Transmission of HDV can occur through contact with human blood or other body fluids (e.g. semen) from a person with an infection. The prevalence of HDV infection is higher in people who inject drugs or engage in high-risk sexual behaviours. The establishment of HDV infection requires co-infection (or prior infection) with hepatitis B virus (HBV).

HCMV is transmitted through body fluids such as saliva, blood, urine, semen, and breast milk, and from mother to foetus during pregnancy. Infection can occur at all ages but is most common during childhood. Reactivation of latent infection in immunocompromised individuals contributes to HCMV pathogenesis.

MCPyV infections are typically acquired in early childhood via close contact with individuals with an infection (who are predominantly asymptomatic), and the virus persists as a common component of the normal skin virome. In Merkel cell carcinoma, which is a rare but aggressive type of mainly skin cancer (although it can be found elsewhere), the virus is commonly found to be integrated into the genome.

3. How widespread is the exposure to these viruses?

Because the establishment of HDV infection depends on HBV infection, estimates of the prevalence of HDV infection are reported predominantly in individuals with HBV infection, among whom the prevalence ranges from 1% to 10% in most regions of the world, although a much higher prevalence has been noted in some countries. The global seroprevalence of HDV within the overall population has been estimated to be between 0.1% and 1%.

The global seroprevalence of HCMV has been estimated to be about 80% for the general population. The prevalence tends to be higher in countries in South America, Africa, and South Asia. In the general population, infection is most often asymptomatic or causes a mild, mononucleosis-like illness. Reactivation of latent infection in immunocompromised individuals contributes to HCMV-related morbidity.

The estimates for MCPyV indicate that the prevalence is high in human populations (usually > 50% across studies). In the general population, infection is most often asymptomatic.

4. Are there treatments or vaccines for these infections?

	Vaccination	Treatment
HDV	HBV vaccination serves as an indirect preventive measure for HDV infection when given before HBV infection.	Treatment is available (e.g. pegylated interferon alpha or, more recently, bulevirtide).
HCMV	No vaccine for HCMV is available.	Usually, HCMV infection is not treated. Treatment is available for immunocompromised patients and pregnant individuals.
MCPyV	No vaccine for MCPyV is available.	No treatment for MCPyV is available.

5. What are the results of the evaluation?

The results of the evaluation are summarized in Table 1.

Table 1. Summary of classifications in *IARC Monographs* Volume 139

Agent	Evidence stream			Overall evaluation
	Cancer in humans	Cancer in experimental animals	Mechanistic evidence	
Hepatitis D virus (HDV)	*Sufficient* (hepatocellular carcinoma)	*Inadequate*	*Strong* in exposed humans and in human primary cells	**Group 1**
Human cytomegalovirus (HCMV)	*Limited* (acute lymphoblastic leukaemia in children)	*Inadequate*	*Limited*	**Group 2B**
Merkel cell polyomavirus (MCPyV)	*Sufficient* (Merkel cell carcinoma)	*Sufficient*	*Strong* in exposed humans and in experimental systems	**Group 1**

6. How did the Working Group arrive at these classifications?

HDV was classified as *carcinogenic to humans* (Group 1) on the basis of *sufficient* evidence for cancer in humans. There was *sufficient* evidence in humans that HDV causes a form of liver cancer called hepatocellular carcinoma. The Working Group restricted its evaluation to studies within individuals with HBV infection to reduce concerns that the results could be explained by HBV instead of HDV. There were multiple studies with different

study populations, designs, and methodologies, and overall they indicated a consistent and strong increase in the risk of hepatocellular carcinoma in individuals with HDV infection and HBV infection. The association remained when limited to studies that accounted for other causes of liver cancer. Evidence that active viral replication was associated with higher risk of liver cancer supported this evaluation. There was also *strong* mechanistic evidence in exposed humans that HDV induces chronic inflammation, including end-points of inflammation and inflammation-related outcomes such as cirrhosis.

HCMV was classified as *possibly carcinogenic to humans* (Group 2B) on the basis of *limited* evidence for cancer in humans. There was *limited* evidence in humans that HCMV causes childhood acute lymphoblastic leukaemia (ALL). The most informative studies were consistent with an increased risk of ALL in childhood, using HCMV DNA positivity in blood spots from newborn babies or immunoglobulin M (IgM) seropositivity of the mother during pregnancy. Concerns were raised about the precision of the study estimates and other causes of both exposure and childhood ALL.

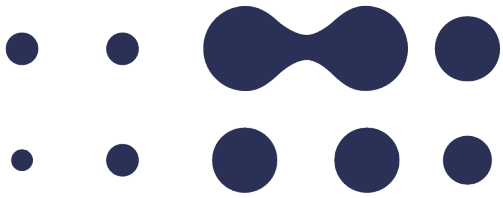
Merkel cell polyomavirus was classified as *carcinogenic to humans* (Group 1) on the basis of *sufficient* evidence for cancer in humans and the combination of *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in exposed humans. There was *sufficient* evidence in humans that MCPyV causes Merkel cell carcinoma. There was a strong positive association between MCPyV-neutralizing antibodies and subsequent risk of Merkel cell carcinoma in a study in which samples were taken well before cancer diagnosis. This finding complemented the results of case–control studies indicating increased odds of MCPyV serological markers in Merkel cell carcinoma cases, as well as observations in samples of Merkel cell carcinomas that the virus was integrated in the cancer cell genome.

The *sufficient* evidence for cancer in experimental animals was derived from seven studies using transgenic mouse models expressing Merkel cell polyomavirus T antigens. These studies showed an increase in the incidence of benign neoplasms (papilloma of the skin) and malignant neoplasms (squamous cell carcinoma in situ of the skin; high anaplastic tumours of the spleen and liver; and tumours that histologically and transcriptionally resemble human Merkel cell carcinoma) in male and female transgenic mice expressing Merkel cell polyomavirus T antigens in a tissue-specific manner.

There was *strong* evidence that MCPyV exhibits key characteristics of carcinogens. There was consistent and coherent evidence that MCPyV is genotoxic in exposed humans and in experimental systems. In experimental systems, MCPyV alters DNA repair or causes genomic instability, causes immortalization, and alters cell proliferation, cell death, or nutrient supply.

7. Are there risk factors that aggravate the development of cancer?

The *IARC Monographs* evaluations focus on individual agents. HDV infection requires co-infection (or prior infection) with HBV, and this influenced the design of the studies used in the evaluation. The Working Group focused its evaluation on studies of individuals with HBV antibodies or records of infection. Therefore, the



evaluation reflects an increased risk of hepatocellular carcinoma over and above the already-high risk of liver cancer that results from HBV infection. Other agents were not evaluated in combination with other risk factors.

8. On the basis of this evaluation, what recommendations does IARC make?

IARC is a research organization that generates and evaluates evidence related to the causes of cancer but does not make health recommendations. However, the evaluations made by the *IARC Monographs* programme are often used as a basis for national and international policies, guidelines, and recommendations to minimize cancer risks. You can find more information on the *IARC Monographs* evaluation process here: https://monographs.iarc.who.int/wp-content/uploads/2018/07/QA_ENG.pdf.

9. What does the *IARC Monographs* classification mean in terms of risk?

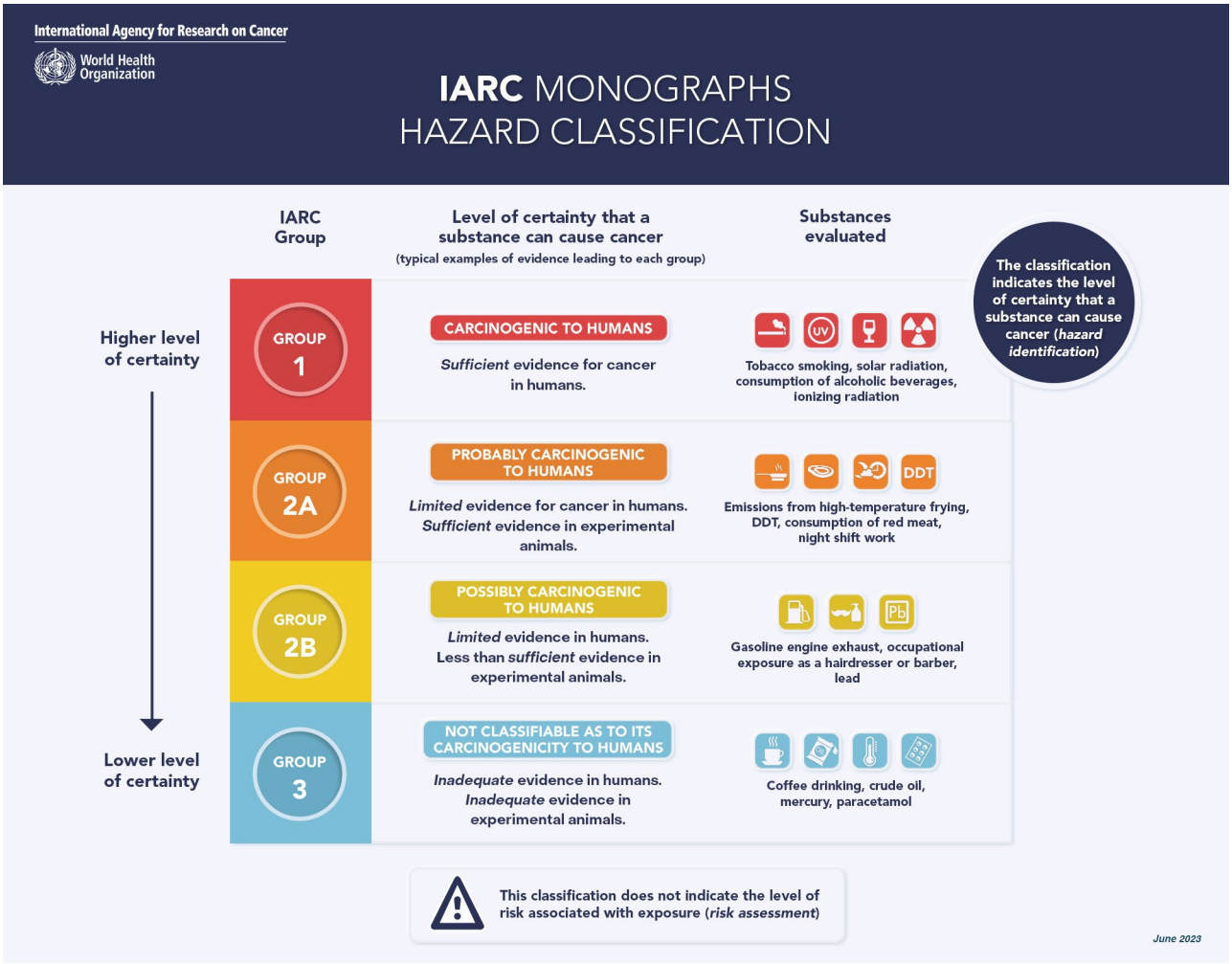
The *IARC Monographs* classification indicates the strength of the evidence that a substance or agent can cause cancer. The *IARC Monographs* programme seeks to identify cancer hazards, meaning agents with the potential to cause cancer under at least some circumstances or levels of exposure. However, the classification does not indicate the level of cancer risk associated with exposure at different levels or in different scenarios. The cancer risk associated with substances or agents that are assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the size of the effect of the agent at a given exposure level.

10. Why is the *IARC Monographs* programme's evaluation important?

The *IARC Monographs* programme's evaluation is a rigorous and comprehensive review, synthesis, and integration of all the available scientific evidence of cancer in humans and experimental animals and of mechanistic evidence related to carcinogenicity. In addition, exposure is characterized globally in a wide variety of settings: occupational, general population (patients), health care, and environmental.

Policy-makers and health-care providers may use the results of the *IARC Monographs* Volume 139 evaluation of HDV, HCMV, and MCPyV to support public health policies to tackle the cancer hazard posed by the viruses. The research community may use the findings in ongoing research efforts to fill gaps in knowledge, to support the development of treatments or vaccines, and to increase awareness of the risks of infection globally among health providers and patients.

11. What does the IARC classification indicate?



The *IARC Monographs* classifications reflect the strength of the scientific evidence as to whether an agent can cause cancer in humans, but they do not indicate the degree of risk of developing cancer at a given exposure level or for a given route of exposure. The types of exposure, the extent of risk, the people who may be at risk, and the cancer types linked with the agent can be very different across agents.

12. What are the different strength-of-evidence evaluation groups used by the *IARC Monographs*?

The strength-of-evidence groups that contribute to each evaluation are summarized in Table 2.

Table 2. Strength-of-evidence groups used by the *IARC Monographs*

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

13. What are the four different categories into which agents are classified by the *IARC Monographs*?

Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient* evidence for cancer in humans. In other words, there is convincing evidence that the agent causes cancer in humans. The evaluation is usually based on the results of epidemiological studies showing the development of cancer in exposed humans. **This was the basis on which HDV reached a Group 1 classification.** Agents can also be classified in Group 1 on the basis of *sufficient* evidence for cancer in experimental animals supported by *strong* evidence in exposed humans that the agent has mechanistic effects that are important for cancer development. **MCPyV reached a Group 1 classification in both of these ways.**

Group 2:

This category includes agents with a range of evidence regarding cancer in humans and experimental animals. At one extreme of the range are agents with positive but not conclusive evidence regarding cancer in humans. At the other extreme are agents for which evidence in humans is not available but for which there is sufficient evidence for cancer in experimental animals. There are two subcategories, which indicate different levels of evidence.

Group 2A: The agent is *probably carcinogenic to humans*.
This category is used in four different scenarios (which can occur simultaneously):

1. When there is *limited* evidence for cancer in humans and *sufficient* evidence for cancer in experimental animals ("*limited* evidence for cancer in humans" means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations, technically termed "chance", "bias", or "confounding", could not be ruled out with reasonable confidence);
2. When there is *limited* evidence for cancer in humans and *strong* mechanistic evidence;
3. When there is *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in human primary cells or tissues;
4. When, based on mechanistic considerations, the agent belongs to a class of agents of which one or more is *probably carcinogenic to humans* (Group 2A) or *carcinogenic to humans* (Group 1).

Group 2B: The agent is *possibly carcinogenic to humans*.
This category is used when there is *limited* evidence for cancer in humans and less-than-*sufficient* evidence for cancer in experimental animals. **This was the basis of the classification for HCMV**. It may also be used when the evidence regarding cancer in humans does not permit a conclusion to be drawn (referred to as *inadequate* evidence) but there is *sufficient* evidence for cancer in experimental animals. It can also be used when there is *strong* mechanistic evidence.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.
This category is used most commonly when the evidence is *inadequate* regarding cancer in humans and *inadequate* or *limited* for cancer in experimental animals, and mechanistic evidence is less than *strong*. "*Limited* evidence for cancer in experimental animals" means that the available information suggests a carcinogenic effect but is not conclusive.

14. How was the evidence reviewed in the *IARC Monographs* evaluation?

During an *IARC Monographs* evaluation, experts critically review the scientific evidence according to strict criteria, which focus on determining the strength of the available evidence that the agent causes cancer. These criteria are described in the Preamble to the *IARC Monographs*, which is available on the *IARC Monographs* website: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf.

The experts critically review four types of data:

- the situations in which people are exposed to the agent;
- epidemiological studies on cancer in humans exposed to the agent (scientific evidence regarding cancer in humans);
- experimental studies of cancer in laboratory animals treated with the agent (scientific evidence regarding cancer in experimental animals); and
- studies on how cancer develops in response to the agent (scientific evidence on carcinogen mechanisms).

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release emailing list, please write to terrassev@iarc.who.int

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