International Agency for Research on Cancer

World Health Organization

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# *IARC Monographs* evaluate the carcinogenicity of hydrochlorothiazide, voriconazole, and tacrolimus

## *IARC Monographs* Volume 137

## Questions and Answers (Q&A)

The meeting for *IARC Monographs* Volume 137: Hydrochlorothiazide, voriconazole, and tacrolimus, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, took place on 5–12 November 2024.

A Working Group of 22 international experts and one Invited Specialist from 14 countries evaluated the carcinogenicity of three pharmaceuticals: hydrochlorothiazide, voriconazole, and tacrolimus.

More information about Meeting 137 is available on the *IARC Monographs* website: https://monographs.iarc.who.int/iarc-monographs-volume-137/.

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 137 of the *IARC Monographs*, to be published in 2025.

### What are the results of the evaluation?

**All three agents were classified as *carcinogenic to humans* (Group 1).**

For all three agents, exposure to patients is expected to be the major exposure source. Environmental and occupational exposures may occur but are poorly documented and are expected to be orders of magnitude lower than exposures from direct use of the pharmaceutical.

**Hydrochlorothiazide**-containing medications are among the most frequently prescribed anti-hypertension pharmaceuticals worldwide. Oral treatment is the major type of exposure. Single drug prescriptions, which are still common in some countries, have been replaced by single-pill combinations, especially in high-income countries.

Hydrochlorothiazide was classified as *carcinogenic to humans* (Group 1) on the basis of *sufficient* evidence for cancer in humans, for squamous cell carcinoma of the skin and cancer of the lip. There was also *limited*

[1] Cogliano VJ, Corsini E, Fournier A, Nelson HH, Sergi CM, Antunes AMM, et al. (2024). Carcinogenicity of hydrochlorothiazide, voriconazole, and tacrolimus. *Lancet Oncol*. Published online 29 November 2024; https://doi.org/10.1016/S1470-2045(24)00685-5

evidence in humans for basal cell carcinoma of the skin, melanoma of the skin, Merkel cell carcinoma, and malignant adnexal skin tumours.

There was also *sufficient* evidence for cancer in experimental animals. Hydrochlorothiazide caused an increase in the incidence of liver tumours in male mice and a significant increase in the incidence of pheochromocytoma of the adrenal gland in female rats.

Hydrochlorothiazide is phototoxic because of interactions of its molecular structure with ultraviolet radiation. There was *limited* mechanistic evidence that hydrochlorothiazide exhibits the key characteristics of carcinogens in experimental systems.

The use of **voriconazole** as a medication is the major exposure pathway. Most patients identified with invasive pulmonary aspergillosis receive voriconazole, either alone or in combination with other therapeutic agents.

Voriconazole was classified as *carcinogenic to humans* (Group 1) on the basis of *sufficient* evidence for cancer in humans, for squamous cell carcinoma of the skin.

The major metabolite of voriconazole, voriconazole N-oxide, is phototoxic. There was *strong* mechanistic evidence that voriconazole exhibits key characteristics of carcinogens (KCs) together with exposure to ultraviolet radiation in exposed humans and human primary cells. Voriconazole in combination with exposure to ultraviolet radiation induces oxidative stress (KC5) in human primary cells and alters cell proliferation, cell death, or nutrient supply (KC10), including the induction of actinic keratosis (a precancerous lesion) in exposed humans.

Oral or intravenous treatment with **tacrolimus** is used mainly for organ rejection prophylaxis, and topical application is used in the treatment of atopic dermatitis and vitiligo.

Tacrolimus was classified as *carcinogenic to humans* (Group 1) via two different ways:

1. On the basis of *sufficient* evidence for cancer in humans, for non-Hodgkin lymphoma and post-transplant lymphoproliferative disorder. There was also *limited* evidence in humans for leukaemia and squamous cell carcinoma of the skin.

2. On the basis of the combination of *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence for key characteristics of carcinogens in exposed humans. There was also *strong* mechanistic evidence in human primary cells and in experimental systems.

   Tacrolimus caused an increase in the incidence of pleomorphic lymphoma in both sexes in mice and a significant increase in the incidence of undifferentiated lymphoma in female rats. Tacrolimus is an immunosuppressive drug. Thus, there was *strong* mechanistic evidence that tacrolimus alters many of the cells and mechanisms involved in immune system-dependent control of tumour growth in exposed

humans, in human primary cells, and in experimental systems. Tacrolimus is genotoxic (KC2) and induces oxidative stress (KC5) in experimental systems.

The results of the evaluation are summarized in Table 1.

**Table 1. Summary of classifications in *IARC Monographs* Volume 137**

| Agent | Evidence stream | | | Overall evaluation |
|---|---|---|---|---|
| | Cancer in humans | Cancer in experimental animals | Mechanistic evidence (key characteristics of carcinogens) | |
| Hydrochlorothiazide | *Sufficient* (squamous cell carcinoma of the skin and cancer of the lip) *Limited* (basal cell carcinoma, skin melanoma, Merkel cell carcinoma, and malignant adnexal skin tumours) | *Sufficient* | *Limited* | Group 1 |
| Voriconazole | *Sufficient* (squamous cell carcinoma of the skin) | *Inadequate* | *Strong* with UVR exposure in exposed humans (KC10) and in human primary cells (KC5) | Group 1 |
| Tacrolimus | *Sufficient* (non-Hodgkin lymphoma and post-transplant lymphoproliferative disorder) *Limited* (leukaemia and squamous cell carcinoma of the skin) | *Sufficient* | *Strong* in exposed humans, human primary cells, and experimental systems (KC7) and in experimental systems (KC2; KC5) | Group 1 |

KC, key characteristic of carcinogens; KC2, is genotoxic; KC5, induces oxidative stress; KC7, is immunosuppressive; KC10, alters cell proliferation, cell death, or nutrient supply; UVR, ultraviolet radiation.

## What conditions are these pharmaceuticals used to treat?

**Hydrochlorothiazide** is listed by the Organisation for Economic Co-operation and Development (for the year 2007) and the United States Environmental Protection Agency as a chemical with a high production volume. It is a commonly used diuretic for the treatment of hypertension and fluid retention (40 million prescriptions per

year in the USA in 2020). It has uses in both human and veterinary medicine. It is often used in combination with other antihypertensive medications.

**Voriconazole** is a broad-spectrum triazole antifungal medication commonly used to treat candidiasis and invasive aspergillosis. It is also administered prophylactically to immunocompromised patients to prevent invasive fungal infections. Its major metabolite, voriconazole N-oxide, is phototoxic.

**Tacrolimus** is a calcineurin inhibitor and immunosuppressive pharmaceutical used to treat non-malignant diseases. It is used for the prophylaxis of organ rejection in adult and paediatric patients receiving allogeneic transplants, or as a second-line therapy for the short-term and non-continuous treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children.

### Have these agents previously been evaluated by the *IARC Monographs* programme? What was the result of the previous evaluation?

**Hydrochlorothiazide** has been previously evaluated by the *IARC Monographs* in Volumes 50 and 108[2] and was classified most recently in 2013 as *possibly carcinogenic to humans* (Group 2B) on the basis of *limited* evidence for cancer in humans, for squamous cell carcinoma of the skin and cancer of the lip. There was also *limited* evidence for cancer in experimental animals.

**Voriconazole** and **tacrolimus** have not been previously evaluated by IARC.

### Why did IARC decide to evaluate these three pharmaceuticals?

In 2019, the Advisory Group to Recommend Priorities for the *IARC Monographs* recommended a wide variety of agents or substances for evaluation or re-evaluation by the *IARC Monographs* programme during 2020–2024[3].

**Hydrochlorothiazide** and other phototoxic pharmaceuticals were accorded high priority for evaluation by the *IARC Monographs* programme on the basis of emerging evidence on cancer in humans and in experimental animals and mechanistic evidence for their shared phototoxic properties.

**Voriconazole** and **tacrolimus** were selected for review on the basis of the information available and recent evidence on cancer in humans or experimental animals.

### What is the position of the World Health Organization (WHO) regarding these three pharmaceuticals?

[2] IARC (2015). Some drugs and herbal products. *IARC Monogr Eval Carcinog Risks Hum*. 108:1–424. Available from: https://publications.iarc.who.int/132.

[3] IARC (2019). Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf.

These three pharmaceuticals are listed as essential medicines by WHO[4].

**Hydrochlorothiazide** is among the elective treatments for hypertension[5], a condition that has the highest prevalence (27%) in the WHO African Region. Worldwide, the number of adults with hypertension increased from 594 million in 1975 to 1.13 billion in 2015; the increase was largely in low- and middle-income countries.

**Voriconazole** is the elective antifungal drug for the treatment of chronic pulmonary aspergillosis (caused mainly by *Aspergillus fumigatus*), which is estimated to affect more than 3 million people worldwide, of whom approximately 1.2 million have had tuberculosis in countries where it is endemic[6], despite the fact that antimicrobial resistance to voriconazole and other azoles is increasing.

**Tacrolimus** is the recommended medicine for the treatment and prevention of failure or rejection of transplanted organs or tissues in adults and children, according to several national and international guidelines. Other than its essential use, it is also applied topically to treat eczema and psoriasis.

### Why is the evaluation from the *IARC Monographs* programme important?

The evaluation carried out by the *IARC Monographs* programme is a rigorous and comprehensive review, synthesis, and integration of all the available scientific evidence on 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 (e.g. occupational, and the general population, including in patients, health-care professionals, and other workers).

### Has the *IARC* Monographs programme previously evaluated pharmaceuticals?

Over the course of its 53-year history, the *IARC Monographs* programme has evaluated approximately 100 pharmaceuticals, described in, for example, Supplement 7, Volumes 72, 76, 79, 91, and, most recently, 100A.[7]

### What does the *IARC Monographs* classification indicate?

The *IARC Monographs* classifications (Fig. 1) 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.

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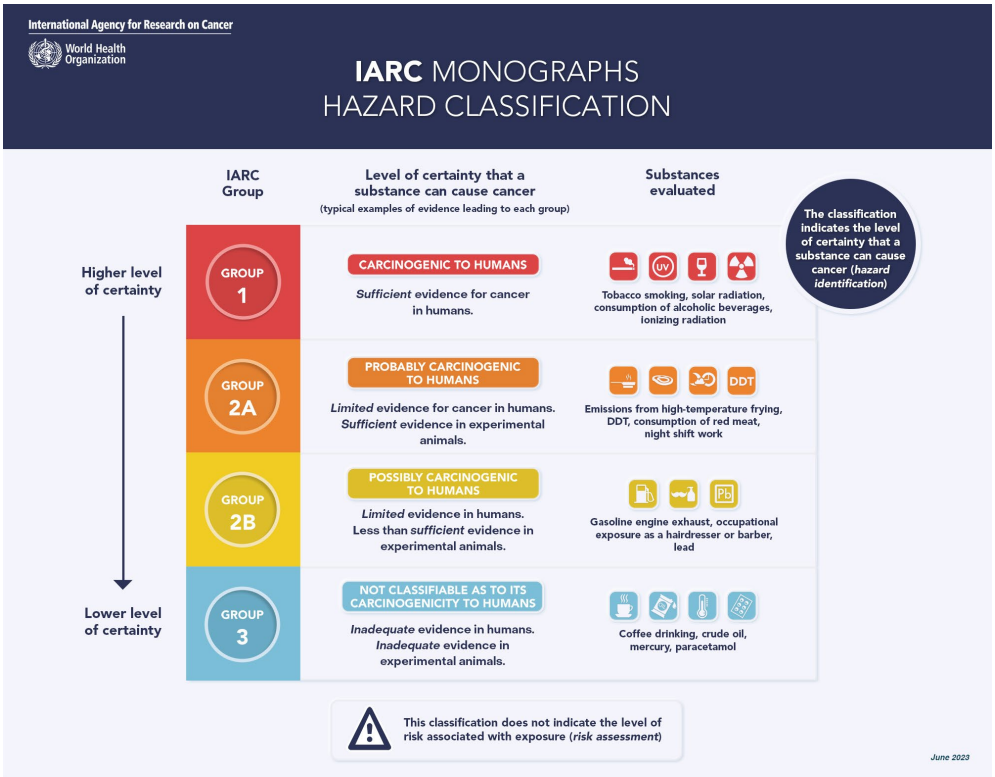
[4] WHO (2024). Model List of Essential Medicines [online database]. Geneva, Switzerland: World Health Organization. Available from: https://list.essentialmeds.org.

[5] WHO (2023). Hypertension. Fact sheet. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension.

[6] WHO (2024). Voriconazole. Model List of Essential Medicines [online database]. Geneva, Switzerland: World Health Organization. Available from: https://list.essentialmeds.org/medicines/288.

[7] All volumes of the *IARC Monographs* are available on the IARC Publications website: https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans.

**Figure 1. The hazard classification system used by the *IARC Monographs* programme**




Because the IARC Group indicates the strength of the evidence regarding a cancer hazard and not the cancer risk at a given level of exposure, the cancer risk (at typical exposure levels) associated with two agents classified in the same IARC Group may be very different.

## 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 development of cancer in exposed humans. 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.

**Group 2:**
This category includes agents with a range of evidence regarding cancer in humans and in 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 three different scenarios:

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.

These scenarios may also occur simultaneously within a Group 2A classification.

**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. It is also 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 or *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.

### How are the *IARC Monographs* classifications used?

IARC is a research organization that evaluates evidence on the causes of cancer but does not make health recommendations. Health and regulatory agencies may include *IARC Monographs* evaluations when considering actions to prevent exposure to potential carcinogens. IARC does not recommend regulations, legislation, or public health interventions, which remain the responsibility of individual national governments and other international organizations.

### What types of study were eligible for review by the IARC Working Group, and where did they come from?

As described in the current Preamble to the *IARC Monographs*[8] (last revised in 2019), the Working Group reviews publicly available scientific data, such as peer-reviewed papers in the scientific literature, and may also

[8] IARC (2019). Preamble to the *IARC Monographs* (amended January 2019). Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/.

review unpublished reports, if they are made available in their final form by governmental agencies and if they contain enough detail for critical review.

### 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).

### Have any public health agencies made recommendations regarding these pharmaceuticals?

With regard to **hydrochlorothiazide**, the European Medicines Agency (EMA)[9], followed by other authorities, including the United States Food and Drug Administration (FDA)[10] and Health Canada[11], has published recommendations for the proper use of hydrochlorothiazide as per the findings of potential association with skin cancers, and requesting also an update of safety data and the package leaflet wording.

Regarding **tacrolimus** and **voriconazole**, similar safety data reports and precaution instructions in the product information and leaflet package were introduced for most of the authorized products in the European Union.

### What does the IARC evaluation mean?

The *IARC Monographs* programme identifies cancer hazards but does not evaluate the risks associated with specific levels or circumstances of exposure, nor the risk-to-benefit ratio for medical treatments. The distinction

[9] EMA (2018). Hydrochlorothiazide – skin cancer (EPITT No. 19138). New product information wording – extracts from PRAC recommendations on signals. Adopted at the 3–6 September 2018 PRAC. Amsterdam, Netherlands: The Pharmacovigilance Risk Assessment Committee (PRAC), European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/other/new-product-information-wording-extracts-prac-recommendations-signals-adopted-3-6-september-2018-prac_en.pdf.

[10] US FDA (2020). FDA approves label changes to hydrochlorothiazide to describe small risk of non-melanoma skin cancer. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-label-changes-hydrochlorothiazide-describe-small-risk-non-melanoma-skin-cancer.

[11] Health Canada (2019). Summary safety review – hydrochlorothiazide – assessing the potential risk of non-melanoma skin cancer. Ottawa, Canada: Health Canada, Government of Canada. Available from: https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR00215.

between hazard and risk is important. An agent is considered a cancer hazard if it is capable of causing cancer under some circumstances. “Risk” measures the probability that cancer will occur, taking into account the level of exposure to the agent. Competent authorities in different countries will evaluate the risk-to-benefit ratio for treatments using these pharmaceuticals.

### What is the relationship between IARC and WHO?

IARC has a unique dual position as an independent international cancer research institute and as the specialized cancer research agency of the World Health Organization within the United Nations system, established in May 1965 by a resolution of the World Health Assembly. IARC is governed by its Governing Council and Scientific Council; the former comprises representatives from each Participating State, plus the WHO Director-General. IARC has its own defined scientific methods as set by the Preamble to the *IARC Monographs*. More information about IARC governance can be found here: https://www.iarc.who.int/cards_page/organization-and-management/.

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