International Agency for Research on Cancer

World Health Organization

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IARC Monographs evaluate the carcinogenicity of anthracene, 2-bromopropane, butyl methacrylate, and dimethyl hydrogen phosphite

Questions and Answers (Q&A)

The meeting for *IARC Monographs* Volume 133: Anthracene, 2-Bromopropane, Butyl Methacrylate, and Dimethyl Hydrogen Phosphite, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, took place on 28 February to 7 March 2023.

The Working Group of 20 international experts from 10 countries evaluated the carcinogenicity of anthracene, 2-bromopropane, butyl methacrylate, and dimethyl hydrogen phosphite.

More information about the meeting is available on the *IARC Monographs* website: https://monographs.iarc.who.int/iarc-monographs-volume-133/.

The outcome of the assessment has been published in a summary article in T*he Lancet Oncology*[1] and will be described in detail in Volume 133 of the *IARC Monographs*, to be published in 2024.

What are the results of the evaluation?

Anthracene was classified as *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* for cancer in experimental animals.

2-Bromopropane was classified as *probably carcinogenic to humans* (Group 2A), based on *sufficient evidence* for cancer in experimental animals combined with *strong* mechanistic evidence in experimental systems and suggestive mechanistic evidence in exposed humans (see more information below).

Butyl methacrylate was classified as *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* for cancer in experimental animals.

Dimethyl hydrogen phosphite was classified as *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* for cancer in experimental animals.

[1] Cattley RC, Kromhout H, Sun M, Tokar EJ, Abdallah MA-E, Bauer AK et al., (2023). Carcinogenicity of anthracene, 2-bromopropane, butyl methacrylate, and dimethyl hydrogen phosphite. *Lancet Oncol*, Published online 23 March 2023; https://doi.org/10.1016/S1470-2045(23)00141-9

What are these chemicals used for?

Anthracene (CAS No. 120-12-7) is used primarily as an intermediate in the manufacture of dyes and pigments, pyrotechnics, coatings, wood preservatives, pesticides; and as an intermediate in the manufacture of organic chemicals. Anthracene is listed as a High Production Volume chemical with a world production of about 20 000 tonnes per year, and it is one of the 16 polycyclic aromatic hydrocarbons (PAHs) listed by the United States Environmental Protection Agency (US EPA) as priority pollutants on the basis of toxicity and exposure.

2-Bromopropane (CAS No. 75-26-3) is used as a solvent and intermediate in the manufacture of organic chemicals, pharmaceuticals, dyes, and adhesives.

Butyl methacrylate (CAS No. 97-88-1) is used in the manufacture of polyvinyl chloride plastics, polypropylene materials, glues, caulks, inks and paints, pesticides, and health-care materials.

Dimethyl hydrogen phosphite (CAS No. 868-85-9) is used as an intermediate in the manufacture of adhesives, lubricants, organophosphate pesticides (e.g. glyphosate), and pharmaceuticals (α-aminophosphonates). It is also used as a reactive flame retardant in textile finishing, cellulosic textiles, acrolein-grafted polyamide fibres, and polyethylene. Dimethyl hydrogen phosphite is listed as a High Production Volume chemical.

Who is exposed to these agents and how?

Anthracene: Anthracene is formed by incomplete combustion of biomass and therefore is ubiquitous in the environment. Various occupational exposures occur mainly by inhalation and dermal contact during the manufacture of carbon black, creosote or creosote-containing products, carbon anodes for aluminium electrolysis, fire-proof material, coking, tear-off of old coal-tar roofs, asphalt paving, and firefighting. Exposure of the general population occurs via multiple routes, for example, cigarette smoke, ingestion of contaminated food and beverages or water, inhalation of polluted air (e.g. by indoor and outdoor biomass burning and industry and traffic emissions), and contact with contaminated soils or consumer products. Contaminated food is the major route of anthracene intake by the non-smoking and non-occupationally exposed population. Anthracene is introduced into food via environmental pollution or processing steps such as drying, smoking, and barbecuing.

2-Bromopropane: Occupational exposure occurs via the respiratory and dermal routes during its production and use as a (dry) cleaning agent (solvent) and in adhesive production and application, and because it is an impurity of 1-bromopropane, which has been used since the 1990s as a substitute for ozone-depleting and other solvents. No data were available on exposure of the general population.

Butyl methacrylate: Occupational exposures may occur in the production of butyl methacrylate; manufacture of paints, coatings, adhesives, and plastics; construction; furniture manufacture; textile manufacture; printing and publishing; maritime vessel repair; health and dental care; and personal care services. Highest exposures were found in paint and adhesive manufacturing. Exposure can occur via all routes, but inhalation is the most significant. Exposure of the general population may occur via contaminated air and water, food contained in

butyl methacrylate-containing plastics, and in personal care and health-care products. Butyl methacrylate has been measured in fingernail polishes and lacquers, and dental and joint-replacement polymers.

Dimethyl hydrogen phosphite: Exposure data were available only for its use in the production of flame retardants. The most relevant occupational exposure route is via inhalation. There were no available data on environmental occurrence or exposure of the general population.

Why are these results important?

Identifying the causes of human cancer is the first step in cancer prevention. Cancer prevention is needed because the global burden of cancer is high and continues to increase because of population growth and ageing, and upward trends in some exposures, especially in low- and middle-income countries. The identification of a cancer hazard may have broad and profound implications. National and international authorities and organizations can and do use information on causes of cancer in support of actions to reduce exposure to carcinogens in the workplace, in the environment, and elsewhere.

How can exposure be reduced?

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* are often used as a basis for national and international policies, guidelines, and recommendations to reduce exposures in order to minimize cancer risks.

Have these agents previously been evaluated by the *IARC Monographs* programme?

Anthracene was evaluated by the *IARC Monographs* programme in 2005 as *not classifiable as to its carcinogenicity to humans (Group 3)*.[2]

Dimethyl hydrogen phosphite was evaluated by the *IARC Monographs* programme in 1998 as *not classifiable as to its carcinogenicity to humans (Group 3)*.[3]

2-Bromopropane and butyl methacrylate have not been previously evaluated by the *IARC Monographs* programme.

[2] IARC (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum, 92:1–853. Available from: https://publications.iarc.fr/110 PMID:21141735
[3] IARC (1999). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part 1, Part 2, Part 3). IARC Monogr Eval Carcinog Risks Hum, 71:1–1586. Available from: https://publications.iarc.fr/89 PMID:10507919

Why were they evaluated?

Anthracene, dimethyl hydrogen phosphite, and butyl methacrylate were accorded medium or low priority for evaluation by the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024.[4]

2-Bromopropane was the subject of a recent positive cancer bioassay, and such agents are always accorded priority for evaluation in forthcoming meetings.

For those that were re-evaluated, was there a key new study or evidence that was used in the re-evaluation?

A positive cancer bioassay that complied with good laboratory practice (GLP) was available to the Working Group for both of the previously evaluated agents, anthracene[5] and dimethyl hydrogen phosphite.[6] Although these studies were available during the previous *IARC Monographs* evaluations, their results were considered to be newly informative under the revised Preamble to the *IARC Monographs*.

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* 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.

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 carcinogenic hazards, meaning the potential for the agent to cause cancer. However, the classification does not indicate the level of cancer risk associated with exposure at different levels or in different scenarios of exposure. The cancer risk associated with substances

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[4] 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.

[5] JBRC (1998). Report of feed carcinogenicity study of anthracene in F344 rats and BDF_1 mice. Study No. 0242, 0243. Kanagawa, Japan: Japan Bioassay Research Center, Ministry of Health, Labour and Welfare of Japan. Available from: https://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/Anthracen_Cancer_MAIN.pdf: https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf. [Japanese]

[6] NTP (1985). NTP technical report on the toxicology and carcinogenesis studies of dimethyl hydrogen phosphite (CAS No. 868-85-9) in F344/N rats and $B6C3F_1$ mice (gavage studies). Technical report 287. Research Triangle Park (NC), USA: National Toxicology Program. Available from: https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr287/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tr287abs</eref>

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.

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 the following table.

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			

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 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 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.

What was the basis of the Group 2A evaluation for 2-bromopropane?

After considering all relevant scientific findings, the Working Group exceptionally assigned 2-bromopropane to a different category than a strict application of the above framework would indicate, consistent with the principles outlined in the Preamble to the *IARC Monographs*. This exceptional assignment was based upon the integration of two streams of evidence. First, the *sufficient* evidence of carcinogenicity in both sexes of animals in a study that complied with good laboratory practice (GLP) was observed to an unusually high degree, based on the occurrence of malignant tumours of various types with high incidence and at numerous sites. Second, the evidence for the key characteristics of carcinogens in experimental systems was strong for end-points of genotoxicity, induction of oxidative stress, and immunosuppression, and this was further supported by suggestive evidence for immunosuppression and for modulation of receptor-mediated effects in two studies of workers exposed to 2-bromopropane.

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 com@iarc.who.int.