参考資料3

Carcinogenicity of gentian violet, leucogentian violet, malachite green, leucomalachite green, and CI Direct Blue 218

In February–March, 2021, a Working Group of 11 scientists from eight countries met remotely at the invitation of the International Agency for Research on Cancer (IARC) to finalise their evaluation of the carcinogenicity of five agents used as dyes and reagents, and for their antibacterial and antifungal properties. For all these agents, the evidence regarding cancer in humans was "inadequate", as no studies were available. Data from humans on exposure, absorption, distribution, metabolism, or excretion and on mechanisms were sparse. Gentian violet, leucomalachite green, and CI Direct Blue 218 were classified as "possibly carcinogenic to humans" (Group 2B) on the basis of "sufficient" evidence of carcinogenicity in experimental animals. Leucogentian violet and malachite green were evaluated as "not classifiable as to its carcinogenicity in humans" (Group 3). These assessments will be published in Volume 129 of the *IARC Monographs*.[1]

Gentian violet and malachite green are cationic triphenylmethane dyes. They are widely used for textiles, paper, and acrylic products; as biological stains; and in some hair dyes and other cosmetics. Because of their antibacterial and antifungal properties, gentian violet and malachite green have had various medical, veterinary, and aquaculture applications, including the treatment of livestock, animal feed, ornamental fish, and farmed fish and shellfish. In many countries, these veterinary or cosmetic applications are restricted, and there is zero tolerance for residues of gentian violet and malachite green and their metabolites, leucogentian violet and leucomalachite green, in food for human consumption. Gentian violet and malachite green can be released into the environment in industrial discharge and persist in soil and aquatic species, primarily as their leucometabolites. Furthermore, leucomalachite green is present in fish and shellfish exposed to malachite green and has a longer residence time than the parent compound.[2] Leucogentian violet and leucomalachite green are used as precursors in the production of their parent compounds and have direct applications as chromogenic reagents in analytical chemistry and radiochromic indicators in dosimeters. Occupational exposure to the parent dyes and their leucometabolites can occur through dermal contact and inhalation in workplaces where these compounds are produced or applied, but data are sparse. General population exposure to both dyes and their leucometabolites can occur through direct application; through contact with textiles, paper, and inks; and from drinking contaminated water. Exposure to leucometabolites could occur when consuming fish or shellfish treated with gentian violet or malachite green.

In rodents, orally administered gentian violet is distributed to tissues, metabolised to various demethylated and reduced metabolites, and excreted primarily in the faeces. Bacteria have been shown to transform gentian violet into leucogentian violet, but data from mammalian species are sparse. For leucogentian violet, the mechanistic evidence was "inadequate", as the available data were sparse, and the evidence regarding cancer in experimental animals was "inadequate" because no studies were available. For gentian violet, the mechanistic evidence was "limited", because the findings pertinent to genotoxicity were inconclusive, and available data on other mechanistic topics were sparse. The evidence for carcinogenicity in experimental animals was "sufficient" because gentian violet increased the incidence of malignant neoplasms in two species in Good Laboratory Practice (GLP) studies. In B6C3F$_1$ mice exposed via the diet, gentian violet caused hepatocellular carcinoma in males and females, and histiocytic sarcoma of the bladder, ovary, uterus, and vagina in females.[3] In F344 rats exposed in utero, followed by lactational and then dietary exposure, gentian violet caused follicular cell adenocarcinoma of the thyroid gland in males and females, and mononuclear cell leukaemia in females.[4]

In orally dosed rats, malachite green is excreted primarily in the faeces. The metabolite leucomalachite green has been detected in the liver of rats fed a diet containing malachite green, in various tissues of rats after intravenous injection of malachite green, and in cultures of human and other mammalian intestinal microflora exposed to malachite green. Various desmethyl malachite green derivatives and malachite green *N*-oxide were detected in liver extracts from F344 rats fed diets containing malachite green and, to a lesser extent, in liver extracts from similarly exposed B6C3F$_1$ mice. The mechanistic evidence was "limited" for these compounds. Although suggestive, there were unresolved inconsistencies in the findings of clastogenicity for malachite green in studies in experimental animals. For leucomalachite green, findings in experimental systems were suggestive of mutagenicity, but the studies were few and narrow in range. There was "limited" evidence for carcinogenicity in experimental animals for malachite green because an increased incidence of an appropriate combination of benign and malignant neoplasms was seen, but only in one sex of a single species in one GLP study. In

Published **Online**
March 25, 2021
https://doi.org/10.1016/S1470-2045(21)00178-9

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Oct 5–12, 2021: volume 130: 1,1,1-Trichloroethane, hydrazobenzene, *N*-methylolacrylamide, diphenylamine, and isophorone
March 8–15, 2022: volume 131: Cobalt metal (without tungsten carbide) and cobalt (II) salts, weapons-grade tungsten (nickel/cobalt) alloy, and antimony trioxide
June 7–14, 2022: volume 132: Occupational exposure as a firefighter

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Declaration of interests
All Working Group members declare no competing interests.

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None

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Declaration of interests
All representatives declare no competing interests.

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Declaration of interests
All secretariat declare no competing interests.

For the **Preamble to the IARC Monographs** see https://monographs.iarc.who.int/wp-content/uploads/2019/01/Preamble-2019.pdf

For **IARC declarations of interests** see https://monographs.iarc.who.int/wp-content/uploads/2021/01/129-participants.pdf

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female F344 rats exposed through the diet, malachite green caused follicular cell adenoma or carcinoma (combined) of the thyroid gland.[5,6] There was "sufficient" evidence for carcinogenicity in experimental animals for leucomalachite green. Leucomalachite green increased the incidence of an appropriate combination of benign and malignant neoplasms in both sexes of one species in a GLP study and in one sex of another species in another GLP study. After dietary exposure, leucomalachite green caused follicular cell adenoma or carcinoma (combined) of the thyroid gland in male F344 rats, adenoma or carcinoma (combined) of the mammary gland in female F344 rats, and hepatocellular adenoma or carcinoma (combined) in female B6C3F$_1$ mice.[5,6]

CI Direct Blue 218 is a copper-chelated dimethoxybenzidine-based azo dye used for cellulose, acetate, nylon, silk, wool, tissue, fine papers, and textile goods. Although there is potential for occupational exposure to CI Direct Blue 218 during manufacturing, processing, and dyeing, no data on occupational exposure levels were identified. General population exposures can occur through contaminated air, water, or soil, and possibly through contact with dyed products. The mechanistic evidence was "inadequate" as the available data were sparse. The evidence for carcinogenicity in experimental animals was "sufficient" on the basis of an increased incidence of malignant neoplasms in both sexes of a single species in a GLP study, and increased incidence of an appropriate combination of benign and malignant neoplasms in one sex of another species in another GLP study. After dietary exposure, CI Direct Blue 218 caused hepatocellular carcinoma in male and female B6C3F$_1$ mice, and squamous cell papilloma or carcinoma (combined) of the pharyngeal epithelium in male F344/N rats.[7]

We declare no competing interests.

IARC Monographs Vol 129 group

International Agency for Research on Cancer, Lyon, France

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China's oncology drug market on the rise

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Published **Online** March 25, 2021 https://doi.org/10.1016/S1470-2045(21)00176-5

For more on **cancer incidence data for China** see https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf

For more on the **forecast for China's cancer drug market** see https://www.globaldata.com/china-continues-dominate-high-value-oncology-strategic-deals-asia-pacific-reveals-globaldata/

China looks set to become a major developer of cancer drugs within a few years after regulatory changes to simplify and encourage drug development, which also opened the door for greater investment by international pharmaceutical brands.

This strategy is a huge turnaround for a country where cancer was long seen as virtually untreatable, with many patients going overseas for treatment or importing their own drugs at great expense because of the lack of options in China. Since 2018, with the launch of the government's Healthy China 2030 initiative, regulators have simplified processes to approve drugs and new trials, while modifications to the country's medical insurance system have greatly reduced out-of-pocket costs to patients. Oncology is seen as a target area for drug development. Increased life expectancy, together with better and earlier detection and screening, has increased China's cancer caseload.

Liu Tianshu (Zhongshan Hospital, Shanghai, China) said that in the past few years, drug prices had dropped by as much as 80%. Even patients with advanced conditions (eg, metastatic colorectal cancer) can now live for 5 or 10 years. It was a very different story when she graduated from medical school in the 1990s. Then, almost no cancer drugs were available and so none of her colleagues were keen to pursue oncology. "At that time there were no effective treatments," said Liu. "It is much better now. Nowadays our patients live longer and we have more drugs and more treatments."

Data from WHO's International Agency for Research on Cancer show China recorded more than 4·5 million new cancer cases in 2020, and more than 3 million deaths. The most common type was lung cancer, driven partly by high rates of smoking, followed by colorectal cancer. Breast cancer is the most common type among Chinese women.

Some Chinese pharmaceutical firms are now even specialising in oncology drugs. BeiGene is now listed on the US Nasdaq stock market and recently made a deal with Novartis, worth up to US$1·3 billion, to market the monoclonal antibody tislelizumab outside China. BeiGene says the immuno-oncology drug, developed in China, has been conditionally approved in the country for use in